Fluid therapy for children: Facts, fashions and questions

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FLUID THERAPY FOR CHILDREN:
FACTS, FASHIONS AND QUESTIONS
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Restoring circulation by expanding extracellular fluid has been the priority of fluid therapy from its beginning. The first example was treating children with diarrheal dehydration. Blackfan and Maxcy\(^1\) in 1918 gave 0.8% saline by intraperitoneal injection to nine infants with dehydration; all recovered. Later Karelitz and Schick\(^2\) using continuous intravenous infusions of isotonic saline to restore extracellular fluid, reported a hospital mortality ~20%. Marriott\(^3\) in 1920 described specifically how extracellular fluid restoration improved circulation and perfusion.

Gamble\(^4\) brought the concept of extracellular fluid as the “internal environment for sustaining cell life” to clinical medicine and pediatrics in a landmark article in 1923. He measured urinary losses of electrolyte and nitrogen in children who were fasted (to induce ketosis for seizure control). From these and changes in plasma (extracellular fluid) composition he described the role of the kidney in maintaining stability of extracellular fluid in response to this stress\(^5\). A summary of his later studies\(^6\) extended this work. This syllabus was used by a generation of medical students to learn extracellular fluid and renal physiology and treatment of its disorders. The major therapeutic lesson was to adequately expand extracellular fluid.

Darrow\(^4\), in the late 1940s, changed this treatment approach by calling attention to the importance of potassium loss\(^7\), which projected to him, a loss of intracellular fluid. He estimated individual deficits of sodium, chloride, potassium and both extracellular and intracellular fluid per kg of body weight. His regimen called for first giving 20 ml/kg of isotonic saline intravenously to restore circulation, followed \textit{deficit therapy}\(^8\) to replace the deficits over a few days using IV, subcutaneous and oral fluid therapy. He also projected insensible and urinary, or \textit{physiological}, losses of water and electrolyte from fasting studies. To take into account growth, these physiological losses were scaled to metabolic rate (100 kcal/da) not body weight\(^9\). Skin insensible water losses, which accounted for a \textit{consistent} 25% \textit{heat loss}, were derived from measurements in adults\(^10\) and children.\(^11\) The insensible losses also agree with measured insensible losses reported by Heely and Talbot\(^12\). Urinary losses were derived from Gamble’s studies of fasting adults\(^13\) and children\(^5\). Replacing these was \textit{maintenance} therapy. His regimen, using Darrow’s solution (\textbf{Table 1}), was designed to replace the deficits of body composition, not just extracellular fluid and to meet physiologic losses. On the first day fluid was given subcutaneously; later, when tolerated it was diluted with 5% dextrose and given orally. The regimen was difficult for practicing physicians to use. It usually took two or more days before deficits were replaced, often more before milk feedings were deemed safe. His concept of intracellular dehydration has not been supported. Cheek\(^14\) showed that weight gain in early recovery from diarrheal dehydration corresponded with gain in extracellular fluid volume. In experimental studies in rats intracellular water was minimally affected with cell potassium loss\(^15\), but was dramatically reduced in hypernatremia\(^16\).
Table 1. Constituent Formulation of Intravenous and Oral Solutions

<table>
<thead>
<tr>
<th>Solution</th>
<th>Osmolality, mOsm/L</th>
<th>Glucose, mmol/L</th>
<th>Na, mEq/L</th>
<th>Cl, mEq/L</th>
<th>HCO3, mEq/L</th>
<th>K, mEq/L</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ringer’s</td>
<td>280</td>
<td>---</td>
<td>130</td>
<td>110</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>0.9% saline</td>
<td>308</td>
<td>---</td>
<td>154</td>
<td>154</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>D5 0.45% saline</td>
<td>454</td>
<td>300</td>
<td>77</td>
<td>77</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>D5 0.22% saline</td>
<td>377</td>
<td>300</td>
<td>38</td>
<td>38</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Darrow</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butler</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral solution</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO-ORS</td>
<td>330</td>
<td>110</td>
<td>90</td>
<td>80</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Low-Na ORS</td>
<td>270</td>
<td>110</td>
<td>60</td>
<td>50</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>Pedialyte</td>
<td>270</td>
<td>140</td>
<td>45</td>
<td>35</td>
<td>30</td>
<td>20</td>
</tr>
</tbody>
</table>

WHO – World Health Organization
ORS – oral rehydration solution

Butler and his colleagues simplified Darrow’s protocol by estimating the need to replace losses and to provide maintenance therapy by defining safe upper and lower homeostatic limits to intake of water and electrolytes. Butler’s solutions (Table 1) would both correct deficits and meet maintenance requirements by infusions scaled to surface area.

