# CORRESPONDENCE

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## Intravenous fluids for seriously ill children

Sir—Trevor Duke and Elizabeth Molyneux (Oct 18, p 1320)[1] once again call attention to a serious clinical problem—hospital-induced hyponatraemia. However, their Viewpoint contains errors of fact and recommendations that are counter to established principles of fluid therapy. The article, like another,[2] inappropriately proposes that isotonic saline be used as maintenance therapy. This strategy poses risks of hypernatraemia and other consequences of sodium overload.[3] These proposals mark a tendency to conflate maintenance therapy with rehydration or restoration therapy—two very separate functions of fluid therapy.

Rehydration or restoration therapy is the first priority of fluid therapy. Rapidly infused isotonic saline, resulting in the restoration of extracellular fluid, is essential in the recovery of adults with cholera and infants with diarrhoeal dehydration. Isotonic saline has been used to treat burn shock since the 1960s. The idea is to temporarily overexpand extracellular fluid to restore circulation.[4] Once accomplished, renal regulation of salt and water balance are also restored. The excess extracellular fluid is mobilised and excreted as urine. Isotonic saline given for these purposes is indexed to bodyweight.

Maintenance therapy, introduced in the 1950s, is replacement of physiological insensible and renal water losses by use of hypotonic saline; these losses vary according to metabolic rate, which is readily estimated from bodyweight, but not to bodyweight itself. The average amount required is 100 mL per 100 kcal (419 kJ) per day; adjustment to that average is appropriate when projected losses differ from average.[5]

We have accumulated evidence that children admitted to hospital because of acute illness or scheduled for surgery are often mildly hypovolaemic; concentrations of plasma antidiuretic hormone are increased, inhibiting free water excretion. Administration of maintenance fluids as hypotonic saline in that setting risks hyponatraemia. Rapid expansion of the extracellular fluid of these patients with 20–40 mL/kg isotonic saline before maintenance therapy is started, and limiting of maintenance therapy to that recommended in the original 1957 protocol outlined above[5] greatly reduces this risk (unpublished data).

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Sir—Trevor Duke and Elizabeth Molyneux[1] underscore the critical role of appropriately or inappropriately secreted antidiuretic hormone in the development of hyponatraemia in children with severe infections. They claim that centrally acting antidiuretic hormone contributes to intracellular water accumulation in the brain by increasing water transport across aquaporin-4, the water-channel protein predominantly expressed in the perivascular astrocyte endfoot processes and in subpopulations of ependymal cells. In support of this contention, they refer to our publication[2] about the effects of intraventricular administration of arginine vasopressin and atrial natriuretic peptide on the brain water content and its localisation into the intracellular and extracellular space in rats with experimentally induced hyponatraemia. In fact, the regulation of brain-specific aquaporin-4 is not yet fully explored, but the involvement of antidiuretic hormone in this process is not substantiated by experimental evidence.

Treatment of cultured rat astrocytes with the protein kinase C (PKC) activator phorbol ester has been shown to cause a rapid time-dependent and dose-dependent decrease in expression of aquaporin-4 mRNA.[3] Inhibition of mRNA concentrations was not related to their stability nor to de-novo protein synthesis, indicating that regulation of aquaporin-4 mRNA via PKC activation could be at the transcriptional level. The water-channel activity of aquaporin-4 has also be been shown to be regulated by phorbol-ester-dependent protein phosphorylation via the PKC pathway, as shown by the presence of typical consensus sites for phosphorylation in the aquaporin-4 protein and by the striking reduction of aquaporin-4 protein concentrations by phorbol diesters.[4]

Moreover, in cultured cells with features of renal medullary collecting ducts, aquaporin-4 expression can be downregulated not only by PKC but also by dopamine.[5] Dopaminergic regulation of brain-specific aquaporin-4, therefore, should be considered as a possible mechanism in the control of brain water metabolism.

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*Author's reply*

Sir—I agree with Malcolm Holliday and colleagues that use of only hypotonic saline as maintenance fluid increases the risk of hyponatraemia. There are several strategies to avoid this outcome, and the most practical might depend on the setting and resources available. Giving normal saline as extracellular fluid expansion followed by 0·18% sodium chloride at volumes that take account of the strikingly reduced free water excretion that occurs in serious infections or after surgery will be safe for many seriously ill children.

Our article was not designed to address the issue of adequate volume resuscitation, which should use isotonic fluid. The alternative approach we suggested to maintenance fluid considered that recommendations often suggest giving too much water (100 mL per kg per day).[1] In many hospitals in developing countries, the fluid management suggested by Holliday (use of two types of intravenous fluid and regular monitoring of serum sodium) is unavailable. Even in developed countries, deciding on the maintenance fluid rate is often difficult and results in overestimation.

