Maintenance fluid therapy in sick children: state of art

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Abstract

Intravenous fluids are frequently used in pediatrics, but they have been associated with significant adverse effects. Understanding the composition of fluids prescribed and administering them at the appropriate infusion rate is essential for a safe prescription. The use of isotonic fluids can reduce the risk of hyponatremia, reducing infant morbidity and mortality as well. However, recent literature shows a higher incidence of acid-base balance disorders and a risk of acute renal injury with isotonic solutions, proposing the use of balanced fluids to minimize these damages. This narrative review aims to verify current recommendations about assessment and management of intravenous fluids in acutely ill child, as well as the recognition of maintenance therapy adverse effects. It was concluded that the intravenous fluids prescription is like the medicines prescription, and their risks must be considered and monitored continuously.

Keywords:
Child Care, Fluid Therapy, adverse effects. Infusions, Intravenous.
INTRODUCTION

Fluid therapy is one of the most relevant matters in the care provided to hospitalized children, with proper fluid administration and patient assessment standing as key elements of achieving successful outcomes. Nevertheless, one in five children develops complications caused by poor intravenous fluid therapy management.  

The recognition of hospital-acquired hyponatremia as an important factor in morbimortality has stirred interest in fluid tonicity and volume in the realm of pediatrics. The Holliday-Segar method, which factors in the use of hypotonic saline solution in volumes based on the energy requirements of healthy hydrated children, does not consider the requirements of sick children or the potential ADH-mediated free water retention derived from diseased states.  

This study aimed to look into current intravenous fluid administration recommendations, recognize the most common adverse effects arising from maintenance therapy, and discuss the rationale underlying the choice of different fluids.

METHOD

This non-systematic review looked into pediatric applications of fluid therapy based on searches carried out on databases PubMed, Cochrane Library, Lilacs, Portal de Periódicos da CAPES/MEC, and SciELO. Additional papers were included from the references cited in the papers found in the searched databases.  

The review included studies published from January 2007 to December 2017 cited in the aforementioned search engines and classical studies for their scientific relevance and historical perspective on the subject. No language restriction was applied in the search for papers. The selected publications included meta-analyses, systematic reviews, non-systematic reviews, and clinical trials covering intravenous fluid therapy for pediatric patients.  

A total of 146 publications were found based on the criteria for age and year of publication; 116 were not relevant to the subject matter; and 30 were eventually included in this non-systematic review.

THE HISTORY OF FLUID THERAPY

Famed English designer and astronomer Christopher Wren performed the first known intravenous fluid injection in 1656, as he infused wine, beer, and opium into the veins of a dog using a cannula lined with porcine bladder, in a poisoning experiment deemed successful. Six years later it was the turn of Johann D. Major, a German scholar from the University of Padua who injected a non-purified compound into the veins of a healthy hydrated child. The poor outcome discouraged other similar attempts for many years.  

In 1827, a cholera epidemic disseminated through India, Russia, England, and the United States and took thousands of lives. Initially thought to be a disturbance of blood treated with bleeding, it was only in 1831, after the studies conducted by William Brook O’Shaughnessy, that dehydration was recognized as a factor tied to death. Three years later, Russian physicians Herman and Jaehnichen were so desperate to find a cure for the disease that they injected some 200 mL of water into the veins of a patient, who was dead two hours after the procedure.  

Intravenous administration of a saline solution was described for the first time in 1832 by British medical pioneer Thomas Latta, an assistant to O’Shaughnessy. He infused an alkaline saline solution into an old woman with severe cholera, who died within 30 minutes of the injection. In 1833, he performed the first successful saline solution infusion on a 52-year-old woman who survived the 12-hour long administration of 330 mL of a solution. A year later, Scottish physician John Mackintosh, one of Latta’s disciples, advised in favor of making the fluid similar to blood by adding egg albumin to the solution.  

Some 40 years later, British physiologist and pharmacologist Sidney Ringer found that animal hearts worked longer when they were instilled with mineral rather than distilled water. He then created Ringer’s solution, which contained small quantities of calcium and potassium in a solution with sodium and chloride. Years later, pediatrician Alexis Hartmann modified the solution by adding sodium lactate into what has since been known as Ringer’s lactate solution.  

