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Intravenous fluid therapy for hospitalized and critically ill children: rationale, available drugs and possible side effects

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Intravenous fluid therapy for hospitalized and critically ill children: rationale, available drugs and possible side effects

Short title: Fluid therapy for children

Abstract

Human beings are constituted mainly of water. In particular, children's total body water might reach 75–80% of their body weight, compared to 60–70% in adults. It is therefore not surprising, that children, especially hospitalized newborns and infants, are markedly prone to water and electrolyte imbalances. Parenteral fluid therapy is a cornerstone of medical treatment and is thus of exceptional relevance in this patient population.

It is crucial to appreciate the fact that intravenous fluids are drugs with very different characteristics, different indications, contraindications and relevant side effects. In the present review, we will summarize the physiology and pathophysiology of water and electrolyte balance, underlining the importance and high prevalence of non-osmotic antidiuretic hormone release in hospitalized and critically ill children. Furthermore, we will discuss the characteristics and potential side effects of available crystalloids for the paediatric population, making a clear distinction between fluids that are hypotonic or isotonic as compared to normal plasma. Finally, we will review the current clinical practice regarding the use of different parenteral fluids in children, outlining both the current consensus on fluids employed for resuscitation and replacement and the ongoing debate concerning parenteral maintenance fluids.

Key words: paediatric critical care; paediatric anaesthesia; intravenous fluids, crystalloids; acid-base equilibrium

Water (H_2O), a transparent chemical substance with a hint of blue, is the main constituent of our planet Earth — *the Blue Planet* — covering about 70% of its surface. Similarly to planet Earth, mammals, such as humans, are also mainly constituted of water. Depending on age, gender and amount of body fat, 50 to 90% of our total body weight consists of water (Fig. 1) [1]. Water has a myriad of chemical, physical and biological functions, e.g., suspending red blood cells to carry oxygen to the tissues; combining with carbon dioxide (CO_2) to form carbonic acid (H_2CO_3) dissociating to hydrogen (H^+) and bicarbonate (HCO_3^-) thus favouring the transport of CO_2 from the tissues to the lungs; and transporting substances such as nutrients, electrolytes and waste products. For these reasons, water is frequently, and not surprisingly, referred to as the "*solvent of life*".

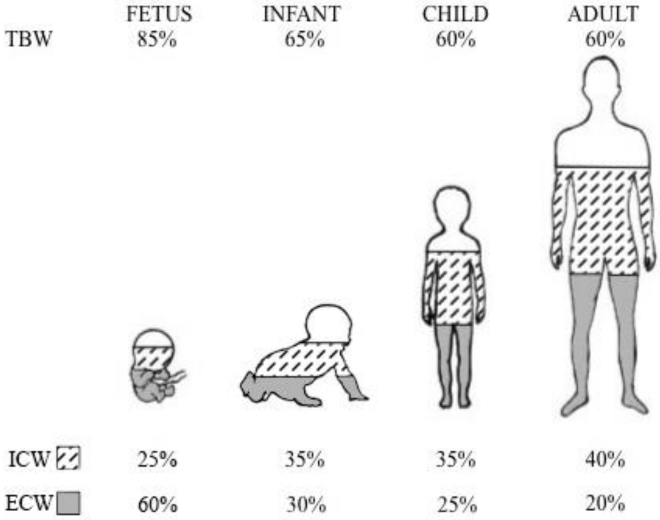


Figure 1. Changes in total body water and its distribution according to age categories. Schematic representation of total body water (TBW) and its distribution between extracellular and intracellular water (ECW and ICW, respectively) in four age categories [1]. Values reported for the *Foetus* refer to a healthy foetus of 7–8 months of gestational age; values reported for the *Infant* refer to a healthy infant of 7–8 months; values reported for the *Child* refer to a healthy child aged approximately 3 years; values reported for the *Adult* refer to an adult male. Of note, percentages of total body, intracellular, and extracellular water are referred to as percentages of total body weight

The water in our body, mainly delimited from the outside through cellular membranes, is in indirect contact with the environment through three major ways: (i) the gastrointestinal system, by means of which water is absorbed in our body; (ii) the urinary system, which physiologically regulates water elimination; and (iii) the skin and respiratory system which, given their important surface area and their contact with a water-poor environment, namely *air,* also contribute significantly, and in a largely unregulated way, to water loss. A malfunction of, or imbalance between these regulatory systems can easily result in disorders of water and electrolyte homeostasis. It is therefore not surprising that the mainstay of medical practice in general, and of critical care medicine and anaesthesiology in particular, deals with water and electrolyte homeostasis.

Children, especially newborns and infants, are particularly prone to water and electrolyte imbalances. Reasons for this predisposition include: (i) a higher total body water content [2]; (ii) a higher metabolic rate and thus a higher need for calories, water and electrolytes [3]; (iii) relatively higher insensible losses due to both a higher surface area to body mass ratio [4]; and a relatively higher production of CO_2 and therefore a higher minute ventilation; and (iv) the possible presence of immature regulatory mechanisms [5, 6]. For the abovementioned reasons, fluid therapy in children is particularly important, challenging and should be considered, in all respects, as a pharmacological treatment with precise indications, contraindications and side effects.

In the present review, we will: (i) briefly highlight water and salt distribution of the human body; (ii) summarize the physiology and pathophysiology of water and electrolyte balance; discuss the peculiarities (iii) and potential side effects (iv) of available intravenous/parenteral fluids for the paediatric population and; finally, (v) outline the current clinical practice regarding the use of different intravenous fluids in children, both as maintenance and as resuscitation/replacement fluids.

Body water, salts and their distribution

In children, the relative amount of body water varies considerably with age [2]. Indeed, total body water (TBW) is extremely high in foetuses and premature newborns, where it represents up to 90% of body weight, predominantly distributed in the extracellular compartment (extracellular fluid [ECF] represents ~65% of TBW) [1]. When the foetus leaves the watery environment of the uterus after a full-term gestation, the transition to a terrestrial habitat is already taking place, and TBW is decreased to 75–80% of body weight. Moreover, the proportion of water enclosed by cellular membranes, i.e., intracellular fluid (ICF), increases to ~ 45% of TBW and, consequently, the proportion of ECF undergoes a relative drop to ~ 55% of TBW. This trajectory proceeds in the first year of life, during which, due to an increase in body fat, a progressive reduction of TBW up to 60% is observed. In parallel, the ratio of ECF to ICF continues to change, in favour of the intracellular compartment, which, at the end of the first year of life, will reach 60% of TBW, the ECF accounting for the remaining 40% (a percentage close to those of adults). Of note is the fact that the relative drop in ECF is mainly due to a reduction in interstitial fluid, while the percentage of intravascular fluid appears to be fairly constant [7]. Finally, TBW will slightly drop in females during puberty to around 55% of total body weight, due to a relatively higher increase in body fat. Table 1 summarizes representative compositions of different body fluid compartments [8].

