REVIEW

Fluid therapy for children: facts, fashions and questions

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Arch Dis Child 2007;**92**:546–550. doi: 10.1136/adc.2006.106377

Fluid therapy restores circulation by expanding extracellular fluid. However, a dispute has arisen regarding the nature of intravenous therapy for acutely ill children following the development of acute hyponatraemia from overuse of hypotonic saline. The foundation on which correct maintenance fluid therapy is built is examined and the difference between maintenance fluid therapy and restoration or replenishment fluid therapy for reduction in extracellular fluid volume is delineated. Changing practices and the basic physiology of extracellular fluid are discussed. Some propose changing the definition of ''maintenance therapy'' and recommend isotonic saline be used as maintenance and restoration therapy in undefined amounts leading to excess intravenous sodium chloride intake. Intravenous fluid therapy for children with volume depletion should first restore extracellular volume with measured infusions of isotonic saline followed by defined, appropriate maintenance therapy to replace physiological losses according to principles established 50 years ago.

Restoring circulation by expanding extracellular fluid has been the priority of fluid therapy since its inception and was first used to treat children with diarrhoeal dehydration. Blackfan and Maxcy[1] in 1918 gave 0.8% saline by intraperitoneal injection to nine infants with dehydration and all recovered. Later Karelitz and Schick[2] using continuous intravenous infusions of isotonic saline to restore extracellular fluid, reported a hospital mortality of ~20%. In 1920 Marriott[3] 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 paediatrics in a landmark article in 1923. He measured urinary losses of electrolyte and nitrogen in children who were fasting (to induce ketosis for seizure control). From these losses and changes in plasma (extracellular fluid) composition he described the role of the kidney in maintaining the stability of extracellular fluid in response to stress.[5] A summary of his later studies[6] extended this work and was used by a generation of medical students to learn about 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 to him suggested a loss of intracellular fluid. He estimated individual deficits of sodium, chloride, potassium and both extracellular and intracellular fluid per kilogram of body weight. His regimen called for first giving 20 ml/kg of isotonic saline intravenously to restore circulation, followed by deficit therapy[8] to replace the deficits over a few days using intravenous, subcutaneous and oral fluid therapy. He also projected insensible and urinary, or physiological, losses of water and electrolyte from fasting studies. To take account of growth, these physiological losses were scaled to metabolic rate (100 kcal/day) not body weight.[9] Skin insensible water losses, which accounted for a consistent 25% 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] and maintenance therapy replaced these. His regimen, using Darrow's solution (table 1), was designed to replace the deficits of body composition, not just extracellular fluid, and to meet physiological 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 as it usually took 2 or more days before deficits were replaced and 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 diarrhoeal dehydration corresponded with gain in extracellular fluid volume. In experimental studies in rats, intracellular water was minimally affected by cell potassium loss[15] but was dramatically reduced in hypernatraemia.[16]

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.[17] 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 diarrhoeal dehydration, including potassium, and minimal maintenance requirements were defined. However, the presence of higher potassium concentrations in the intravenous solutions (table 1) slowed the rate of infusion of sodium and chloride and consequently the time needed to restore extracellular fluid was prolonged. No commercial company was ready to market solutions with potassium in concentrations higher than those in Ringer's lactate solution.[4]

Holliday and Segar[18] in 1957 made estimating metabolic rate simpler by calculating the changing relationship of average daily metabolic rate to body

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Accepted 20 November 2006
Published Online First 15 December 2006

Table 1 Constituent formulation of intravenous and oral solutions

Solution	Osmolality, mOsm/l	Glucose, mmol/l	Na, mEq/l	Cl, mEq/l	HCO_3, mEq/l	K, mEq/l
Intravenous solutions						
Ringer's	280	–	130	110	25	4
0.9% saline	308	–	154	154	–	–
D_5 0.45% saline	454	300	77	77	–	–
D_5 0.22% saline	377	300	38	38	–	–
Darrow's	–	–	122	104	53	35
Butler's	456	300	46	40	20	35
Oral solution						
WHO-ORS	330	110	90	80	30	20
Low-Na ORS	270	110	60	50	30	20
Pedialyte	270	140	45	35	30	20

ORS, oral rehydration solution; WHO, World Health Organization.

weight[19] using simple empiric equations (infant: 3–10 kg, 100 kcal/kg; preschool: 10–20 kg, 1000+100 kcal for each 2 kg >10; older: 20–70 kg, 1500+100 kcal for each 5 kg >20). The average physiological (insensible plus urinary) losses conveniently came to 100 ml/100 kcal/day and fluid therapy could be planned by practicing physicians at the bedside. The basis for relating insensible loss to metabolic rate[10 11] 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 there was a possibility that urine output might be limited by non-osmotic stimulated antidiuretic hormone activity (table 2).[20] The goal was to give just enough free water, but not excess. Segar and Moore[21] in 1968 and Friedman and Segar[22] in 1979 demonstrated the sensitivity of antidiuretic hormone to non-osmotic stimuli (posture, environmental temperature) and other clinical factors and its rapid reversal.