In 1882, Dutch physiologist Hartog Jacob Hamburger developed the 0.9% saline solution for in vitro use in experiments on hemolysis. He later presumed that the solution might be used safely to infuse medication and blood products.  

Since then, restoring circulation through extracellular fluid volume expansion has become the main target of fluid therapy. Blackfan and Macx were the first to use it in children in 1918. They infused nine patients suffering from dehydration with 0.8% saline solution via the intraperitoneal route, and all recovered. In 1920, Marriott specifically described how extracellular fluid replacement improved circulation and perfusion.  

There is little doubt over the fact that the best year for pediatric was 1957, when Holliday and Segar established the fundamentals of prescription of fluids to children still in use today. They estimated that the energy requirement of hospitalized children was situated between the basal metabolic rate and the energy expenditure derived from activities of daily living. Holliday and Segar developed an easy-to-use formula based on one’s body weight - 100 cal/kg/day (patients weighing up to 10 kg); 1000 cal + 50 cal/kg/day per kilogram of weight above 10 kg (children weighing 10-20 kg); and 1500 cal + 20 cal/kg/day per kilogram of weight above 20 kg (patients weighing 20+ kg) - and estimated average physiological losses of water via a correlation with energy expenditure. The authors postulated that for each spent calorie there was a loss of one milliliter of insensible water and urinary water, which allowed one to estimate energy expenditure vis-à-vis fluid loss and thus calculate a patient’s daily fluid requirements.
The estimation of electrolytes proposed by Holliday and Segar was not particularly sophisticated, and was based on the mean content of electrolytes in human and cow’s milk, which led to the recommendation of adding 3 mEq of sodium for every 100 calories spent. These recommendations were developed 50 years ago and had been in use until recently.

**FLUID TYPES**

Different fluids have different properties in terms of volume expansion, duration of effect, impact on vascular integrity, acid-base balance, inflammatory response, and changes in homeostasis. The two main types of volume expanders are crystalloids and colloids.

Crystalloids (Table 1) contain water, ions freely permeable through the capillary membrane (primarily sodium and chloride), and organic molecules. They may also contain other ions - potassium, calcium, or magnesium - and buffers - bicarbonate, lactate, acetate, or gluconate - to maintain electrical neutrality. Crystalloids are the first choice among solutions for maintenance therapy and the most widely used saline solution in the world.

Colloids (Table 2) are suspensions containing high molecular weight proteins in a dispersion medium. The molecules are in suspension in a solvent, which in most cases is a crystalloid. Isotonic saline solution is the most commonly used solvent in colloidal solutions. They tend to persist for longer and produce more efficient expansion of the intravascular volume than crystalloids on account of oncotic pressure. Since they cannot cross the vascular membrane, colloids can be administered in lower volumes than crystalloids - a 1:3 ratio - to yet meet the same hemodynamic goals.

Human albumin in saline solution is the natural colloid of reference. Semi-synthetic colloids have been linked to increased risk of acute disease, kidney injury, and death compared with crystalloids, and thus are not generally recommended.

Crystalloids and colloids may be hypo-, iso-, or hypertonic depending on osmolarity relative to human plasma.

**PEDIATRIC FLUID AND ELECTROLYTE THERAPY**

In addition to selecting the best fluid type, recognizing infusion volumes and indications is a requirement in successful pediatric care.

Although many factors interfere with water-electrolyte balance, a systematic and well organized approach helps to meet each patient’s specific ongoing needs. Patients require specific prescriptions based on their needs, ranging from fluid therapy to correct existing water/electrolyte deficits, maintenance fluid therapy, fluid replacement therapy, to fluid resuscitation.

**Water/electrolyte deficit correction**

Water/electrolyte deficit correction revolves around managing fluid and electrolyte losses occurred before hospitalization. Children present with water/electrolyte deficit when, among other things, they suffer from gastroenteritis, vomiting, diarrhea, blood loss due to trauma, or have inadequate fluid intake levels. Patients in this situation are first assessed for dehydration and then treated to have the water/electrolyte deficit corrected.

