

## Viewpoint

## Intravenous fluids for seriously ill children: time to reconsider

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Intravenous (iv) fluids are used for many sick and injured children. Such fluids generally used are 0.18% or 0.2% saline with 5% dextrose. These fluids are often given at maintenance rates—100 mL/kg for the first 10 kg of bodyweight, 50 mL/kg for the next 10 kg, and 20 mL/kg for bodyweight exceeding 20 kg.<sup>1</sup> Some standard paediatric texts caution the need to modify maintenance requirements according to disease states, but this specification has been lost in some recent empirical recommendations: for example, WHO now suggests full maintenance fluids for the routine treatment of bacterial meningitis (albeit with a caution about cerebral oedema), with an emphasis on glucose but not sodium content.<sup>2</sup> This is partly based on concerns about dehydration, but there is no strong evidence that this advice is ideal.<sup>3,4</sup> Hypotonic iv fluids given at maintenance rates might be unsafe, especially in hospitals in developing countries where serum sodium concentration often cannot be measured.

The traditional use of hypotonic maintenance fluid in paediatric medicine is based on requirements of normal physiology—eg, if an infant weighing 6 kg receives 0.18% saline fluid for 24 h, they will receive 3 mmol/kg sodium chloride, 100 mL/kg water, and 3.5 mg/kg per minute glucose. These are the amounts of (1) sodium and chloride needed for normal metabolism and growth; (2) water needed by the kidneys to excrete nitrogenous wastes in urine with similar osmolarity to plasma (so that the kidneys do not need to excessively concentrate or dilute urine); and (3) glucose needed to avoid hypoglycaemia and glycogen breakdown. This sounds ideal, but is it? Most healthy people do not drink this much water each day (average for adults is 2.5–3 L), so their kidneys usually concentrate, or if they drink more than usual dilute, their urine. Healthy people are able to excrete large amounts of free water. This is not the case for many children after surgery, or with serious infections.

Large volumes of hypotonic fluid were generally given after surgery, until reports led to recognition that postoperative patients have reduced free-water clearance, and hypotonic saline solutions at maintenance rates or greater put patients at risk of hyponatraemia and encephalopathy—the syndrome of water intoxication.<sup>5–8</sup>

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Children with serious infections share similar pathophysiological mechanisms and risks of adverse neurological outcomes if given hypotonic iv solutions. We outline the pathophysiology of hyponatraemia in acute infections, and argue that the safest empirical iv fluid for most children with serious infections, who cannot take enteral fluids, is 0.9% sodium chloride with dextrose, at rates of infusion that take account of reduced free-water clearance.

### Impaired free-water excretion during severe infections

Antidiuresis during fever and sepsis has been known for over a century, especially in pneumonia and meningitis. Hippocrates' description of pneumonia included scanty and high-coloured urine. In a rhesus monkey model of pneumococcal sepsis, urine volume and free-water clearance decreased to 25% and 17% of baseline values, respectively, during the first 9 h of infection.<sup>9</sup> When 0.45% saline, equal to 105% of urine output in controls, was intravenously infused into septic monkeys, their bodyweight expanded by more than 10% during 9 h of experimental sepsis. Of note, serum sodium concentration or serum osmolarity did not change greatly. In a clinical investigation, 70% of infants with

Mechanism	Setting
<b>Dilution of ECFV</b>	
High ADH activity	Despite normal or expanded ECFV and hypo-osmolarity, so-called SIADH Because of hypovolaemia Other non-osmotic ADH stimuli <sup>18,19</sup> Pain Nausea Hypoxaemia Drugs Mechanical ventilation
Increased sensitivity of renal tubules to ADH	Drugs Severe illness
Increased intake of free water	Excessive enteral water intake
Iatrogenic administration of free water	iv administration of hypotonic solutions
<b>Increased urinary sodium loss</b>	
ECFV expansion	Retention of free-water from high ADH activity Unrestricted oral intake Iatrogenic administration Increased right atrial pressure
Natriuretic peptide activity (ANP/BNP)	
Cerebral 'salt wasting'	Described in tuberculous meningitis and traumatic brain injury
Diuretic administration	..
Corticosteroids	..
ADH	ADH may have a direct effect on increasing urinary sodium excretion

ECFV=extracellular fluid volume. ANP=atrial natriuretic peptide. BNP=brain natriuretic peptide. ADH=antidiuretic hormone. SIADH=syndrome of inappropriate ADH secretion.