Glucose was added to maintenance solutions to support brain metabolism and reduce body protein catabolism and sodium loss.[12] By reducing the need for glucose production from muscle catabolism (gluconeogenesis), potassium loss was reduced and ketosis was prevented.[23 24]

By the 1960s the incidence of severe dehydration in the developed world had sharply declined. The teaching of 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.[25] Maintenance therapy, using more liberal definitions, became the principle method used. However, its safety was not tested and the results sometimes led to children developing either salt deficiency or hyponatraemia.[26 27]

Table 2 Calculation of maintenance fluid needs (in ml/100 kcal) as described by Holliday[20]

	Average normal renal responses	Maximal concentration of urine	Anuria, isosthenuria, hyposthenuria
Insensible water loss	40–50	40–50	40–50 (0.5–1.0×UO)
Urinary water loss	60–75	15–20	*
Total loss	100–125	55–70	40–50
Water of oxidation, gain	20–10	20–10	20–10
Net need, average	100	50	25+(0.5–1.0×UO)

UO, urine output.

Parents often were advised to ''push clear liquids'' with the result that this too led to hyponatraemia and convulsions.[28] Later, this also was recognised as a problem among infants fed dilute formula or children drinking commercial sweetened beverages.[29]

In the same period, hypernatraemia was being reported as a serious complication in children with diarrhoeal dehydration and was likely in those given, for example, boiled skim milk, which produced an osmotic, low salt diarrhoea.[30] Correcting this practice made hypernatraemia less common.[31]

In 1980, Hirschhorn[32] reviewed intravenous therapy for diarrhoeal 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).

Hirschhorn[32] 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) with a goal of 100 ml/kg in 8 h. Three findings stood out: (a) 90% of patients did not require intravenous therapy; (b) children with either hyper- or hyponatraemia promptly recovered and serum sodium became normal[33]; and (c) the oral rehydration solutions used were hypotonic with respect to sodium (table 1) but did not cause hyponatraemia.

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

Over the last 25 years, children acutely ill from all causes presenting to emergency departments are noted to be at risk for hyponatraemia.[34] A case study[35] 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 and after admission. Both measurements were elevated with 80/103 children having initial levels above the normal range. Most of those with elevated antidiuretic hormone had ketosis.

A second case study[36] from a large Canadian children's hospital reviewed children presenting to the emergency department over a 3 month period. On presentation 4% of these children were hyponatraemic and 37 of 432 (9%) children admitted to the hospital became hyponatraemic in the hospital. Most of these children received a documented intravenous free water intake in excess of any published recommendation; oral free water intake was not recorded.

Table 3 Comparison of two approaches to treatment of dehydrating diarrhoea

	Traditional teaching	Recent recommendations
1. The physiological model	Varying degrees of dehydration and tonicity require careful tailoring of fluid therapy	Within broad limits a simple and unified therapeutic approach may be taken
2. Speed of rehydration	24–48 h	4–6 h
3. Choice of initial rehydrating solution	Hypotonic with sodium content of 30–60 mEq/l, especially for infants	Polyelectrolyte solution with sodium content of 80–130 mEq/l for all ages
4. Use of potassium	Only after urination commences	In polyelectrolyte solution
5. Use of base	Only for severe acidosis	In polyelectrolyte solution (bicarbonate, lactate or acetate)
6. Use of oral fluids	Small, infrequent sips of water in first 24 h	Ad libitum intake of glucose-electrolyte solutions for those able to drink (in mM/l: Na^+ 90, K^+ 20, HCO_3^- 30, glucose 111); need for intravenous fluid can often be eliminated
7. Feeding	Fasting for 24–48 h; careful reintroduction of food	Tolerated feeds as soon as appetite restored (usually within 6–24 h) in small frequent amounts
8. Principal concerns	Over-hydration, hypernatraemia, persisting loose stools	Under-hydration, hyponatraemia, under-nutrition

We have argued that many acutely ill children are hypovolaemic.[37] Sometimes the clinical signs are too subtle to detect hypovolaemia, but a measured expansion of extracellular fluid with 20–40 ml/kg given over 2–4 h to these children is safe. By the end of the infusion, children who had subtle hypovolaemia will demonstrate signs of improved circulation and perfusion supporting the initial assumption with improved well-being and normal urine output indicating that non-osmotic antidiuretic hormone activity, if originally present,[38] is no longer so.