Table 3 describes the clinical signs of dehydration. Despite the relevance of weight loss, factors such as thirst, dry mucosae, and decreased urine output have been more significantly correlated with dehydration. Clinical examination is followed by an assessment of the patient’s degree of dehydration (Table 4).

### Table 1. Main crystalloid solutions and their compositions (adapted from Correa, 2015).

<table>
<thead>
<tr>
<th>Properties</th>
<th>Human plasma</th>
<th>0.9% saline solution</th>
<th>Hartmann solution</th>
<th>Ringer’s lactate solution</th>
<th>Plasma Lyte</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.35 – 7.45</td>
<td>5.5</td>
<td>6.5</td>
<td>6.5</td>
<td>7.4</td>
</tr>
<tr>
<td>Osmolality (mOsm/L)</td>
<td>291</td>
<td>308</td>
<td>279</td>
<td>273</td>
<td>294</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>135 - 145</td>
<td>154</td>
<td>131</td>
<td>130</td>
<td>140</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.5 – 5.5</td>
<td>-</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Calcium (mmol/L)</td>
<td>2.2 – 2.6</td>
<td>-</td>
<td>2</td>
<td>1.5</td>
<td>-</td>
</tr>
<tr>
<td>Magnesium (mmol/L)</td>
<td>0.8 – 1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.5</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>94 - 111</td>
<td>154</td>
<td>111</td>
<td>109</td>
<td>98</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>23 - 27</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>1.0 – 2.0</td>
<td>-</td>
<td>29</td>
<td>28</td>
<td>-</td>
</tr>
<tr>
<td>Acetate (mmol/L)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>27</td>
</tr>
<tr>
<td>Gluconate (mmol/L)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>23</td>
</tr>
</tbody>
</table>
Table 2. Main colloid solutions and their compositions (adapted from Correa, 2015).

<table>
<thead>
<tr>
<th>Properties</th>
<th>5% albumin</th>
<th>25% albumin</th>
<th>Hydroxyethyl starch</th>
<th>Dextran</th>
<th>Gelatins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>69</td>
<td>-</td>
<td>100 - 450</td>
<td>40 - 70</td>
<td>30 - 35</td>
</tr>
<tr>
<td>Osmolality (m0sml/L)</td>
<td>300</td>
<td>1500</td>
<td>300 - 326</td>
<td>280 - 324</td>
<td>300 - 350</td>
</tr>
<tr>
<td>Oncotic pressure (mmHg/L)</td>
<td>19 - 30</td>
<td>74 - 120</td>
<td>23 - 82</td>
<td>20 - 60</td>
<td>25 - 42</td>
</tr>
<tr>
<td>Plasma duration expansion (h)</td>
<td>70 - 100</td>
<td>200 - 300</td>
<td>100 - 160</td>
<td>100 - 200</td>
<td>70 - 100</td>
</tr>
<tr>
<td>Plasma duration expansion (h)</td>
<td>&lt; 24</td>
<td>&lt; 24</td>
<td>&lt; 12</td>
<td>&lt; 8</td>
<td>2 - 9</td>
</tr>
<tr>
<td>Plasma half life (h)</td>
<td>16 - 24</td>
<td>16 - 24</td>
<td>2 - 12</td>
<td>2</td>
<td>2 - 9</td>
</tr>
</tbody>
</table>

Table 3. Clinical signs of dehydration (adapted from Meyers, 2009).

<table>
<thead>
<tr>
<th></th>
<th>Mild dehydration</th>
<th>Moderate dehydration</th>
<th>Severe dehydration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss (%)</td>
<td>3 - 5</td>
<td>6 - 9</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Level of consciousness</td>
<td>Normal</td>
<td>Normal to confused</td>
<td>Normal to lethargic</td>
</tr>
<tr>
<td>Mucosae</td>
<td>May be normal</td>
<td>Dry</td>
<td>Dry</td>
</tr>
<tr>
<td>Anterior fontanelle</td>
<td>Normal</td>
<td>Depressed</td>
<td>Depressed</td>
</tr>
<tr>
<td>Eyes</td>
<td>Normal</td>
<td>Sunken</td>
<td>Severely sunken</td>
</tr>
<tr>
<td>Skin turgor</td>
<td>Normal</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal to decreased</td>
</tr>
<tr>
<td>Heart beat rate</td>
<td>Normal</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Urine output</td>
<td>Decreased</td>
<td>Considerably decreased</td>
<td>Anuria</td>
</tr>
</tbody>
</table>

Table 4. Degrees of dehydration in approximated percentage of body weight (adapted from Meyers, 2009).