Table 1. Fluid compartments and their composition

	ECF			ICF		TBF
	Plasma	ISF	CSF	ICF_{ST}	ICF_{RBC}	
% of body weight	4.7	20	0.3	31.5	3.5	60
Na^{+} [mEq L^{-1}]	143	137	145	10	19	64
K^{+} [mEq L^{-1}]	4	3	3	155	95	88
Ca^{2+} [mEq L^{-1}]	2	2	2	< 0.1	< 0.1	0.8
Mg^{2+} [mEq L^{-1}]	2	2	2	10	5	6
Cl^{-} [mEq L^{-1}]	107	111	125	10	52	54
Lac^{-} [mEq L^{-1}]	1	1	1.5	1	1	1
Other Anions [mEq L^{-1}]	–	–	–	34	9	18
HCO_3^{-} [mEq L^{-1}]	25	31	24	11	15	19
Albumin [g dL^{-1}]	5	< 1	< 0.1	< 0.1	< 0.1	< 1
A^{-} [mEq L^{-1}]	16	< 1	1	118	42	66
SID [mEq L^{-1}]	42	31	24	130	57	85

The table summarizes the simplified composition of different body fluid compartments of a child aged 12 months or more, schematically divided into extracellular (ECF) and intracellular fluid (ICF) [8]. In addition, the theoretical average composition of total body fluid (TBF), resulting from the mixing of ICF and ECF, i.e., total body electrolytes divided by total body water (TBW), was calculated and reported in Table. *Definition of abbreviations:* ISF = interstitial fluid; CSF = cerebrospinal fluid; ICF = “standard” intracellular fluid; ICF_{RBC} = red blood cells fluid; Na^+ = sodium concentration; K^+ = potassium concentration; Ca^{2+} = ionized calcium concentration; Mg^{2+} = ionized magnesium concentration; Cl^- = chloride concentration; Lac^- = lactate concentration; other anions = sum of the concentration of other anions; HCO_3^- = bicarbonate concentration; A^- = dissociated, electrically charged part of ‘non-carbonic buffers’ (A_{TOT}); SID = Strong Ion Difference. All concentrations, except for Albumin, are expressed in mEq L^{-1}

By far, the major component of ECF is interstitial fluid (ISF), which is composed of a huge number of extremely thin layers of solution surrounding the cells [9], and is therefore quite difficult to sample and analyze. The remaining part of ECF is composed of the following: (i) plasma, which we use to sample, analyze and draw inferences regarding disorders of water, electrolyte and the acid-base of the whole body; (ii) cerebrospinal fluid, which, despite its tiny quantitative amount, plays a key physiologic role in the regulation of spontaneous ventilation [10, 11]; and (iii) other small volumes of fluids, such as the aqueous humour filling the anterior and posterior chambers of the eye [12]. As can be noted in Table 1, all ECFs are mainly composed of sodium salts, i.e., the main extracellular electrolytes being sodium and chloride.

Intracellular fluid (ICF) is composed of the sum of billions of minuscule drops of solutions contained by the cells of our body. Of course, there exists no such thing as standard ICF: as cells have significantly different tasks, their internal composition changes considerably. For instance, the ICF of red blood cells, which is extremely specialized in oxygen transport, fairly easy to sample/analyze and constantly exchanges fluids and electrolytes with plasma [13, 14], is supposed to differ significantly from the “standard” ICF of other cells (Table 1). Regardless of these differences and in contrast to ECF, ICF is always composed of potassium salts, which, given the low intracellular concentration of chloride, tend to have an organic accompanying anion (phosphates and proteins).

Cell membranes are freely permeable to water and the different fluid compartments are therefore in osmotic equilibrium. The same osmolarity (290–300 mOsm L^{-1}) is ensured in the ECF by sodium salts and in the intracellular fluid by potassium salts (Equation 1). Osmolarity is finely tuned by several hormonal axes (*see below*), which, however, frequently malfunction during critical illness.

$$Osmolarity = \frac{2Na^+ + 2K^+}{TBW} = \frac{2Na^+}{ECW} = \frac{2K^+}{ICW} \qquad \text{Equation 1}$$

Where Na^+ and K^+ represent the total *amount* of sodium and potassium, respectively, TBW stands for total body water; ECW and ICW stand for extracellular and intracellular water, respectively. Of note is the fact that the amounts of sodium (main extracellular cation) and potassium (main intracellular cation) are doubled in order to also take into account the osmoles resulting from the accompanying anions.

Additionally, the glycocalyx, an integral part of the vascular barrier, constituted of a complex layer of glycoproteins and proteoglycans to which negatively charged glycosaminoglycans side chains are attached, plays a central role in regulating the movements of water between plasma and the interstitium [15, 16]. The glycocalyx interacts with plasma components, such as proteins (mainly albumin), to form the so-called *endothelial surface layer* [17],a layer that virtually separates circulating blood and endothelium of blood vessels, thus substantially forming an intravascular barrier that regulates endothelial permeability. In addition, it has important roles in regulating leukocytes' diapedesis, and in inhibiting intravascular thrombosis. The fundamental importance of the glycocalyx and of the *endothelial surface layer* becomes evident in conditions in which it is disrupted, such as sepsis [18] and trauma [19], rapidly leading to altered endothelial permeability and favouring oedema formation.

Physiology and pathophysiology of water balance and osmolarity

In healthy subjects, the difference between introduced (*input*) and lost (*output*) water, i.e., *water balance*, equals zero, despite considerable variations in water and salt intake through the gastrointestinal tract. Indeed, water absorption through the intestine, mainly occurring in the small bowel (~80%), is poorly regulated and almost complete (~99%) [20]. Water is lost in an unregulated way through the skin and respiratory tract (*insensible* losses). However, the majority of water is excreted through the kidneys, whose activity is finely regulated by several hormonal axes (*see below*). Of note is the fact that the kidneys can vary the osmolarity of their product, namely *urine*, from as low as 50 to as high as 1200 mOsm L^{-1}. This ability to change urinary osmolarity is fundamental in order to keep its plasma value within very tight ranges, despite great variations in water and electrolyte input.