Both the Darrow and Butler models were instructive. Losses from diarrheal dehydration, including potassium, and minimal maintenance requirements were defined. However the presence of higher potassium concentrations in the IV solutions (Table 1) slowed the rate of infusion of sodium and chloride; consequently the time needed to restore extracellular fluid was prolonged. No commercial company was ready to market solutions with potassium in concentrations more than those in Ringer’s lactate solution.

Holliday and Segar in 1957 made estimating metabolic rate simpler by calculating the changing relation of average daily metabolic rate to body weight using simple empiric equations. The average physiologic-insensible plus urinary-losses conveniently came to 100 ml/100 kcals/da. Fluid therapy planning could be done by practicing physicians at the bedside. The basis for relating insensible loss to metabolic rate was the same as that used by Darrow. The need to make exceptions, for example, when urine output was projected to be less, was noted. The article concluded “—it should be emphasized that these figures provide only maintenance needs for water. It is beyond the scope of this paper to consider repair of deficits or replacement of continuing abnormal losses. These must be considered separately.” In 1972 half average maintenance was recommended if urine output might be limited by nonosmotic stimulated antidiuretic hormone activity (Table 2). The goal was to give just enough

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a Infant: 3-10 kg, 100 kcals/kg
Preschool: 10-20 kgs, 1000 + 100 kcals for each 2 kg > 10.
Older: 20-70 kgs, 1500 +100 kcals for each 5 kg > 20.
free water, but not excess. Segar and Moore in 1968 and Friedman and Segar in 1979 demonstrated the sensitivity of antidiuretic hormone to nonosmotic stimuli—posture, environmental temperature, other clinical factors and its rapid reversal.

Table 2. Calculation of maintenance fluid needs as described by Holliday from Maxwell and Kleeman

<table>
<thead>
<tr>
<th>Summary of water exchange under various conditions (in milliliters/100 kcal)</th>
<th>Average normal renal responses</th>
<th>Maximal concentration of urine</th>
<th>Anuria, isosthenuria, hyposthenuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insensible water loss</td>
<td>40-50</td>
<td>40-50</td>
<td>40-50 (0.5-1.0 x UV)</td>
</tr>
<tr>
<td>Urinary water loss</td>
<td>60-75</td>
<td>15-20 *</td>
<td></td>
</tr>
<tr>
<td>Total loss</td>
<td>100-125</td>
<td>55-70</td>
<td>40-50</td>
</tr>
<tr>
<td>Water of oxidation – gain</td>
<td>20-10</td>
<td>20-10</td>
<td>20-10</td>
</tr>
<tr>
<td>Net need – average</td>
<td>100</td>
<td>50</td>
<td>25+ (0.5-1.0 UV)</td>
</tr>
</tbody>
</table>

Glucose was added to maintenance solutions to support brain metabolism and reduce body protein catabolism and sodium loss. By reducing the need for glucose production from muscle catabolism (gluconeogenesis). Potassium loss was reduced and ketosis was prevented.

By the 1960s the incidence of severe dehydration in the developed world had sharply declined. Teaching fluid therapy for children, most of whom were not overtly dehydrated, became less precise. Textbook chapters, written by pediatric nephrologists, no longer familiar with emergency room and ward practices, failed to reflect these developments and their risks. Maintenance therapy, using more liberal definitions, became the principle solution used. Its safety was not tested. The results sometimes led to children developing either salt deficiency or hyponatremia.

Parents often were advised to “push clear liquids” with the result that this too led to hyponatremia and convulsions. Later, this also was recognized as a problem among infants fed dilute formula or children drinking commercial sweetened beverages.

In the same period, hypernatremia was being reported as a serious complication of children with diarrheal dehydration. Hypernatremia was likely in those given, for example, boiled skim milk, which produced an osmotic, low salt diarrhea. Correcting this practice made hypernatremia less common.