<table>
<thead>
<tr>
<th></th>
<th>Mild dehydration</th>
<th>Moderate dehydration</th>
<th>Severe dehydration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>3%</td>
<td>6%</td>
<td>9%</td>
</tr>
<tr>
<td>Infants</td>
<td>5%</td>
<td>10%</td>
<td>15%</td>
</tr>
</tbody>
</table>

The next step is to determine the type of dehydration affecting the patient, a verification confirmed via serum sodium testing. The majority of dehydrated patients have isotonic dehydration. Dehydration accompanied by serum sodium levels of less than 135 mmol/L is deemed hypotonic, whereas serum sodium levels greater than 145 mmol/L are the telltale sign of hypertonic dehydration, a situation that requires additional attention for the potential ensuing complications, which include cerebral edema.1,15

Patients with mild/moderate dehydration may be rehydrated with oral fluids, even if they are vomiting or have diarrhea. Oral rehydration solutions generally contain adequate amounts of carbohydrates and electrolytes.15

Intravenous rehydration is reserved for patients with severe dehydration. Firstly, blood volume is restored with isotonic fluids at a dose of 20 ml/kg, until adequate perfusion has been achieved. Then the total fluid volume required to correct water/electrolyte deficits is calculated based on the degree of dehydration (Table 4). In hypo- or isotonic dehydration, patients are offered a third of the calculated volume within the first eight hours and the remaining two-thirds within the next 16 hours. In hypertonic dehydration, losses may be corrected within up to 48 hours given the risk of cerebral edema and seizures.15

**Maintenance therapy**

Maintenance therapy is used to compensate for continuous fluid losses - sensible losses include fluids lost from urine and diarrhea; insensible losses include fluids lost from the likes of the skin and respiratory tract - and is required for every patient. Maintenance therapy is usually administered intravenously, although oral rehydration may be offered to patients when tolerated.

Patient physiological characteristics play an important role in fluid therapy, and fluid requirements change dramatically as children grow. Children have relatively higher metabolic rates and greater energy expenditures than adults, which combined translate into proportionally higher fluid requirements. They also have relatively much larger body surface areas, a trait that increases fluid loss from the skin, and higher respiratory rates, a factor that increases insensible water losses. The smaller the child, the larger the relative fluid requirement.15

Pediatric patients must be constantly monitored during maintenance therapy. If the calculations are right, electrolyte levels remain stable and the child stays clinically euolemic. Altered electrolyte levels and clinical signs of hypervolemia or hypovolemia call for a reassessment of each element in the planned course of therapy.1
Maintenance fluids are not infused to correct water/electrolyte imbalances. There is a specific therapy for each anomalous clinical condition. There is no off-the-shelf recipe to cater to the needs of all patients. Individual clinical findings must be considered before the prescription of fluid therapy, and adjustments to parenteral fluid must be regularly assessed during administration.16

**Fluid replacement**

Fluid replacement therapy is designed to replenish the water and electrolyte needs of patients with drains, untreated nausea, persistent diarrhea, or other conditions in which there is continuous loss of fluid that cannot be counteracted via maintenance therapy.1,15

In most cases, the constituting elements found in lost fluid are substantially different from the ingredients present in maintenance therapy fluid (Table 5). Therefore, simply increasing fluid volumes might be dangerous. Ideally, administered fluid should be physiologically similar to lost fluid.

**Fluid resuscitation**

Limited oxygen transport combined with tissue hypoperfusion is the primary mechanism leading to organ failure and death in septic shock. Fluid resuscitation aims to reverse or at least minimize the damage.

