Fluid management of bacterial meningitis in developing countries

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Bacterial meningitis causes more than 100,000 deaths worldwide each year in infants and young children. It is predominantly a problem in developing countries, where there is an incidence of between 38 and 110 cases each year per 100,000 of the population aged less than 5 years, and a case fatality of 22–45%.

Severe neurological sequelae occur in up to 50% of survivors. Fluid restriction in the initial management of meningitis in children has been widely advocated, but has now been challenged.

This review examines some theoretical and clinical evidence on which decisions about fluid management in bacterial meningitis could be made. There are currently no adequate controlled clinical trials to make definitive recommendations about the volume, composition, or the route of administration of fluids that could be empirically given to children with meningitis.

Hyponatraemia, fluid volume status, and antidiuretic hormone

The practice of fluid restriction is based on many reports of hyponatraemia, attributed to increased concentrations of circulating antidiuretic hormone (ADH); the so-called “syndrome of inappropriate ADH secretion” (SIADH). Over 50% of children have hyponatraemia at the time of admission, and there are relations between the degree of hyponatraemia and the presence of seizures and severity of acute disease, and the degree of hyponatraemia and adverse neurodevelopmental outcomes.

Several workers have linked these findings and the high incidence of cerebral oedema in patients who die from acute bacterial meningitis, and have suggested that inappropriately increased concentrations of ADH lead to water retention, which in turn exacerbates cerebral swelling. Some have concluded that fluid restriction will avoid exacerbating cerebral oedema and may improve neurological outcome.

The percentage of children with meningitis in whom hyponatraemia can be attributed to “inappropriately” increased concentrations of ADH is uncertain. Estimates range from 7% to 88%. This discrepancy partly reflects differences in the definitions of SIADH. In addition, the proportions of children who have fluid depletion, euvoalaemia, and hyponatraemia at the time of presentation with meningitis also varies between studies. Kaplan and Feigin, in an early report, showed that serum ADH concentrations were higher in children with bacterial meningitis than in normal controls and those with non-meningitic febrile illnesses. These workers managed their patients with fluid restriction and noted that this resulted in an increase in serum sodium and in urine output. They defined SIADH as hyponatraemia with continued renal excretion of sodium, the absence of clinical evidence of volume depletion, and an osmolarity of urine greater than that appropriate for the plasma osmolarity (that is, less than maximally dilute).

Shann and Germer estimated that almost half the children with meningitis in the highlands of Papua New Guinea had fluid overload at the time of presentation, and a similar proportion had hyponatraemia attributable to SIADH. They did not use rigid criteria for diagnosing SIADH, but speculated that in an acutely ill child who has neither excessive sodium loss nor excessive water intake, hyponatraemia is likely to be caused by water retention secondary to the increased secretion of ADH.

In support of these findings, Kumar et al found increased total body water and extracellular water in 27 of 30 children at the time of presentation with meningitis, and only one child had dehydration. The excess amount of extracellular water was negatively correlated with serum sodium and positively correlated with urine osmolarity. Kumar et al diagnosed SIADH if the serum sodium was <130 mEq/l, the serum osmolarity <280 mmol/l, the urine osmolarity more than twice the serum osmolarity, and urine sodium >30 mEq/l, in the absence of the clinical signs of dehydration. SIADH, according to these criteria, was present in 47% of children.

The series by Kanakriyeh et al from North America of 88 children with meningitis required the following for the diagnosis of SIADH: serum sodium <135 mEq/l, serum osmolarity <270 mmol/l, urine osmolarity greater than twice the serum osmolarity, and urine sodium >20 mEq/l, in the absence of the clinical signs of dehydration. SIADH, according to these criteria, was present in 47% of children.

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children based on an increase in weight from admission to discharge.

Clinical dehydration was also found in 22% of 297 children with acute bacterial meningitis in a study from Mali and Niger, but was not a significant risk factor for mortality (Varaine F et al, unpublished data). Powell et al measured ADH concentrations during bacterial meningitis and found that in children who received maintenance fluid, plus replacement of volume deficits, the high ADH concentrations normalised over 24 hours, whereas in those who were restricted to two thirds maintenance fluids ADH remained high. They concluded that ADH concentrations are increased in children with meningitis because of hypovolaemia, and only become normal when sufficient sodium and fluid are given.

Thus although it is widely accepted that hyponatraemia is a marker of severe disease in childhood bacterial meningitis, there are different opinions regarding the cause of hyponatraemia and the hydration state at the time of presentation. Interpretation of published data is difficult because of the non-standardised application of definitions of “inappropriately” increased antidiuresis and the differing methods, and imprecision, of accurately estimating hydration. In addition, there may be epidemiological reasons why the hydration state will differ from one geographical region to another, and from one patient to another.