In 1980, Hirschhorn reviewed intravenous therapy for diarrheal dehydration worldwide from 1950-1980. Mortality varied inversely to sodium intake/kg given on the first day of treatment (children given ~15 meq/kg- equivalent to 100 ml extracellular fluid/kg had lower mortalities). He recommended a more rapid restoration of extracellular fluid. (Table 3)
Table 3. Comparison of two approaches to treatment of dehydrating diarrhea

<table>
<thead>
<tr>
<th></th>
<th>Traditional teaching</th>
<th>Recently developed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The physiological model</td>
<td>Varying degrees of dehydration and tonicity require careful tailoring of fluid therapy.</td>
<td>Within broad limits a simple and unified therapeutic approach may be taken.</td>
</tr>
<tr>
<td>2. Speed of rehydration</td>
<td>24-48 hr</td>
<td>4-6 hr</td>
</tr>
<tr>
<td>3. Choice of initial rehydrating solution</td>
<td>Hypotonic with sodium content 30-60 mEq/liter, especially for infants.</td>
<td>Polyelectrolyte solution with sodium content 80-130 mEq/liter for all ages.</td>
</tr>
<tr>
<td>4. Use of potassium</td>
<td>Only after urination commences</td>
<td>In polyelectrolyte solution</td>
</tr>
<tr>
<td>5. Use of base</td>
<td>Only for severe acidosis</td>
<td>In polyelectrolyte solution (bicarbonate, lactate or acetate)</td>
</tr>
<tr>
<td>6. Use of oral fluids</td>
<td>Small, infrequent sips of H₂O in first 24 hrs.</td>
<td>Ad libitum intake of glucose-electrolyte solutions for those able to drink (in mM/liter: Na⁺ 90, K⁺ 20, HCO₃⁻ 30, glucose 111). Need for intravenous fluid can often be eliminated.</td>
</tr>
<tr>
<td>7. Feeding</td>
<td>Fasting for 24-48 hr; careful reintroduction of food</td>
<td>Tolerated feeds as soon as appetite restored (usually within 6-24 hr) in small frequent amounts.</td>
</tr>
<tr>
<td>8. Principal concerns</td>
<td>Overhydration, hypernatremia, persisting loose stools</td>
<td>Under hydration, hyponatremia, undernutrition</td>
</tr>
</tbody>
</table>

Hirschhorn also cited the evidence that oral rehydration therapy was a safer and more efficient means for correcting dehydration and restoring extracellular fluid than conventional intravenous therapy. The oral rehydration therapy model, used extensively in underdeveloped countries, calls for aggressive feeding of oral rehydration solution (Na⁺ 60-90 meq/l); 100 ml/kg in 8 hours was the goal. Three findings stood out: 1) 90% of patients did not require intravenous therapy; 2) children with either hyper or hyponatremia promptly recovered and serum sodium became normal; 3) the oral rehydration solutions used were hypotonic with respect to sodium (Table 1), but did not cause hyponatremia.

Despite these findings, the choice in the developed world for children with diarrhea seen in emergency departments has been to use intravenous therapy to restore extracellular fluid- mostly with isotonic saline. It is time saving and more efficient.

Over the last twenty-five years, acutely ill children from all causes coming to the emergency departments for medical care are noted to be at risk for hyponatremia. A case study of 103 children admitted with acute illness to a children’s hospital in Germany over a 5-month period reported antidiuretic hormone and plasma renin activity measured on admission and later. Both were elevated; 80/103 had initial levels above the normal range. A preponderance of those with elevated antidiuretic hormone had ketosis.

A second case study from a large Canadian children’s hospital reviewed children presenting to the emergency department over a 3-month period. Four per cent were hyponatremic on presentation. Thirty-seven of four hundred thirty two (9%) children admitted to the hospital became hyponatremic in the hospital. Most of these
children received a documented IV free water intake in excess of any published recommendation; oral free water intake was not recorded.

We have argued that many acutely ill children are *hypovolemic*\(^\text{37}\). Sometimes the clinical signs are too subtle to detect hypovolemia, but a measured expansion of extracellular fluid with 20-40 ml/kg given over 2-4 hours to these children is safe. By the end of the infusion, children who had subtle hypovolemia will demonstrate signs of improved circulation and perfusion supporting the initial assumption: improved well being and *normal urine output* signaling that nonosmotic antidiuretic hormone activity, if originally present\(^\text{38}\), is no longer.