Fluids infused in systemic venous circulation expand the volume of the intravascular compartments and contribute with venous return, thereby increasing cardiac output and alleviating cell and mitochondrial dysfunction.11,12,13 For each hour that blood pressure and capillary refill go by unrestored, mortality increases twofold.16

Recommendations dictate the administration of a rapid 20ml/kg bolus of 0.9% saline solution over five minutes, followed by an assessment of perfusion or fluid overload based on cardiac rhythm, increased respiratory effort, hypoxemia by pulmonary edema, and hepatomegaly. Up to 60ml/Kg of resuscitation isotonic fluid may be administered within the first hour of shock.16,17

**HYPOTONIC FLUIDS**

A great deal of the millions of children that are hospitalized each year is administered some form of intravenous fluid infusion based on a longstanding tradition of prescribing hypotonic solutions to replenish their water and electrolyte levels.

Due to adaptive renal mechanisms thought to effectively excrete excess free water and maintain sodium balance, hypotonic fluid infusion was amply deemed safe for children.14 However, after concerning reports and observational studies indicated that hypotonic fluids might be correlated with hyponatremic encephalopathy and death, there was a clear push for the organization of reviews and trials.19

In the early 2000s, Moritz and Ayus compiled 15 retrospective studies and reported more than 50 cases of children who died or sustained severe neurological injuries for hospital-acquired hyponatremia.20 In 2006, a systematic review by Choong et al. linked increased potential harm to prescribing hypotonic solutions to children. The authors concluded that hypotonic solutions exacerbated the risk of hyponatremia, while isotonic solutions might have a protective effect. The study did not find volumes or compositions that might be ideal for pediatric use, although isotonic fluids, known for being more physiological, should be chosen in acute disease and during surgery.21

A year later, Yung and Keeley published a double-blind randomized trial in which 50 children with normal electrolyte levels at admission who required maintenance fluid therapy for more than 12 hours were randomized to receive 0.9% or 0.45% saline solution administered at traditional infusion rates or at 60% of the usual infusion rate. In children with normal sodium levels, hypotonic fluid decreased sodium concentrations by 2.3 mmol/L, while isotonic saline solution increased sodium concentrations by 0.8 mmol/L.22

A systematic review published in the same year compared maintenance fluid therapy with intravenous hypotonic and isotonic solutions administered to pediatric inpatients. The review included only observational - and generally inconclusive - studies. The authors warned against the routine use of hypotonic solutions in maintenance fluid therapy, although use was not always tied to hyponatremia.23

In an attempt to clarify these findings, Montañana et al. randomized 122 pediatric inpatients on intensive care prescribed maintenance fluid therapy into treatments based on isotonic or hypotonic solutions. After 24 hours of infusion, the proportion of individuals with hyponatremia in the group given hypotonic fluid was 20.6% vs. 5.1% in the group given isotonic solution.24

A subsequent study randomized 124 children and compared 0.9% and 0.45% saline solution administered at the usual and 50% of the usual infusion rate. The authors found that the prescription of isotonic fluid, and not fluid restriction, lowered the risk of hyponatremia.4

The risk of hyponatremia and severe adverse events linked to hypotonic fluids, particularly in intensive care units, has been explored in recent double-blind randomized trials without controversy between different publications.

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**Table S. Bodily fluids and their compositions (adapted from Snyder, 2017).**

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Sodium (mEq/L)</th>
<th>Potassium (mEq/L)</th>
<th>Chloride (mEq/L)</th>
<th>Bicarbonate (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>70</td>
<td>5 – 15</td>
<td>120</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>140</td>
<td>5</td>
<td>50 – 100</td>
<td>100</td>
</tr>
<tr>
<td>Biliary</td>
<td>130</td>
<td>5</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>Ileostomy</td>
<td>130</td>
<td>15 – 20</td>
<td>120</td>
<td>25 - 30</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>50</td>
<td>35</td>
<td>40</td>
<td>50</td>
</tr>
</tbody>
</table>
There is enough evidence to support the prevention of hyponatremia based on the administration of isotonic fluids. The availability of low-sodium solutions should be limited to intensive care units, specialized wards, or to a limited number of scenarios in which extra free water is needed. If introduced in pediatric care, this change may save lives and significantly decrease morbidity.