If inappropriately increased antidiuresis is not a major factor in the pathogenesis of hyponatraemia in meningitis, then the rationale for fluid restriction is open to question. Other mechanisms for hyponatraemia have been suggested, which have different implications for approaches to fluid management. Urine sodium loss owing to the increased activity of natriuretic peptide has been implicated in several acute central nervous system disorders. Narotam et al found that in 24 patients with tuberculous meningitis and hydrocephalus there was a negative correlation between plasma atrial natriuretic peptide (ANP) and serum sodium ($r = -0.68$). In this study there were wide ranges in serum ANP concentrations, and no difference in ANP between non-meningitic control subjects (15 patients with tuberculous meningitis and hyponatraemia, and seven with meningitis and normonatraemia). So although salt wasting may be a factor in the genesis of hyponatraemia in meningitis, the current evidence is not persuasive.

### Risk of cerebral oedema induced by inappropriate fluid management

Although standard dogma has said that in treating the brain injured patient crystalloid fluid administration should be minimised to limit cerebral oedema, some evidence suggests that it is the composition of fluid given that determines the effect on the brain water content. The osmolarity of a solution is a measure of the number of solute particles per kilogram of solute, but the osmolarity of an administered solution says little about its effect on the movement of water between the intravascular and interstitial or intracellular spaces of the brain.

The tonicity of a solution is the number of osmotically active particles. An osmotically active solute cannot freely cross a semipermeable membrane such as the blood–brain barrier, therefore such a solute can produce an osmotic pressure gradient. A solution of urea, for example, will be hyperosmolar compared with plasma, but will not remain osmotically active in the brain, as urea freely crosses the blood–brain barrier. The endothelial tight junctions of the blood–brain barrier prevent the rapid distribution of intravascular sodium across the whole of the extracellular compartment. An acute increase in serum sodium by just 1 mEq/l will result in a 39 mm Hg increase in the osmotic pressure in cerebral capillaries, favouring the movement of water out of the interstitium and intracellular space. An acute decrease in serum sodium caused by the administration of a hypotonic crystalloid solution, or free water, will theoretically lead to a similar reduction in osmotic pressure in cerebral capillaries, resulting in an increase in the extravascular brain water content. Although many dextrose/saline solutions are iso-osmotic compared with plasma, the dextrose freely crosses the blood–brain barrier or is metabolised, resulting in a net hypotonic effect in the cerebral circulation. Overhydration with low sodium containing solutions has induced hyponatraemia, seizures, and cerebral oedema in young children. An infant with pneumonia given 150 ml/kg/day of 4% dextrose and 0.18% sodium chloride developed seizures and a serum sodium of 107 mEq/l.

From the above theoretical considerations it could be concluded that hyponatraemia, whether due to excessive water retention from SIADH, salt loss, or excessively administered free water, will favour an accumulation of extravascular brain water.

Does fluid restriction result in less cerebral oedema than the liberal use of isotonic fluids? This was tested in a rabbit model of *Escherichia coli* meningitis. Experimental meningitis produced an increase in brain water content compared with control subjects, but the increase was almost identical in animals given 0.9% sodium chloride solution (75 ml/kg subcutaneously at time 0 and 14 hours) and those who received no fluid. In addition, subjects not receiving fluids had a significantly higher cerebral spinal fluid (CSF) lactate and lower CSF glucose concentrations than those given isotonic saline. High CSF lactate follows anaerobic glycolysis in the brain, which may be exacerbated in meningitis by fluid restriction and the resulting reduced cerebral blood flow. This hypothesis was supported by a rabbit model of pneumococcal meningitis. Fluid restriction to 50% of normal maintenance, as has been suggested as a standard treatment for children with meningitis, may, however, be very different to giving no fluid at all. There is now abundant evidence that hyponatraemia is associated with decreased survival in traumatic brain injury. In 58 children studied prospectively and 509 studied retrospectively...
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from the US National Pediatric Trauma Registry, an episode of hypotension (defined as a systolic blood pressure less than 90 mm Hg), was associated with a fourfold increase in mortality.23 It was a recommendation of a task force from the American Association of Neurological Surgeons that, in traumatic brain injury, hypovolaemia should be avoided, and euvoalaemia maintained by adequate fluid replacement.25