The mechanism responsible for hypovolaemia[39] in this setting can be understood from a review of the physiology of extracellular fluid[40] that incorporates newer physiological concepts relating extracellular fluid circulation to arterial circulation. Extracellular fluid consists of three compartments (table 4): (a) plasma, lymph and circulating proteins which is the delivery and collecting system; (b) cell interstitial fluid which is the bridge between capillaries and cells across which solute exchanges between capillary blood and cells takes place; and (c) skin interstitial fluid, a large reservoir that gives shape and form to skin (skin turgor) and connective tissue, and acts as a reserve when plasma volume is compromised.

The circulation of extracellular fluid as plasma ultrafiltrate[41] begins when it leaves 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.[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 signalling agents that respond to local change in oxygen tension.[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.[44] This phase of extracellular fluid circulation depends on muscle activity to drive the circulating extracellular fluid as lymph forward towards 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 keep the film of cell interstitial fluid constant in overall volume and fixed in place.[45]

Table 4 Distribution of extracellular fluid

System	Infant	Adult
Plasma and lymph (ml/kg)	60	55
Muscle and organs (ml/kg)	80	85
Skin and connective tissue (ml/kg)	160	130
Total extracellular fluid (ml/kg)	300	270

The third and largest phase is the reserve extracellular fluid in skin and connective tissue which has a 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 min as lymph and venous return are impaired by gravity.[46] Simulated quiet standing leads to a 15% drop in circulating plasma and albumen despite the transfer of skin extracellular fluid and albumen to the 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.[47] When the subject lies 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, and serum antidiuretic hormone values decreases despite dehydration.[48]

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 hypovolaemic. 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 a smaller decline in antidiuretic hormone.[49] 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.[50] Children with severe burn shock had extreme elevations of antidiuretic hormone on admission; with aggressive extracellular expansion, these levels fell over 12 h to near normal values.[51] Children with acute diarrhoeal dehydration had elevated antidiuretic hormone levels on admission which declined after 4 h of extracellular fluid expansion, but not always to normal. The above findings have led us to conclude that the non-osmotic stimulation of antidiuretic hormone seen in acutely ill children is often due to hypovolaemia. It is reversed by restoring extracellular fluid. Emphasis in therapy should be on rapid extracellular fluid expansion with isotonic saline, then oral or, if needed, intravenous maintenance, tailored to half average or average as indicated if urine output has not improved (table 5). In addition, antidiuretic hormone can be stimulated directly by the presence of vomiting, nausea, anaesthesia, 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

BW (kg)	MR (kcal)	Maintenance allowance Average (ml/day)	Half average (ml/day)	Average (ml/h)	Half average (ml/h)
3	300	300	150	12	6
5	500	500	250	20	10
7	700	700	350	25	12
10	1000	1000	500	40	20
12	1100	1100	550	45	22
16	1300	1300	650	50	25
20	1500	1500	750	60	30
30	1700	1700	850	70	35
45	2000	2000	1000	80	40
70	2500	2500	1250	100	50

Two groups have proposed using isotonic saline whenever maintenance therapy is indicated.[52 53] For children admitted for surgery, isotonic saline to counter any hypovolaemia may be given as a measured expansion, 20–40 ml/kg followed by a ''keep open'' rate, modified as clinical events during surgery and recovery dictate, including urine output and evidence of reduced lymph and venous return from loss of muscle tone. The dose and rate can 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 may become a problem as its use is extended. Needless sodium load may have consequences, comparable to the case following needless free water load. The overuse of hypotonic saline and its consequences would have been less if those delivering excess loads had carried out appropriate studies. The same may be the case with excess use of isotonic saline.

We propose a controlled trial testing whether our approach requiring more supervision to monitor both patient and therapy is superior to an algorhythmic 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 antidiuretic hormone in acutely ill children to re-expansion. 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 lowered serum sodium.[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 critically ill 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, an understanding of the limitations of and exceptions to the system is required. Even more essential is the clinical judgment to modify the system as circumstances dictate''.

This article 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. A physiological approach to restoration and maintenance fluid therapy is recommended.

What is already known on this topic

- A dispute has arisen regarding the nature of intravenous therapy for acutely ill children following the development of acute hyponatraemia 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 excess intravenous sodium chloride intake.

What this study adds

- We propose that intravenous fluid therapy for children be considered, as it was historically, as therapy to restore circulation with measured infusions of isotonic saline followed by defined minimal maintenance therapy to replace physiological losses according to principles established 50 years ago.
- We review changing practices and the basic physiology of extracellular fluid to support our recommendations.

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Competing interests: None.

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