**ISOTONIC FLUIDS**

Evidence accumulated in recent decades has challenged the sexagenarian approach to prescribing fluids, making isotonic solutions a mainstay in pediatric care. However, despite significant progress, fluid therapy was still based on the physiology of healthy children and thereby overestimated the daily requirements of individuals with disease, who in addition to slower metabolism and decreased energy expenditure, produce non-osmotic stimuli for ADH release, thus impairing the renal clearance of free water.

Children are usually able to concentrate urine within a range of osmolality that goes from 50 to 700 mOsmol/kg, and none of the commonly prescribed fluids should disturb this adaptive capacity. However, not every child is fully able to do it, either for reasons of renal impairment or acute disease.

Stressful situations cause increases in the secretion of adrenaline, cortisol, and ADH. The latter plays a pivotal role in the management of water balance in the body by increasing renal sodium reabsorption and consequently exacerbating water retention. ADH secretion is usually regulated by hemodynamic and osmotic stimuli, while ADH production increases in situations of hypovolemia and increased plasma osmolality. However, a number of non-osmotic stimuli trigger ADH secretion and practically all inpatients are at risk of having excess ADH and hyponatremia.

In addition to the role of ADH in the genesis of hyponatremia, expansion of the intravascular volume with isotonic solutions triggers secondary desalination, in a process that forms hypertonic urine by the disproportional excretion of sodium and potassium in relation to water. Hyponatremia sets in, since excess electrolyte-free water is not excreted due to the non-osmotic nature of ADH release. Although substantially less common than in patients on hypotonic solutions, hyponatremia is yet seen in 1.7 to 16% of the patients on isotonic fluid therapy.

The pathophysiology of this process has not been fully elucidated. It is probably a multifactorial event related to the volumes of saline solution infusion, combined with excess ADH, and aldosterone suppression.

Prescribing 0.9% saline solution in maintenance fluid therapy increases the daily intake of calcium by two or three times in relation to the traditional regime. In addition to the ability to concentrate urine, our bodies also posses a powerful ally in thirst. If thirst regulation is intact and patients are allowed unlimited access to free water, only in rare occasions will hyponatremia develop. The administration of 0.9% saline solution is safe and produces no relevant adverse effect. Inadequate fluid volumes - not sodium concentration - determines the development of hypernatremia. The proportion of individuals with hypernatremia is not different when patients given hypotonic solutions are compared to subjects offered isotonic fluids.

**ADVERSE EFFECTS OF 0.9% SALINE SOLUTION**

Despite the superiority of isotonic fluids over hypotonic solutions, the most active topic of research in fluid therapy revolves around the potential deleterious effects of saline solution. Saline solutions were not designed for in vivo use. They are not physiological and associations with adverse outcomes have sparked interest in the so-called balanced salt solutions.

The status of isotonic fluid has been attributed to 0.9% saline solution for its osmolality close to that of plasma and the sodium and chloride concentrations of 154 mEq/L. Sodium concentration in saline solution is virtually the same of human plasma, but chloride levels are up to 1.5 times higher than physiological levels (154 mmol/L vs. 95-105 mmol/L). This is why saline solution has been deemed a non-balanced fluid. This trait defines its risk profile and may trigger hyperchloremic metabolic acidosis.

Chloride is the main anion in our bodies and accounts for 70% of all circulating negative ions. It is the most abundant electrolyte in serum second only to sodium, and plays key roles in osmotic pressure maintenance, acid-base balance, muscle activity, and in the movement of water between different compartments. Hyperchloremia causes damages to the endothelial glyocalyx, increases capillary permeability, and leads to pleural, renal, and myocardial effusion, and organ dysfunction.

By their turn, decreases in pH affect a variety of vasoregulatory mechanisms and increases the release of catecholamines, thereby inducing the production of pro- and anti-inflammatory cytokines. Microvasculature, renal function, coagulation, and immune response are compromised in the process.

Acidosis and hyperchloremia have been associated with renal vasoconstriction, hypoperfusion, interstitial edema, and intracapsular hypertension, which lead to decreases in the glomerular filtration rate. Increased chloride concentration in the macula densa also leads to decreased renin production and hyporeninemic hypoaldosteronism, the most common cause of type-4 renal tubular acidosis. Increased chloride supply to macula densa cells also triggers the release of adenosine into the circulatory system, thereby constricting the afferent arterioles and compromising blood flow, the glomerular filtration rate, and renal function.