We will now briefly and schematically discuss the most important hormonal axes contributing to fluid balance and osmolarity maintenance.

Arginine vasopressine/antidiuretic hormone

Antidiuretic hormone (ADH), also referred to as arginine vasopressin (AVP), is the most important hormone regulating the renal excretion of free water [21]. ADH is synthesized in the hypothalamus and released from the posterior pituitary after appropriate stimuli, namely (i) hyperosmolarity and (ii) depletion of the effective circulating volume. Accordingly, this hormonal axis is equipped with both osmo- and volume/pressure receptors [22].

Osmoreceptors are specialized cells primarily found in the hypothalamus, sensing changes in osmotic pressure and, with their efferent signals, influencing ADH secretion. Given the central role of plasma sodium concentration in determining extracellular osmolarity (Equation 1), it is not surprising that sodium is the main osmotic determinant of ADH release. Of note is the fact that increases in plasma osmolarity as small as 1 mOsm L^{-1} are sufficient to trigger an increase in ADH release [23]. Physiologically, the highest plasma ADH levels (4–5 pg mL^{-1}), are reached for increases in plasma osmolarity in the order of 5–10 mOsm L^{-1}, leading to the maximal concentration of urine, i.e., maximal renal reabsorption of water.

Receptors designed for the signalling of changes in effective circulating volume are located in the carotid and aortic sinuses, as well as in the left atrium, and are stretch-sensitive (baroreceptors). A reduction of the stretch of these receptors, as in cases of reduced pressure/volume, will favour ADH release, this also occurring in the presence of low plasma osmolarity (*non-osmotic stimulation*).

Finally, and very importantly, ADH release may change in response to additional factors, not necessarily related to osmotic pressure and volume status. These factors, such as pain, stress, nausea and several drugs, are of particular interest in hospitalized, critically ill children. Indeed, they are implicated in alterations in water and electrolyte handling, i.e., a reduced ability to manage water loads, often observed in these patients, especially in the first postoperative days [24, 25].

Regardless of the stimulus leading to its release, ADH binds to two major receptors, V1 and V2. While V1 receptors are responsible for the vasoconstricting effect of ADH, V2-receptors mediate its water-retaining function. The ADH-V2 bond causes the release of preformed aquaporin-2 and its exposure on the luminal membrane of renal collecting tubules, significantly increasing their permeability to water and thus favouring free water reabsorption.

Thirst

Besides ADH release, thirst is the other physiological mechanisms designed to deal with hypernatremia and hyperosmolarity [22]. As stated above, the hypothalamic-pituitary-kidney axis keeps, in physiologic conditions, osmolarity in very narrow ranges (fluctuations of 1–2%). Thirst, however, has a slightly higher osmotic threshold (~2–4%), limiting the feeling of thirst in daily life [21]. If, however, osmolarity increases, despite the maximum ADH release/maximum renal water reabsorption, thirst is stimulated. This will usually result in an increased oral fluid intake, which will lead to an immediate, although transient, suppression of the feeling of thirst and ADH secretion. This mechanism, which is mediated by oropharyngeal receptors, will allow a slow and gradual restoration of the water deficit.

Aldosterone

Unlike ADH and thirst, which are designed to avoid hyperosmolarity, aldosterone is primarily involved in the regulation of plasma potassium concentration and the effective circulating volume. Indeed, aldosterone increases potassium excretion, at the level of the distal nephron, in response to a rise in its plasma concentration. Furthermore, and more importantly in the context of the topic of the review, its release represents the final step of the *renin-angiotensin-aldosterone* system. In cases of intravascular volume depletion, aldosterone is synthesized in the *zona glomerulosa* of the adrenal cortex and mainly acts in the distal nephron by increasing sodium and chloride reabsorption and potassium excretion. Consequently, water will be reabsorbed along with the primary extracellular solutes, determining, *de facto*, a reabsorption of extracellular fluid.

Atrial natriuretic peptide

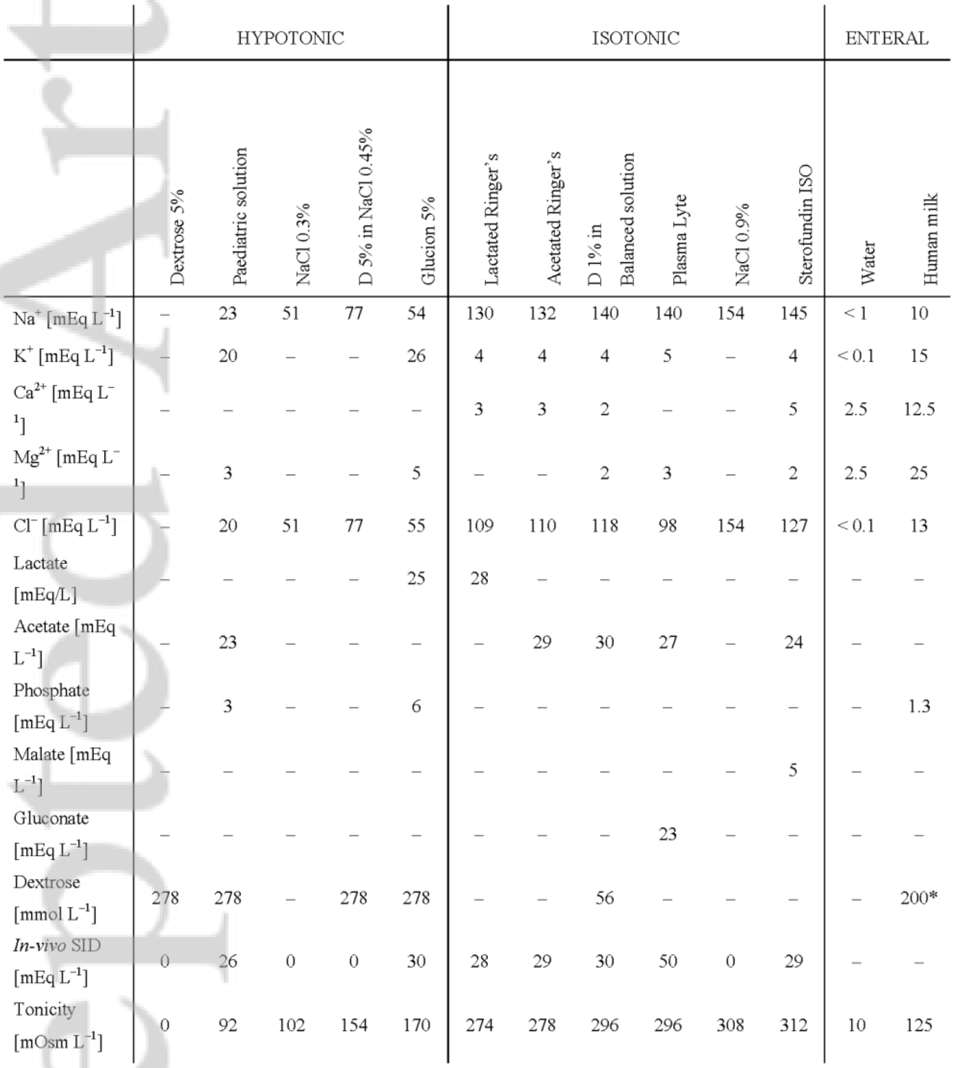
Atrial natriuretic peptide (ANP) is released by the cardiac atria, in response to atrial wall stretch, i.e., in cases of volume expansion. Once released, ANP increases renal sodium and water excretion by means of a reduced sodium reabsorption at the level of the collecting tubules and through an increased glomerular filtration rate. Indeed, ANP and aldosterone act as antagonists on sodium balance, with the purpose of restoring normal values for the effective circulating volume. Furthermore, ANP has also direct vasodilating effects, determining a reduction in blood pressure [22].