Table 1: **Causes of hyponatraemia in severe childhood illness**



**Serum sodium in well hydrated and dehydrated children with meningitis**

$p=0.03$ . Well hydrated,  $n=286$ ; dehydrated,  $n=40$ . Horizontal lines represent mean (SD).

acute bronchiolitis had impaired free-water excretion; at recovery, free-water clearance was up to 15 times more than at the time of admission.<sup>10</sup>

### Hyponatraemia in severe infections

Hyponatraemia arises in between 20% and 45% of children with meningitis,<sup>11,12</sup> pneumonia,<sup>13</sup> encephalitis,<sup>14</sup> septicaemia,<sup>15</sup> cerebral malaria,<sup>16,17</sup> and somewhat less often in those with bronchiolitis.<sup>10</sup> The pathophysiological basis is not fully understood, but many factors could be active in the same patient (table 1). Dilution of extracellular fluid because of impaired free-water excretion and increased urinary sodium losses seem to be the main mechanisms. Other mechanisms, including shifts of water from intracellular to extracellular spaces, have been shown in some models of sepsis,<sup>20</sup> but not in others, and are less likely to be important in practice.<sup>21</sup>

### Antidiuretic hormone

High concentrations of antidiuretic hormone are seen in many acute febrile illnesses,<sup>22</sup> and are traditionally described as inappropriate. When applied generally, this term indicates our incomplete understanding of the potency of different stimuli to antidiuretic hormone

release and suppression (table 1). Hypovolaemia might be a more potent stimulus for secretion of antidiuretic hormone than hypo-osmolality is to its suppression. In a retrospective study of 300 children with meningitis, investigators noted that serum sodium was lower in those with dehydration than in those with normal hydration.<sup>12</sup> Conversely, a prospective investigation showed that serum sodium concentrations were lower in children with normal hydration than in those with clinical signs of dehydration (figure).<sup>23</sup> Such conflicting data suggest that hyponatraemia arises either as a result of an appropriate pathophysiological response of antidiuretic hormone to restore extracellular fluid volume at the expense of hypo-osmolality, or as a result of hormonal activity that is inappropriate to both osmolality and fluid volume status. Antidiuretic hormone also acts centrally, via aquaporin-4 water-transporting proteins expressed in astrocyte foot processes near capillaries and in ependymal cells lining ventricles, to increase brain water.<sup>24,25</sup> Administration of sodium results in a more rapid return to normal of antidiuretic hormone concentrations than does use of low sodium-containing fluid.<sup>4</sup>

### Adverse effects of hyponatraemia

In the peripheral circulation, sodium moves freely throughout the extracellular fluid; the hydrostatic pressure gradient and oncotic pressure (predominantly made up of plasma proteins) are responsible for preventing the movement of water out of the vasculature. Cerebral circulation is different. Endothelial tight junctions prevent free movement of sodium across the intact blood-brain barrier, and therefore effective osmolality is the major determinant of water movement into the brain interstitium or into brain cells.<sup>18</sup> When the blood-brain barrier is intact, an abrupt fall in effective serum osmolality of 5 mmol/L decreases osmotic pressure difference between the capillary lumen and the brain interstitium by 95 mm Hg (17.5%), favouring water accumulation in the interstitium or brain cells.<sup>26</sup> Many case reports have described acute neurological deterioration in children with serious infections, associated with progressive hyponatraemia and hypotonic intravenous fluid administration (table 2). Researchers who examined the aetiology of extreme hyponatraemia (<115 mmol/L) in a tertiary children's hospital, reported iatrogenic administration of excessive free water as the most common cause.<sup>31</sup>