The mechanism responsible for *hypovolemia*\(^\text{39}\) in this setting can be envisioned from a review of the physiology of extracellular fluid\(^\text{40}\) that incorporates newer physiological concepts relating extracellular fluid circulation to arterial circulation. Extracellular fluid consists of three compartments (*Table 4*) plasma, lymph and circulating proteins which is the delivery and collecting system; 2) cell interstitial fluid which is the bridge between capillaries and cells across which solute exchanges between capillary blood and cells takes place; 3) skin ISF, a large reservoir that gives shape and form to skin (skin turgor) and connective tissue is a reserve when plasma volume is compromised.

*Table 4. Distribution of extracellular fluid*

<table>
<thead>
<tr>
<th>System</th>
<th>Infant</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma and lymph (ml/kg)</td>
<td>60</td>
<td>55</td>
</tr>
<tr>
<td>Muscle and organs (ml/kg)</td>
<td>80</td>
<td>85</td>
</tr>
<tr>
<td>Skin and connective tissue (ml/kg)</td>
<td>160</td>
<td>130</td>
</tr>
<tr>
<td>Total ECF (ml/kg)</td>
<td>300</td>
<td>270</td>
</tr>
</tbody>
</table>

The circulation of extracellular fluid as plasma ultrafiltrate\(^\text{41}\) begins by leaving arterial capillary blood both by filtration and diffusion across capillary endothelia into the interstitium - a process controlled by Starling forces. Albumen, in lesser amounts, is filtered into the interstitium through larger clefts in capillary endothelial cells.\(^\text{42}\) Exchange of oxygen for carbon dioxide and substrate for end products of metabolism is effected across the thin film of cell interstitial fluid bridging capillaries to cells. Both local rate of capillary flow and albumen filtration are controlled by signaling agents that respond to *local* change in oxygen tension\(^\text{43}\). A variable fraction of filtered extracellular fluid is returned by counter Starling forces to capillaries; the balance and *all* filtered albumen are returned to the vena cava via lymphatics.\(^\text{44}\) This phase of extracellular fluid circulation depends on muscle activity to drive the circulating extracellular fluid as lymph forward toward the lymph duct and vena cava. The traffic of water through the thin film of interstitial fluid surrounding each cell is modulated by the presence of cell surface proteoglycans. These proteoglycans coils that keep the film of cell interstitial fluid constant in overall volume and fixed in place.\(^\text{45}\)

The third and largest phase is the reserve extracellular fluid in skin and connective tissue with lower turnover. With dehydration or dislocation, a substantial portion of this extracellular fluid phase is transferred to plasma as plasma volume is compromised.

Agents controlling arterial circulation include antidiuretic hormone in its pressor role as arginine vasopressin. The impact of simply standing and consciously relaxing
lower extremity muscles, “quiet standing”, upon circulation causes syncopy and hypotension within 15 minutes as lymph and venous return are impaired by gravity. Simulated quiet standing leads to a 15% drop in circulating plasma and albumen despite transfer of skin extracellular fluid and albumen to circulation due to large dislocation of plasma extracellular fluid and albumen into the lower extremities causing antidiuretic hormone and plasma renin activity levels to increase. When the subjects lie down all is reversed. The converse is noted when moderately dehydrated subjects are immersed (head out) in warm water. Central blood volume and pressure increase, antidiuretic hormone decreases despite dehydration.

Applying these concepts to acutely ill children in the emergency department or hospital, we argue that many who have elevated antidiuretic hormone levels will be hypovolemic. For example, elevated levels of antidiuretic hormone in children with meningitis, declined into the normal range if the children were given both saline to expand extracellular fluid and maintenance; those given maintenance alone had less of a decline in antidiuretic hormone. Children given isotonic saline during minor surgery had lower antidiuretic hormone values than those who received none; but there was no difference in serum sodium. Children with severe burn shock had extreme elevations of antidiuretic hormone on admission; with aggressive extracellular expansion, these fell over twelve hours to near normal values. Children with acute diarrheal dehydration had elevated antidiuretic hormone levels on admission that declined after four hours with extracellular fluid expansion, but not always to normal. The above have led us to conclude that the nonosmotic stimulation of antidiuretic hormone seen in acutely ill children is often due to hypovolemia. It is reversed with restoring extracellular fluid. Emphasis in therapy should be rapid extracellular fluid expansion with isotonic saline, then oral or, if needed, IV maintenance, tailored to half average or average as indicated if urine output has not improved (Table 5). In addition, ADH can be stimulated directly by the presence of vomiting, nausea, anesthesia, or drugs per se, and all these additional stimuli should be considered and treated appropriately according to the circumstances.