Finally, ANP also appears to play a role in the detrimental side effects of hypervolaemia. Indeed, it seems that, during hypervolaemia, ANP is co-responsible for the degradation of the glycocalyx, resulting in increased vascular permeability and the formation of tissue oedema [26].

Available intravenous fluids and their indication

Intravenous fluids are administered directly into the plasma, where they initially mix with the intravascular fluid volume, following which and according to their tonicity, they redistribute mainly to the interstitial fluid (*isotonic fluids*) or the interstitial and intracellular fluid compartment (*hypotonic fluids*). When comparing the compositions of available intravenous fluids (Table 2) with the composition of the different body fluid compartments (Table 1), it is clear that: (i) *isotonic* fluids have a composition that is more similar to the ECF; (ii) *hypotonic* fluids, despite having a lower potassium concentration and tonicity, have a composition which is more analogous to that of 'total body fluid'; (iii) no available intravenous fluid resembles ICF composition. These differences underline the important fact that different fluids have *different therapeutic targets*.

Table 2. Characteristics of intravenous fluids employed in the paediatric population



	HYPOTONIC					ISOTONIC						ENTERAL	
	Dextrose 5%	Paediatric solution	NaCl 0.3%	D 5% in NaCl 0.45%	Glucion 5%	Lactated Ringer's	Acetated Ringer's	D 1% in Balanced solution	Plasma Lyte	NaCl 0.9%	Sterofundin ISO	Water	Human milk
Na^+ [mEq L^{-1}]	–	23	51	77	54	130	132	140	140	154	145	< 1	10
K^+ [mEq L^{-1}]	–	20	–	–	26	4	4	4	5	–	4	< 0.1	15
Ca^{2+} [mEq L^{-1}]	–	–	–	–	–	3	3	2	–	–	5	2.5	12.5
Mg^{2+} [mEq L^{-1}]	–	3	–	–	5	–	–	2	3	–	2	2.5	25
Cl^- [mEq L^{-1}]	–	20	51	77	55	109	110	118	98	154	127	< 0.1	13
Lactate [mEq/L]	–	–	–	–	25	28	–	–	–	–	–	–	–
Acetate [mEq L^{-1}]	–	23	–	–	–	–	29	30	27	–	24	–	–
Phosphate [mEq L^{-1}]	–	3	–	–	6	–	–	–	–	–	–	–	1.3
Malate [mEq L^{-1}]	–	–	–	–	–	–	–	–	–	–	5	–	–
Gluconate [mEq L^{-1}]	–	–	–	–	–	–	–	–	23	–	–	–	–
Dextrose [mmol L^{-1}]	278	278	–	278	278	–	–	56	–	–	–	–	200*
In-vivo SID [mEq L^{-1}]	0	26	0	0	30	28	29	30	50	0	29	–	–
Tonicity [mOsm L^{-1}]	0	92	102	154	170	274	278	296	296	308	312	10	125

Intravenous fluids have been divided in *hypotonic* and *isotonic* and listed according to increasing tonicity. For comparison, the composition of drinking water and human milk have been added (*enteral*). List of abbreviations: *In-vivo* SID = all organic molecules contained in balanced solutions are strong anions. The resulting calculated SID (*in-vitro* SID) is equal to 0 mE L^{-1}. Once infused, the organic molecules are metabolized to CO_2 and water; the resulting *in-vivo* SID corresponds to the amount of organic anions metabolized. Tonicity = number of solutes to which cell membranes are impermeable. In this context, glucose, which rapidly crosses cell membranes, is not included in the calculation. *200 refers to mmol L^{-1} of lactose, in the case of human milk

On the one hand, isotonic fluids are typically employed both for *fluid resuscitation*, i.e., to correct an acute *intravascular* fluid deficit, and for the *replacement* of *extracellular* fluid losses, which cannot be compensated by oral fluid intake alone [27, 28]. On the other, the administration of hypotonic fluids generates the necessary osmotic driving force needed to allow the movement of water from the extracellular to the intracellular compartment. Insofar, they hydrate both the extracellular and intracellular fluid compartments. For the abovementioned reason, hypotonic fluids are only suitable for so-called *fluid maintenance*, i.e., to provide water and electrolytes in haemodynamically stable children that are not able/allowed to drink water. Maintenance fluids are thus intended to replace the anticipated water and electrolyte needs due to insensible losses and physiologic urinary output [29, 30].

Finally, it is important to notice that most intravenous fluids employed in the paediatric population contain a certain amount of glucose, which usually ranges between 1 and 5%.

It should be noted that a discussion on the use of colloidal solutions in the paediatric population is beyond the scope of the present review.

Side effects of intravenous fluid therapy

As with all medical/pharmacological treatments, intravenous fluids are also burdened by side effects. Schematically, these are caused by: (i) an excessive fluid administration causing oedema (*see below*); and (ii) by the dilution of the “receiving” fluid compartment with resulting electrolyte, acid-base, and glycaemic alterations. Of note is the fact that the entity of both categories of side effects is certainly dependent on the quantity of administered fluids — *the dose makes the poison*. Furthermore, pathological processes frequently encountered in hospitalized, critically ill children, such as inappropriate ADH secretion (SIADH) [24, 31] and renal failure [32], amplify these side effects by impairing the normal fluid and electrolyte homeostasis.