Hyperchloremia also causes acidosis indirectly, on account of its stoichiometric relationship with bicarbonate.
Changes in serum chloride trigger a redistribution of fluids to restore water and electrolyte levels back to normal values. In order for that to happen, chloride and bicarbonate must move inside and outside erythrocytes and renal tubules to maintain electrical neutrality. Increased serum chloride leads to decreased bicarbonate levels, thereby increasing positive charges in plasma and the risk of acidosis. Although these deleterious events have been primarily linked to rapid infusion or the infusion of large volumes, hyperchloremia contributes to renal dysfunction, acute kidney injury, and death regardless of the total volume of fluid infused. Hyperchloremic metabolic acidosis by fluid therapy is a frequent and rarely recognized adverse event often treated ineffectively.

There are not enough cases to state that 0.9% saline solution is unsafe in maintenance fluid therapy. Despite the inconsistent results published to date on the matter, studies are yet to describe the benefits of using chloride-rich solutions relative to balanced solutions.

**BALANCED SOLUTIONS**

Balanced crystalloid solutions were developed as an alternative to saline solutions. The best-known solutions in this group are Ringer’s lactate solution and Plasma-Lyte.

The first has an osmolality of 310 mOsm/L and has 130 mMol/L of sodium combined with approximately 110 mMol/L of chloride. It is produced by adding sodium lactate to Ringer’s solution. The latter has an osmolality of 294 mOsm/L and sodium and chloride concentrations of 140 mMol/L and 98 mMol/L, respectively. Other present electrolytes and buffers include potassium, magnesium, acetate, and gluconate. On account of their constitution, these fluids attenuate a great deal of the adverse events connected to the use of non-balanced fluids.

When compared with non-balanced solutions, Plasma-Lyte infusion improves blood flow and oxygen consumption in the kidneys of patients diagnosed with shock. It also decreases the risk of hyperchloremia and the incidence and severity of acute kidney injury. Volume resuscitation with fluids showing lower chloride concentrations may also mitigate the incidence of fluid and electrolyte imbalance. In addition to their role in acid-base balance, electrolyte levels and the constituting elements in these fluids may modulate cytokine production and leukocyte recruitment. Balanced solutions have anti-inflammatory properties compared with saline solutions, as they decrease the recruitment of granulocytes in microcirculation.

Infusion with Ringer’s lactate solution may increase lactate serum levels in more severely compromised patients. Plasma-Lyte should be avoided in patients with a history of renal failure, since it increases the risk of hyperkalemia.

Despite the attention devoted to balanced solutions and the expectations surrounding possible future uses, the literature lacks reports in which balanced solutions decreased the need for renal replacement therapy or shortened hospital stays. In addition, the level of the evidence supporting the use of balanced solutions in clinical practice is weak. Trials with sufficient scientific rigor enrolling pediatric populations are still missing, and most of the studies on the matter focus on volume resuscitation instead of maintenance fluid therapy.

**CONCLUSION**

The sexagenarian approach to fluid prescription has been challenged in recent decades, triggering significant changes in fluid therapy recommendations. Data scarcity results in ample variation in clinical practice. Defining the ideal composition and rate of infusion of intravenous fluids has gained additional complexity and requires decisions based on careful assessment of the individual needs of pediatric patients.

Isotonic solutions with sodium concentrations similar to plasma are recommended for most pediatric patients. There is no shortage of routine-use fluids to choose from, but balanced isotonic solutions with lower chloride levels seem to be the more adequate choice. Infusion rates lower than the ones described by Holliday and Segar must be considered for non-dehydrated children and individuals at risk of presenting altered ADH secretion.

The prescription of intravenous fluids is a medical procedure with risks and adverse events if performed injudiciously. Continuous monitoring during fluid therapy and adjustments to the prescriptions made to healthy individuals are required for safe and effective pediatric fluid therapy.

**REFERENCES**

27. Coulthard MG. Will changing maintenance intravenous fluid from 0.45% to 0.45% saline do more harm than good? Arch Dis Child. 2008;93(4):335-40.