Investigation	Disease state	Reduction in serum [sodium] or value at time of complication (mmol/L)	Intravenous fluid type and volume	Adverse event	Comments
Cooke <sup>27</sup>	2-year-old girl with tuberculous meningitis	From 130 to 120	Not stated	Coma, seizures	
McJunkin <sup>14</sup>	La Crosse encephalitis (13 of 127 children had neurological deterioration while in hospital)	All children with adverse neurological deterioration had a reduction in sodium. From 138.2 to 134.2 (reduction in mean)	Not stated	Neurological deterioration including cerebral herniation, status epilepticus, and intracranial hypertension	27 children developed hyponatraemia while in hospital, of whom 13 had neurological deterioration
Mor <sup>28</sup>	Infant with pneumonia	107	0.18% saline at 150 mL/kg per day for 2 days	Seizures and cerebral oedema	
Potts <sup>29</sup>	17-month-old with minor burns	From 133 to 113	0.2% saline at 250 mL/kg/day	Seizures	Complications ascribed to SIADH but really represent iv free water intoxication
Jackson <sup>30</sup>	Two children: one with viral respiratory tract infection and one with <i>Streptococcus pneumoniae</i> meningitis	121 and 128, respectively, after administration of fluid	5% dextrose at 35–40 mL per kg	Seizures, cerebral oedema, and death	

Table 2: Adverse events after progressive hyponatraemia induced by hypotonic solutions in children with serious infection or injury

Fluid	Volume (mL/kg/day)	Volume per day (mL)	Urine output (mL)	Insensible losses (mL)	Total output (mL)	Total net water added (ICF/ECF) (mL)	Na <sup>+</sup> added (mmol)	24-h serum [Na] <sup>*</sup>
0.18% saline	100	600	210	180	390	210 (84/126)	7.2	130.6
0.9% saline	75	450	210	180	390	60 (0/60)	13.5	137.5

Total body water=70% of bodyweight (35% ECF, 35% ICF. ICF=intracellular fluid. ECF=extracellular fluid. Free-water excretion reduced by 50% normal (urine volume from 70–35 mL/kg/day) due to increased activity antidiuretic hormone. Starting serum [Na] 135 mmol/L; total ECF Na=0.35×6×135=283.5 mmol.

<sup>\*</sup>24-h serum [Na]=(pre-existing ECF [Na]+[Na] added)/(pre-existing ECF+ECF added).

Table 3: Expected changes after 24 h of fluid administration to an infant weighing 6 kg

Avoidance of hyponatraemia is essential, but not sufficient, to prevent adverse events associated with iv fluid in all children. Fluid overload occurs in children with impaired free-water clearance who receive 100% or more of maintenance fluid. In a randomised trial of fluid management in bacterial meningitis, facial oedema developed 48 h after admission in 45 of 176 (25.6%) children who received 100% of maintenance fluids using 0.45% saline. The relative risk of death or severe neurological sequelae when facial oedema was present was 2.5 (95% CI 1.4–4.8), despite the absence of differences in serum sodium or osmolality (Duke T, unpublished). This finding suggests that fluid overload, even without progressive hyponatraemia, can contribute to adverse neurological events, which might be explained by disruptions to the blood-brain barrier in children with meningitis. Thus, generation of cerebral oedema in severe infections is multifactorial: the effective osmolar gradient, administered fluid volume, and a direct effect of antidiuretic hormone on aquaporin proteins are each important.

Table 3 shows the estimated effect of two types of fluid management regimens on serum sodium and volume status in an infant weighing 6 kg, with impaired free-water excretion. Renal function was assumed to be otherwise normal. After use of 0.18% saline at 100 mL/kg per day, serum sodium would be expected to fall from 135 mmol/L to 131 mmol/L within 24 h, associated with a 5% increase in total body water. With 0.9% saline at 75 mL/kg per day, serum sodium would increase by 2 mmol/L and total body water by 1.5%, with no increase in intracellular water. These are the initial changes; secondary effects might include part correction of the fall in serum sodium in those receiving 0.18% saline, because of intracellular water shifts, but increased urinary sodium losses because of expansion of the extracellular fluid.