Excessive fluid administration

Regardless of the chosen fluid (Table 2), an excessive dose will cause fluid overload, potentially leading to tissue and organ oedema, dysfunction and failure.

Excessive *isotonic* fluids cause an expansion of the extracellular fluid — *water and salt overload* — causing tissue oedema, with all related consequences, including *indirect* worsening of cellular function [33, 34]. Concerning salt overload, one should keep in mind that 1 L of 0.9% NaCl contains 154 mmol of sodium (3.5 g) and 154 mmol of chloride (5.5 g). It should be noted that these quantities are significantly higher than the recommended daily sodium and chloride intakes for adults [35]. Furthermore, the infusion of *isotonic* fluids, leaving plasma osmolarity substantially unchanged, will not suppress ADH secretion, thus favouring the occurrence of positive fluid balances [34, 36].

On the other hand, the excessive administration of *hypotonic* fluids will cause a reduction in total body osmolarity (see Equation 1) and will determine, after fluid redistribution, both an extracellular and an intracellular dilution, namely *water overload/intoxication*.

The typical sign of water excess is a reduction in osmolarity and, given the central role of sodium in determining extracellular osmolarity, this will be recognized as *hyponatremia*. Hyponatremia is, however, a surrogate marker for *water excess,* which is the biggest problem as it will affect cellular function both *indirectly* (tissue oedema) and *directly* (cellular oedema/swelling). In particular, the movement of electrolyte-free water into brain cells will determine cerebral oedema with the resulting increase in intracranial pressure [37, 38]. Not surprisingly, the most striking manifestations of water intoxication are neurological, ranging from mild, non-specific symptoms such as nausea and vomiting, up to extremely severe and fatal events, such as seizures, coma, brain stem herniation and death. It should be noted that due to neuroanatomical characteristics, i.e., a high ratio between the brain and skull, these symptoms are particularly frequent in children [39, 40]. As already mentioned, *hypotonic* fluids should be prescribed only for *maintenance*, the rate of which is traditionally based on paediatric metabolism and calculated on body weight, applying the usual ‘4/2/1’ rule of Holliday and Segar [30]. Not surprisingly, quantities of fluids administered for maintenance are significantly lower than amounts of crystalloids infused for replacement or resuscitative purposes. For these reasons, one would expect side effects related to iatrogenic water intoxication to be infrequent. However, apart from few reported cases of erroneous prescriptions [41], in which high volumes of *hypotonic* fluids were administered in a short time frame, there are plenty of reports of severe, often lethal, complications of hypotonic fluid administered at a correct maintenance rate [39, 42, 43] likely as a result of an ineffective free water excretion. Indeed, while in physiologic conditions, the administration of *hypotonic* fluids suppresses ADH secretion, fostering renal excretion of free water, thus limiting positive fluid balance [34], this is not always the case in pathological conditions due to the presence of SIADH.

Electrolyte and Acid-base alterations resulting from dilution

The hydrogen concentration of a biological solution, and its negative logarithm — *pH* — are independently regulated by three variables, namely: partial pressure of carbon dioxide; strong ion difference (SID); and the total amount of weak acids (A_{TOT}) [44].

Crystalloids are aqueous solutions containing mineral salts and/or salts of organic acids, which, by definition, do not contain albumin and/or phosphates. Thus, the administration of any type of crystalloid will cause a reduction in A_{TOT}, with the resulting alkalizing effect [45]. Additionally, all crystalloids affect plasma SID, depending on their own *in vivo* SID, i.e., their SID following the metabolism of organic anions such as lactate and acetate. If the SID of the administered crystalloid is lower than plasma SID, as it always is in the case of 0.9% NaCl, plasma SID will reduce and pH will tend toward acidosis. The opposite will occur in case of crystalloids with high infusional *in vivo* SID, e.g. PlasmaLyte (Table 2). To summarise, when fluids are administered parenterally, plasma SID and A_{TOT} are forced in the direction of the SID and A_{TOT} of the infused fluid. Therefore, the infusion of crystalloids can potentially alter A_{TOT} and SID, two independent variables of extracellular fluid that regulate its pH. As a result, and depending on the composition of the chosen fluid, pH can be lowered, increased or left unchanged by dilution. Schematically, crystalloids having an *in vivo* SID (Table 2) greater than plasma bicarbonate concentration (HCO_3^-) cause an increase in plasma pH (alkalosis), those having an *in vivo* SID lower than HCO_3^- a decrease in plasma pH (acidosis), while crystalloids with an *in vivo* SID equal to HCO_3^- do not alter plasma pH independently of the degree of plasma dilution [46]. Of note is the fact that balanced crystalloid solutions [47], i.e., solutions whose electrolyte composition is closer to the composition of plasma, thus having a lower chloride concentration, cause fewer plasma acid-base alterations as compared to the “unbalanced” 0.9% NaCl. Finally, given the possible detrimental effects of plasma chloride on renal function [48, 49], they should, theoretically, be less harmful.

Hyperglycaemia

Children are at increased risk for in-hospital/perioperative hypoglycaemia and lipolysis, due to higher metabolic rates and lower glycogen storages potentially associated with prolonged preoperative fasting [50]. Additionally, general anaesthesia in the operating room (or sedation in the intensive care unit) can mask symptoms of hypoglycaemia. For these reasons, it is usual to add a certain amount of glucose to fluids prescribed to children. Usually, 10 to 50 g of glucose is mixed into each litre of crystalloid solution, i.e., 1,000–5,000 mg dL^{-1}. When comparing these concentrations with physiologic plasma glucose levels, and also taking into account stress due to surgery, hospitalization and/or critical illness, it is not surprising that hyperglycaemia frequently develops and that, in this context, it may be considered as a side effect of fluid therapy [50]. Of note is the fact that most studies on fluid-related hyperglycaemia report intraoperative data, while very little is known about the risk of hyperglycaemia due to glucose-containing fluids employed for maintenance.

Fluids for maintenance, replacement, and resuscitation in the paediatric population: current clinical practice

There is a strong consensus regarding the indication of tonicity for fluids employed intraoperatively and for resuscitation/replacement both in the operating theatre and in the paediatric intensive care unit. In these cases *isotonic*, possibly *balanced* fluids, containing little (1%) or no glucose at all, should be administered [27]. It should be noted that despite these clear statements of experts and scientific societies, there is still important heterogeneity in clinical practice, as reported in a survey performed by Way *et al.*, in which about 10% of anaesthesiologists stated that they prescribed a bolus of hypotonic dextrose saline solutions to treat hypovolaemia in the intraoperative period [51].