I recently cared for an 8-week-old infant with streptococcal meningitis who presented to an outside hospital with poor perfusion and a serum sodium concentration of 137 mmol/L. She was resuscitated with 50 mL/kg 0·9% saline. The infant was alert and interactive, and had a normal neurological examination and normal hydration when transferred to our hospital. She then received 0·18% saline intravenously at 69 mL/kg per h. 9 h later she developed seizures and a dilated right pupil. The serum sodium concentration was 131 mmol/L, and a CT scan showed extensive bilateral cerebral oedema. Although the clinical course of meningitis might have had a role in the child's deterioration, iatrogenic hyponatraemia due to hypotonic fluid administration, despite initial appropriate normal saline bolus resuscitation, is the most likely cause of the extensive cerebral oedema.

We proposed that for children with meningitis, other brain injury, or serious illness associated with reduced free water excretion, administration of reduced volumes of isotonic saline plus dextrose (after adequate volume expansion) might be a practical approach. No empirical strategy will be ideal for all children: in renal failure, cardiac disease, or severe malnutrition, the risk of salt retention and water overload might be greater if isotonic saline is used. Although I think that dangerous levels of hypernatraemia are less likely to occur with the strategy we proposed than are dangerous levels of hyponatraemia if 0·18% saline is used, this hypothesis should be tested. Empirical fluid strategies should be assessed in various acute clinical conditions for their effects on serum sodium, body water (measurable by very accurate serial bodyweight), and urinary sodium excretion.

The reference we cited by Vajda and colleagues[2] supports the statement that antidiuretic hormone can act centrally to increase water permeability of the cerebral vasculature and intracellular brain water, and other research by them[3] suggest that aquaporin-4 receptors mediate increases in intracellular brain water. However, Vajda and colleagues are right to correct us that there is no good evidence of a link between these two processes.

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Sir—Trevor Duke and Elizabeth Molyneux's article[1] on the fluid management of severely ill children is an important step in the reassessment of the current recommendations for fluid management in critically ill children in tropical settings. However, we believe that three issues deserve further emphasis. First, in many children, iatrogenic hyponatraemia can be averted by avoiding the unnecessary use of intravenous fluids: in most disorders that lead to hospital admission in tropical countries, including respiratory distress, children are able to take fluid orally after initial management. Second, as Duke and Molyneux's title suggests, their recommendations are for "seriously ill children"—a group that includes malnourished children, in whom WHO currently recommends the avoidance of sodium-rich resuscitation fluids, for fear of salt overload and cardiogenic failure. Finally, many seriously ill children also present in hypovolaemic shock and require resuscitation, often with large boluses of isotonic solutions.

The emergency triage assessment and treatment guidelines, developed by WHO for use in developing countries, define shock on the basis of a delayed capillary refill time (dCRT; >3 s), cold hands, and a weak, fast pulse.[2] However, studies in Brazil[3] and Malawi[4] suggest that these criteria are insensitive, since in both studies shock was rarely diagnosed (<0·5%), although the case fatality rate in those defined as shock approached 100%. In our hospital on the coast of Kenya, clinical assessment for shock has been part of our routine admission practice for several years. A review of data from children admitted to our paediatric ward during the past 12 months shows that dCRT was present in 8% (case fatality rate 24%), a temperature gradient in 4% (12%), and a weak pulse volume in 3% (23%; unpublished data). Mortality in children without any of these features was 2·6%, suggesting that these signs are useful in identifying

| | Sodium concentration (mmol/L) | | | | Total |
|---|---|---|---|---|---|
| | <125 | 125–135 | 135–144 | ≥145 | |
| Number of children | 26 (5%) | 257 (50%) | 212 (42%) | 17 (3%) | 512 (100%) |
| Age (median [IQR], months) | 28 (8–74) | 23 (10–44) | 25 (11–52) | 19 (7–37) | 24 (10–47) |
| MUAC <12 cm | 12 (46%) | 54 (21%) | 38 (18%) | 7 (41%) | 111 (22%) |
| Falciparum-positive | 9 (35%) | 172 (66%) | 111 (52%) | 8 (47%) | 300 (59%) |
| Respiratory distress | 16 (62%) | 74 (29%) | 79 (37%) | 8 (47%) | 177 (35%) |
| Impaired consciousness | 13 (50%) | 170 (66%) | 143 (68%) | 14 (82%) | 327 (64%) |
| Coma | 7 (27%) | 102 (40%) | 89 (42%) | 11 (65%) | 203 (40%) |
| CRT ≥3 s | 10/26 (39%) | 78/236 (33%) | 51/185 (28%) | 7/16 (44%) | 146/463 (32%) |
| Hypotension* | 6/25 (24%) | 33/234 (14%) | 16/191 (8%) | 2/14 (14%) | 57/464 (12%) |
| Seizures before or at admission | 7 (27%) | 145 (56%) | 116 (55%) | 9 (53%) | 277 (54%) |
| Inpatient seizures | | | | | |
| Non-malarial | 2 (14%) | 20 (24%) | 21 (24%) | 3 (33%) | 46 (23%) |
| Falciparum-positive | 3 (33%) | 36 (21%) | 47 (43%) | 4 (56%) | 90 (31%) |
| Mortality | 8 (31%) | 40 (16%) | 46 (22%) | 6 (35%) | 100 (20%) |

MUAC=mid-upper-arm circumference. CRT=capillary refill time. *Systolic blood pressure <70 mm Hg if younger than 1 year and <80 mm Hg if older than 1 year.