Few clinical trials have assessed these differences. A non-randomised comparison of 0.18% and 0.9% saline in 24 postoperative patients, showed a similar biochemical effect to our predicted result. Adults receiving 0.18% saline at 3 L per 24 h had a median fall in serum sodium at 24 h and 48 h of 5.4 mmol/L and 7.1 mmol/L, respectively, but serum sodium did not change in those receiving 0.9% saline.<sup>32</sup> In patients in whom renal clearance of free water is reduced by more than 50%, maintenance fluid will need to be considerably less than 75% of normal maintenance volumes to avoid oedema. This approach is not fluid restriction, as it is sometimes interpreted: restriction of fluids to the point of dehydration in the hope of avoiding cerebral oedema is dangerous, and will result in worse outcomes.<sup>23</sup>

### Potential pitfalls

Use of an isotonic, rather than hypotonic, solution does not mean that progressive hyponatraemia would not take place, but that it is much less likely. Although use of high-sodium-containing solutions in children with meningitis in the first 24 h was not associated with

development of hypernatraemia,<sup>6</sup> during the later phases of illness there is a theoretical risk of hypernatraemia if isotonic saline is used. Diuresis and low urine osmolality is a feature of the convalescent phase of childhood infections. However, during this phase of illness iv fluid rates are reduced, and enteral feeding reintroduced. Children with severe infections, who are not taking enteral feeds, are at risk of hypoglycaemia; isotonic saline should always have glucose added (5–10%) when given as maintenance fluid. Early correction of clinical signs of severe dehydration or shock is essential.<sup>23</sup>

In renal failure there is no safe substitute for measurement of urine output and serum sodium, and adjustment of water and solute intake accordingly. Severe hyponatraemia should be corrected slowly to avoid the demyelinating syndrome.<sup>33</sup> Although there is no evidence that correction of moderate hyponatraemia in children with isotonic saline causes a large risk of this syndrome, to increase sodium by no more than 1 mmol/L every 2 h, seems sensible when this can be measured. Isotonic saline has a pH of 5–6. When it is used in large volumes for children in shock, metabolic acidosis can persist, and in some circumstances bicarbonate or other buffer might be needed.

### Possible solution

We postulate that 0.9% saline (with 5% dextrose) at less than standard maintenance volumes results in a lower frequency of hyponatraemia, seizures, and adverse neurological events than do hypotonic solutions (0.18%–0.3% saline), in acutely unwell children with brain injury of any type (meningitis, encephalitis, cerebral malaria, febrile seizures); serum sodium less than 138 mmol/L;<sup>30</sup> or severe infection associated with greatly impaired free-water excretion.

Ideal testing of this hypothesis would be done in a large randomised controlled trial of hypotonic versus isotonic saline in children with severe infections, stratified for types of infections. However, we think it would be unethical to include some infections, particularly encephalitis and meningitis, because there is already substantial experience of harm from hypotonic solutions and pathophysiological plausibility of the cause of such harm. Such infections also have a much higher risk than do other infections of cerebral oedema and adverse outcomes if hyponatraemia occurs.

An alternative approach, in hospitals in which hypotonic fluids at maintenance volumes are the routine standard of care, would be to change the policy such that isotonic saline at reduced infusion rates (60–70% of maintenance) becomes the standard iv fluid for seriously ill children. Although not as robust as a randomised control trial, this approach might allow for a detailed before-and-after analysis. Outcomes could include differences in the proportions of children who have neurological events associated with progressive falls in serum sodium. Assessment of harm could include differences in frequencies of severe hypernatraemia, or neurological complications associated with rapidly rising serum sodium.

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