On the contrary, a great debate is still ongoing on the ideal *tonicity* of parenteral fluids prescribed for *maintenance* therapy [31, 42, 52, 53]. Maintenance fluids are needed *only* for children that cannot drink/receive fluids enterally, in order to provide an amount of water similar to the amount expected to be lost physiologically through *insensible* losses and urinary output. Conceptually, maintenance fluids should hydrate both the extracellular and the intracellular compartments. For this reason, maintenance fluids should, in theory, be *hypotonic*. Indeed, the dilution of plasma with a *hypotonic* fluid reduces plasma osmolarity, thus generating the osmotic driving pressure that allows water movement from the extra- to the intracellular compartment. Furthermore, the reduction in plasma osmolarity should suppress ADH secretion, thus favouring, in physiologic conditions, the excretion of electrolyte-free water through a diluted urine. However, as already mentioned, hospitalization may be characterized by the presence of several *non-osmotic* stimuli to ADH secretion. These stimuli are stronger than the osmotic control for ADH secretion, yielding to high ADH levels and the inability to excrete free water through dilute urine. This fact favours the development of positive water balances and, particularly in the case of hypotonic fluid administration, increases the risk of water intoxication/hyponatremia with consequent neurologic disorders. Importantly, recent data suggest that the incidence of SIADH in very sick children admitted to the paediatric intensive care unit and in children admitted to the general paediatric ward are similar [25].

For the abovementioned reasons, several authors suggest the use of *isotonic* instead *hypotonic* fluids (Table 2) for maintenance therapy in hospitalized children. The fact that the use of *isotonic* fluids, i.e., fluids having a sodium concentration that ranges between 130 and 154 mEq L^{-1}, significantly reduces the risk of hyponatremia as opposed to the administration of *hypotonic fluids* (sodium concentration < 70 mEq L^{-1}) is strongly supported both by simple logic and by several randomized controlled trials on the topic [25, 54]. Interestingly, all trials performed on this topic included as a primary outcome the incidence of hyponatremia, which, as stated above, is a typical side effect only of *hypotonic* fluids. Side effects of *isotonic* fluids, such as fluid and salt overload, expansion of the extracellular fluid compartment, hyperchloremia and metabolic acidosis were seldom evaluated and, in fact, included only as secondary outcomes. Of note is the fact that most randomized controlled trials use 0.9% NaCl as *isotonic* fluid, which is slightly *hypertonic* and has a very high chloride concentration, therefore frequently causing hyperchloremic metabolic acidosis.

Monitoring of fluid therapy

Whenever parenteral fluids are prescribed to a hospitalized child, it is important to review their indication, namely replacement, resuscitation or maintenance. Especially regarding *maintenance* fluids, it is important to double-check the indication, i.e., evaluate the conditions that do not allow the child to drink spontaneously and thus to autoregulate the amount of water she/he ingests. Indeed, while some cases of enteral water intoxication are reported in the literature, either voluntary [55] or as form of child abuse [56], their incidence is infinitesimally lower than water intoxication due to parenteral fluid administration. Therefore, if the child is able/allowed to drink, we should favour the oral route and autoregulation of water intake. If, however, parenteral maintenance fluids are indicated, it is important to monitor the clinical course of the hospitalized child, including neurologic status, serum electrolytes, water balance and changes in body weight. Interestingly, despite the striking evidence of important, potentially lethal side effects of fluid therapy, recent data indicate that serum sodium concentrations are measured only in few hospitalized children before intravenous therapy and are monitored throughout the time-course of parenteral fluid therapy [25]. Of course, given the high prescription rates of parenteral fluids, it is unfeasible to strictly monitor all children.

Therefore, what should we do in everyday clinical practice when facing our next hospitalized/critically ill child needing parenteral fluid therapy? If our patient needs fluids to restore the extracellular compartment, then we should certainly prescribe *isotonic*, and possibly *balanced* solutions.

If the child needs maintenance fluids, and we have the possibility to strictly monitor the patient’s water and electrolyte balance, therefore having the possibility to adjust our treatment based on the clinical course, we should, in our opinion, choose *hypotonic* fluids. If, however, the hospitalized child is admitted to a ward were, due to organizational issues, monitoring and frequent adjustments of the treatment are not feasible, *isotonic* maintenance fluids should be preferred. In this latter case, in fact, we prefer to run the risk of side effects associated to *isotonic* as compared to *hypotonic* fluids, thus limiting the occurrence of water intoxication/hyponatremia and associated neurologic sequelae.

Conclusions

In the present review, we addressed the crucial importance of water and electrolyte homeostasis and the importance of intravenous hydration in hospitalized/critically ill children, underlining the pathophysiological basis of this daily medical practice.

Intravenous fluids for children (and adults) are drugs, with clear indications, contraindications and relevant, potentially lethal, side effects. The type of fluid is important, as is the dose and the duration of fluid therapy while at some point, when fluids are no longer needed, de-escalation must be considered [57]. Whenever an intravenous fluid is prescribed to a hospitalized/critically ill child, one should answer the following questions: Why am I prescribing intravenous fluids? Which body fluid compartment is my target? Where am I starting from (water and electrolyte imbalances)? How am I going to monitor the effects and side effects of my treatment? Which type of fluid should I therefore choose?

We strongly believe that combining the pathophysiological comprehension of water and electrolyte balance, the awareness that oral hydration should be preferred whenever possible, and a rigorous approach concerning parenteral fluid prescription, significantly increases the efficacy and safety of fluid therapy for hospitalized and critically ill children.

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International Medical Education and Research Initiative, under Belgian law. The IFA website (http://www.fluidacademy.org) is now an official SMACC affiliated site (Social Media and Critical Care) and its content is based on the philosophy of FOAM (Free Open Access Medical education — #FOAMed). The site recently received the HONcode quality label for medical education (https://www.healthonnet.org/HONcode/Conduct.html?HONConduct519739).