Table 5. Relating body weight (BW) to metabolic rate (MR) and to average and half average maintenance allowances for daily and hourly periods.

<table>
<thead>
<tr>
<th>Kg</th>
<th>Kcals</th>
<th>MR</th>
<th>Maintenance Allowance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>ML/DAY</td>
</tr>
<tr>
<td>3</td>
<td>300</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>5</td>
<td>500</td>
<td>500</td>
<td>700</td>
</tr>
<tr>
<td>7</td>
<td>700</td>
<td>700</td>
<td>1000</td>
</tr>
<tr>
<td>10</td>
<td>1000</td>
<td>1000</td>
<td>1100</td>
</tr>
<tr>
<td>12</td>
<td>1100</td>
<td>1100</td>
<td>1300</td>
</tr>
<tr>
<td>16</td>
<td>1300</td>
<td>1300</td>
<td>1500</td>
</tr>
<tr>
<td>20</td>
<td>1500</td>
<td>1500</td>
<td>1700</td>
</tr>
<tr>
<td>30</td>
<td>1700</td>
<td>1700</td>
<td>2000</td>
</tr>
<tr>
<td>45</td>
<td>2000</td>
<td>2000</td>
<td>2500</td>
</tr>
</tbody>
</table>
Two groups have proposed using isotonic saline as *maintenance initial* therapy.\textsuperscript{52, 53} They call for using isotonic saline *whenever maintenance* therapy is indicated. For children admitted for surgery, isotonic saline to counter any hypovolemia may be given as a measured expansion, 20-40 ml/kg followed by a “keep open” rate, modified as clinical events through surgery and recovery dictate, including urine output and evidence of reduced lymph and venous return from loss of muscle tone. The dose and rate would be determined by follow up clinical observations, as has been the practice over the years.

Isotonic saline as *maintenance therapy* imposes a sodium load that would become a likely problem as its use is extended. There may be consequences of a needless sodium load, comparable to the case following a needless free water load. The overuse of hypotonic saline and its consequences would have been diminished if those using excess loads had done appropriate studies. The same may be the case with excess use of isotonic saline.

Addressing the following three points may give validity to one of these two approaches. Foremost, we propose a controlled trial testing whether our approach requiring more supervision to monitor both patient and therapy is superior to an algorhytmic approach in which directions are simple but extra loads of sodium are given. Second, we propose a study detailing the follow-up of the responses of antiuretic hormone in acutely ill children to reexpansion. Third, we propose a study that examines why oral hypotonic rehydration fluid (Na 60-90 meq/l) is effective whereas intravenous hypotonic saline (Na- 77 meq/l results in lowering serum sodium.\textsuperscript{54} However, even after all these questions are answered, it should be acknowledged that no hydration or laboratory method will ever replace the presence of a physician with good clinical judgment and the careful follow up that each critical patient deserves. We hope that there will be common agreement among the medical community, with one of the conclusions of the Holliday and Segar’s 1957 paper, which stated: “as with any method, and understanding of the limitations of and exceptions to the system are require. Even more essential is the clinical judgment to modify the system as circumstances dictate”.

This manuscript reviews the foundation on which correct maintenance fluid therapy is built. It clearly delineates the difference between maintenance fluid therapy and restoration or replenishment fluid therapy for reduction in extracellular fluid volume. The manuscript recommends a physiologic approach to restoration and maintenance fluid therapy.

The authors have no competing financial interests.

What is already known(?):

A dispute has arisen regarding the nature of intravenous therapy for acutely ill children following the development of acute hyponatremia from overuse of hypotonic saline. Some propose changing the definition of "maintenance therapy" and recommend isotonic saline be used as maintenance and restoration therapy in undefined amounts leading to intravenous sodium chloride intakes well in excess of need.
What this article adds:

We propose that intravenous fluid therapy for these children be considered, as it was historically, as therapy first to restore circulation with measured infusions of isotonic saline followed by defined minimal maintenance therapy to replace physiological losses according to principles established fifty years ago. We review changing practices and basic physiology of extracellular fluid to support our recommendations.
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