**Clinical characteristics of all children older than 1 month admitted to high-dependency unit**

children with a poor prognosis in whom volume expansion should be considered. In developing countries, a change in culture towards early recognition of compensated shock and implementation of rapid volume resuscitation might improve outcome irrespective of cause.

We agree that hyponatraemia commonly complicates many serious infections in children. Prompted by their article, we examined data from critically ill children older than 1 month admitted to our high-dependency unit between September, 1999, and December, 2000. Admission criteria included impaired consciousness—defined as prostration (inability to sit up) or coma (inability to localise pain)—and deep acidotic breathing.[5] Hyponatraemia was present in only 5%, being more common in children with respiratory distress, hypotension, and severe malnutrition (mid-upper-arm circumference <12 cm). It was not more frequent in those with impaired consciousness or seizures (table). Moreover, despite a higher case fatality rate in those with hyponatraemia, the clinical significance was less pronounced, since only eight of the 100 children who died were admitted with sodium concentrations of less than 125 mmol/L. Throughout this period, our routine fluid management for all children with impaired consciousness was intravenous maintenance with 0·18% saline and 4% dextrose at 4 mL/kg hourly. Boluses of normal saline were reserved for children with clinical features of shock or with metabolic acidosis (base deficit >8). In-hospital seizures were not more common in children who were already hyponatraemic on admission. These data are, however, inadequate to make any recommendations regarding fluid management and we acknowledge that this issue can only be addressed satisfactorily through prospective randomised trials.

We agree that reconsideration of the current WHO recommendations for fluid management is timely; however, we suggest that more basic research is needed to help define the "whole package". We suggest the formal assessment of a simple management plan for fluid administration that encompasses a broader range of children admitted to hospitals that are unable to measure electrolytes or renal function.

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## HIVNET 012 and Petra

Sir—J Brooks Jackson and colleagues (Sept 13, p 859)[1] report 18-month follow-up data from their study of single-dose nevirapine for prevention of mother-to-child transmission of HIV-1. Although some people doubt the lasting relevance of their findings in terms of the regimen they used, there is no doubting the importance of HIVNET 012 as a "proof-of-principle" study of intrapartum intervention.

Jackson and colleagues are remiss, however, in not highlighting an apparent decline over time in postnatal transmission of HIV-1 in Kampala. This decrease might affect the relevance of their findings to other settings. Compared with the findings of the earlier Petra study,[2] which included their study hospital, transmission between 3 and 6 months was much lower (compare top of figure 2 from the recent HIVNET 012 paper[1] with the group C survival curve in figure 3B of Petra).

Why are the findings of HIVNET 012 and Petra so different? The magnitude of the difference will only be revealed if the two study teams do a combined analysis. However, discussion of the reason for the difference need not—and should not—wait for such an analysis. Both trials recruited over a lengthy period, but only Jackson and colleagues examined time as a covariate. Because they found no time-dependent effect, any change in postnatal transmission must have occurred during the lifetime of Petra, which started almost 18 months earlier, or result from a qualitative difference between the two trials—either recruitment bias or content of counselling. Jackson and colleagues should describe any differences in the counselling given in their study compared with the early stages of Petra.

By November, 1997, when HIVNET 012 started recruiting, there was growing acceptance of the findings of a paper published in 1993 showing a strong relation between sexual behaviour during pregnancy and mother-to-child transmission of HIV-1.[3] The interpretation of that study has never been fully resolved. However, the increasing recognition of HIV-1 superinfection[4] raises the possibility that sexual exposure to an HIV-1-infected partner contributes to mother-to-child transmission in women who are already HIV-1-infected. The increased postnatal transmission in Petra between 3 and 6 months coincides with resumption of sexual activity in many couples. Abstinence from sex with an HIV-1-infected partner is associated with diminution of CD8 responses and increased risk of infection.[5] There is no reason why the same should not be true of superinfection.

Although Jackson and colleagues might not be able to provide evidence for or against the above hypothesis, they can still get more out of their data. For example, there is no discussion of the importance of the timing of the paediatric dose in relation to the maternal dose. Reluctance of midwives to use the HIVNET 012 regimen could partly relate to the need to tailor the timing to each woman, especially when postnatal care will be by someone on the next nursing shift. Transmission rates in the nevirapine group should also be reported according to whether a maternal dose was given within 2 h of delivery or given well before delivery.

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