References:

1. Friis-Hansen B. Body water compartments in children: changes during growth and related changes in body composition. Pediatrics. 1961; 28: 169–181, indexed in Pubmed: 13702099.
2. Friis-Hansen BJ, Holiday M, Stapleton T, et al. Total body water in children. Pediatrics. 1951; 7(3): 321–327, indexed in Pubmed: 14827634.
3. Darrow DC, Pratt EL, Darrow DC, et al. Fluid therapy; relation to tissue composition and the expenditure of water and electrolyte. J Am Med Assoc. 1950; 143(4): 432–439, indexed in Pubmed: 15415272.
4. HEELEY AM, TALBOT NB. Insensible water losses per day by hospitalized infants and children. AMA Am J Dis Child. 1955; 90(3): 251–255, indexed in Pubmed: 13248225.
5. O'Brien F, Walker IA. Fluid homeostasis in the neonate. Paediatr Anaesth. 2014; 24(1): 49–59, doi: 10.1111/pan.12326, indexed in Pubmed: 24299660.
6. Mårild S, Jodal U, Jonasson G, et al. Reference values for renal concentrating capacity in children by the desmopressin test. Pediatr Nephrol. 1992; 6(3): 254–257, indexed in Pubmed: 1616834.
7. Bellini C, Boccardo F, Bonioli E, et al. Lymphodynamics in the fetus and newborn. Lymphology. 2006; 39(3): 110–117, indexed in Pubmed: 17036631.
8. Kellum JA, Elbers PW. Stewart's textbook of acid-base. Lulu Press, Inc 2013.
9. Fogh-Andersen N, Altura BM, Altura BT, et al. Composition of interstitial fluid. Clin Chem. 1995; 41(10): 1522–1525, indexed in Pubmed: 7586528.
10. Siesjö BK. Symposium on acid-base homeostasis. The regulation of cerebrospinal fluid pH. Kidney Int. 1972; 1(5): 360–374, indexed in Pubmed: 4599953.
11. Langer T, Zanella A, Caironi P. Understanding the role of the cerebrospinal fluid in acid-base disorders. Intensive Care Med. 2016; 42(3): 436–439, doi: 10.1007/s00134-015-4059-8, indexed in Pubmed: 26399889.
12. Goel M, Picciani RG, Lee RK, et al. Aqueous humor dynamics: a review. Open Ophthalmol J. 2010; 4: 52–59, doi: 10.2174/1874364101004010052, indexed in Pubmed: 21293732.
13. Giebish G, Berger L, Pitts RF. The extrarenal response to acute acid-base disturbances of respiratory origin. J Clin Invest. 1955; 34(2): 231–245, doi: 10.1172/JCI103076, indexed in Pubmed: 13233345.
14. Langer T, Scotti E, Carlesso E, et al. Electrolyte shifts across the artificial lung in patients on extracorporeal membrane oxygenation: interdependence between partial pressure of carbon dioxide and strong ion difference. J Crit Care. 2015; 30(1): 2–6, doi: 10.1016/j.jcrc.2014.09.013, indexed in Pubmed: 25307980.
15. Alphonsus CS, Rodseth RN. The endothelial glycocalyx: a review of the vascular barrier. Anaesthesia. 2014; 69(7): 777–784, doi: 10.1111/anae.12661, indexed in Pubmed: 24773303.

16. Woodcock TE, Woodcock TM. Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. Br J Anaesth. 2012; 108(3): 384–394, doi: 10.1093/bja/aer515, indexed in Pubmed: 22290457.
17. Pries AR, Secomb TW, Gaehtgens P. The endothelial surface layer. Pflugers Arch. 2000; 440: 653–666.
18. Becker BF, Jacob M, Leipert S, et al. Degradation of the endothelial glycocalyx in clinical settings: searching for the sheddases. Br J Clin Pharmacol. 2015; 80(3): 389–402, doi: 10.1111/bcp.12629, indexed in Pubmed: 25778676.
19. Pierce A, Pittet JF. Inflammatory response to trauma: implications for coagulation and resuscitation. Curr Opin Anaesthesiol. 2014; 27(2): 246–252, doi: 10.1097/ACO.0000000000000047, indexed in Pubmed: 24419158.
20. Love AH, Mitchell TG, Phillips RA. Water and sodium absorption in the human intestine. J Physiol. 1968; 195(1): 133–140, indexed in Pubmed: 5639796.
21. Andersson B, Leksell LG, Rundgren M. Regulation of water intake. Annu Rev Nutr. 1982; 2: 73–89, doi: 10.1146/annurev.nu.02.070182.000445, indexed in Pubmed: 6764737.
22. Rose B. Clinical physiology of acid-base and electrolyte disorders. McGraw-Hill Education/Medical 2017.
23. Verbalis JG. Disorders of body water homeostasis. Best Pract Res Clin Endocrinol Metab. 2003; 17(4): 471–503, indexed in Pubmed: 14687585.
24. Burrows FA, Shutack JG, Crone RK. Inappropriate secretion of antidiuretic hormone in a postsurgical pediatric population. Crit Care Med. 1983; 11(7): 527–531, indexed in Pubmed: 6861500.
25. Choong K, Arora S, Cheng Ji, et al. Hypotonic versus isotonic maintenance fluids after surgery for children: a randomized controlled trial. Pediatrics. 2011; 128(5): 857–866, doi: 10.1542/peds.2011-0415, indexed in Pubmed: 22007013.
26. Chappell D, Bruegger D, Potzel J, et al. Hypervolemia increases release of atrial natriuretic peptide and shedding of the endothelial glycocalyx. Crit Care. 2014; 18(5): 538, doi: 10.1186/s13054-014-0538-5, indexed in Pubmed: 25497357.
27. Sümpelmann R, Becke K, Crean P, et al. German Scientific Working Group for Paediatric Anaesthesia. European consensus statement for intraoperative fluid therapy in children. Eur J Anaesthesiol. 2011; 28(9): 637–639, doi: 10.1097/EJA.0b013e3283446bb8, indexed in Pubmed: 21654319.
28. Van Regenmortel N, Jorens PG, Malbrain ML. Fluid management before, during and after elective surgery. Curr Opin Crit Care. 2014; 20(4): 390–395, doi: 10.1097/MCC.0000000000000113, indexed in Pubmed: 24979553.
29. Chesney CR. The maintenance need for water in parenteral fluid therapy, by Malcolm A. Holliday, MD, and William E. Segar, MD, Pediatrics, 1957;19:823-832. Pediatrics. 1998; 102(1 Pt 2): 229–230, indexed in Pubmed: 9651436.
30. HOLLIDAY MA, SEGAR WE. The maintenance need for water in parenteral fluid therapy. Pediatrics. 1957; 19(5): 823–832, indexed in Pubmed: 13431307.
31. Duke T, Molyneux EM. Intravenous fluids for seriously ill children: time to reconsider. Lancet. 2003; 362(9392): 1320–1323, doi: 10.1016/S0140-6736(03)14577-1, indexed in Pubmed: 14575980.
32. Bailey D, Phan V, Litalien C, et al. Risk factors of acute renal failure in critically ill children: A prospective descriptive epidemiological study. Pediatr Crit Care Med. 2007; 8(1): 29–35, doi: 10.1097/01.pcc.0000256612.40265.67, indexed in Pubmed: 17251879.

33. Marik PE. Iatrogenic salt water drowning and the hazards of a high central venous pressure. Ann Intensive Care. 2014; 4: 21, doi: 10.1186/s13613-014-0021-0, indexed in Pubmed: 25110606.
34. Van Regenmortel N, De Weerdt T, Van Craenenbroeck AH, et al. Effect of isotonic versus hypotonic maintenance fluid therapy on urine output, fluid balance, and electrolyte homeostasis: a crossover study in fasting adult volunteers. Br J Anaesth. 2017; 118(6): 892–900, doi: 10.1093/bja/aex118, indexed in Pubmed: 28520883.
35. Lichtenstein AH, Appel LJ, Brands M, et al. American Heart Association Nutrition Committee. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. Circulation. 2006; 114(1): 82–96, doi: 10.1161/CIRCULATIONAHA.106.176158, indexed in Pubmed: 16785338.
36. Lobo DN, Stanga Z, Simpson JA, et al. Dilution and redistribution effects of rapid 2-litre infusions of 0.9% (w/v) saline and 5% (w/v) dextrose on haematological parameters and serum biochemistry in normal subjects: a double-blind crossover study. Clin Sci (Lond). 2001; 101(2): 173–179, indexed in Pubmed: 11473492.
37. Tommasino C. Fluids and the neurosurgical patient. Anesthesiol Clin North America. 2002; 20(2): 329–346, indexed in Pubmed: 12165997.
38. Tommasino C, Picozzi V. Volume and electrolyte management. Best Pract Res Clin Anaesthesiol. 2007; 21(4): 497–516, indexed in Pubmed: 18286834.
39. Arieff AI, Ayus JC, Fraser CL. Hyponatraemia and death or permanent brain damage in healthy children. BMJ. 1992; 304(6836): 1218–1222, indexed in Pubmed: 1515791.
40. Arieff AI, Llach F, Massry SG. Neurological manifestations and morbidity of hyponatremia: correlation with brain water and electrolytes. Medicine (Baltimore). 1976; 55(2): 121–129, indexed in Pubmed: 1256311.
41. Grissinger M. Hyponatremia and death in Healthy children From plain dextrose and Hypotonic Saline Solutions after Surgery. P T. 2013; 38(7): 364–388, indexed in Pubmed: 24049421.
42. Moritz ML, Ayus JC. Prevention of hospital-acquired hyponatremia: a case for using isotonic saline. Pediatrics. 2003; 111(2): 227–230, indexed in Pubmed: 12563043.
43. Hoorn EJ, Geary D, Robb M, et al. Acute hyponatremia related to intravenous fluid administration in hospitalized children: an observational study. Pediatrics. 2004; 113(5): 1279–1284, indexed in Pubmed: 15121942.
44. Stewart PA. Modern quantitative acid-base chemistry. Can J Physiol Pharmacol. 1983; 61(12): 1444–1461, indexed in Pubmed: 6423247.
45. Langer T, Ferrari M, Zazzeron L, et al. Effects of intravenous solutions on acid-base equilibrium: from crystalloids to colloids and blood components. Anaesthesiol Intensive Ther. 2014; 46(5): 350–360, doi: 10.5603/AIT.2014.0059, indexed in Pubmed: 25432555.
46. Langer T, Carlesso E, Protti A, et al. In vivo conditioning of acid-base equilibrium by crystalloid solutions: an experimental study on pigs. Intensive Care Med. 2012; 38(4): 686–693, doi: 10.1007/s00134-011-2455-2, indexed in Pubmed: 22273748.
47. Langer T, Santini A, Scotti E, et al. Intravenous balanced solutions: from physiology to clinical evidence. Anaesthesiol Intensive Ther. 2015; 47 Spec No: s78–s88, doi: 10.5603/AIT.a2015.0079, indexed in Pubmed: 26588483.
48. Wilcox CS. Regulation of renal blood flow by plasma chloride. J Clin Invest. 1983; 71(3): 726–735, indexed in Pubmed: 6826732.

49. Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA. 2012; 308(15): 1566–1572, doi: 10.1001/jama.2012.13356, indexed in Pubmed: 23073953.
50. Nishina K, Mikawa K, Maekawa N, et al. Effects of exogenous intravenous glucose on plasma glucose and lipid homeostasis in anesthetized infants. Anesthesiology. 1995; 83(2): 258–263, indexed in Pubmed: 7631946.
51. Way C, Dhamrait R, Wade A, et al. Perioperative fluid therapy in children: a survey of current prescribing practice. Br J Anaesth. 2006; 97(3): 371–379, doi: 10.1093/bja/ael185, indexed in Pubmed: 16873386.
52. Holliday MA. Isotonic saline expands extracellular fluid and is inappropriate for maintenance therapy. Pediatrics. 2005; 115(1): 193–4; author reply 194, doi: 10.1542/peds.2004-1769, indexed in Pubmed: 15630005.
53. Mattheij M, Van Regenmortel N. Maintenance Fluids for Children: Hypotonic Fluids Are Still the Best Choice. Pediatr Emerg Care. 2016; 32(2): e4, doi: 10.1097/PEC.0000000000000711, indexed in Pubmed: 26835578.
54. McNab S, Duke T, South M, et al. 140 mmol/L of sodium versus 77 mmol/L of sodium in maintenance intravenous fluid therapy for children in hospital (PIMS): a randomised controlled double-blind trial. Lancet. 2015; 385(9974): 1190–1197, doi: 10.1016/S0140-6736(14)61459-8, indexed in Pubmed: 25472864.
55. Dugan S, Holliday MA. Water intoxication in two infants following the voluntary ingestion of excessive fluids. Pediatrics. 1967; 39(3): 418–420, indexed in Pubmed: 6018972.
56. Arieff AI, Kronlund BA. Fatal child abuse by forced water intoxication. Pediatrics. 1999; 103(6 Pt 1): 1292–1295, indexed in Pubmed: 10353946.
57. Malbrain MLNG, Van Regenmortel N, Owczuk R. It is time to consider the four D's of fluid management. Anaesthesiol Intensive Ther. 2015; 47 Spec No: s1–s5, doi: 10.5603/AIT.a2015.0070, indexed in Pubmed: 26575163.

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