Although it is arguable whether these data can be extrapolated to bacterial meningitis, there is evidence that the maintenance of an adequate cerebral perfusion pressure is also important in infective encephalopathies. Goeitein et al26 in a series of 17 children with severe meningitis or encephalitis, found that all 11 children with a minimal cerebral perfusion pressure greater than 30 mm Hg survived, whereas all those with a lower cerebral perfusion pressure died. In bacterial meningitis many potential causes of hypovolaemia, and therefore impaired cerebral perfusion, exist. These include poor fluid intake, vomiting, and the systemic inflammatory response syndrome with vasodilatation and increased capillary permeability. Some of this hypovolaemia may be minimised by increased ADH secretion and water retention, as suggested by Powell et al.8 If this compensatory mechanism leads to hyponatraemia, however, the net effect would be reduced plasma tonicity and a shift of water from cerebral capillaries into the extravascular space. Thus the maintenance of euvoalaemia with an intravenous isotonic saline solution, plus additional glucose, may be an optimum empirical management for bacterial meningitis. Hyponatraemia, hypotonicity, increases in cerebral oedema, and reductions in cerebral perfusion pressure caused by hypovolaemia may be avoided.23

By implication from data on the physiology of the normal cerebral circulation and from traumatic brain injury may be flawed for the following reasons. Firstly, in meningitis there is a generalised increase in blood–brain barrier permeability,27 rather than the focal increase that occurs at the site of a traumatic lesion. The potential beneficial effect of increases in the tonicity of plasma on water movement from extravascular to intravascular space only applies if much of the blood–brain barrier is intact.28 Secondly, although there are many potential causes of hypovolaemia in children with meningitis, the data on the frequency of this are contradictory, as explained earlier, with at least two studies from developing countries suggesting that total body water is commonly increased at the time of presentation.11 14 Normal or increased body water does not mean that the intravascular volume is adequate for the perfusion of tissues, however, it may be that although excess total body water is common in meningitis, tissue perfusion, and more specifically cerebral perfusion, is reduced. This is analogous with the situation of sepsis syndrome, where the administration of relatively large volumes of fluid are often required to achieve a stable intravascular volume and ensure adequate tissue perfusion.28

Practical issues in developing countries

There would be significant practical advantages if it were optimum to manage children with meningitis without intravenous hydration. These include saving the cost of intravenous fluid, intravascular catheters, and lines. In most developing countries the accurate titration of fluids administered is impossible because of inadequate numbers of skilled nursing staff. The risks of inadvertent overhydration may be substantial.22 On the other hand, the use of fluids given by mouth alone in children with an impaired conscious state may mean that dehydration, if present, remains uncorrected. The risks of pulmonary aspiration of orally or nasogastrically administered fluid in unconscious children should also be considered. Nasogastric hydration with breast milk would avoid the interruption of breast feeding during acute illness; however, acceptance by mothers of this mode of giving breast milk will be low in some cultures. Breast milk, although iso-osmotic, is hypotonic with plasma, and contains low concentrations of sodium (1.0–1.5 mEq per 70 ml29). If breast milk is given as the sole means of hydration in patients who already have high ADH concentrations or a mechanism for renal salt loss, serum sodium may be further reduced; however, this remains untested.

Trials of fluid restriction and liberal fluid administration in meningitis

There are three separate papers comparing different fluid regimens in children with bacterial meningitis. Shann5 analysed the results from three studies in Papua New Guinea where either intravenous antibiotics and fluids, or intramuscular antibiotics and fluids by mouth, were given. There was a 50% lower mortality in the children receiving intramuscular antibiotics and fluids by mouth. He concluded that bacterial meningitis can be treated in all but the rare circumstance of shock with restricted breast milk given by mouth only. This conclusion, however, was based on a combination of two retrospective trials and part of a prospective study, of which the predetermined aim was to evaluate antibiotic regimens, not fluid management.

Powell et al studied the effect of different fluid regimens on ADH concentrations in a randomised controlled trial.8 Nineteen children were either fluid restricted to two thirds of the calculated maintenance, or given maintenance fluid plus an estimated deficit replacement (a mean of 140 ml/kg/day). The plasma ADH concentration was significantly lower after 24 hours of maintenance plus deficit fluids compared with the group receiving restricted fluids. These workers concluded that serum ADH concentrations are increased because of hypovolaemia and that patients with meningitis should be given maintenance plus replacement fluids. There was no clinical end point to this small study.

The only prospective randomised trial of fluid restriction versus maintenance fluids with a clinical end point was carried out by Singhi et al in India.7 Although increased extracellular
water at presentation was associated with a poor outcome, children who had a reduction in extracellular water of > 10% induced by fluid restriction for the first 48 hours had a higher mortality than those who received normal maintenance fluids (p < 0.05). The difference was found in this retrospectively identified subset. There was no significant difference in mortality or neurological sequelae between groups when the fluid regimen actually given (restricted versus normal maintenance), rather than the effect on extracellular water, was analysed. They concluded that the excess extracellular water, increased plasma ADH, and mild systemic hypertension in the presence of increased intracranial pressure are part of the compensatory mechanisms to maintain cerebral perfusion in severe meningitis. Therefore efforts to reduce excess extracellular water by fluid restriction may adversely affect cerebral perfusion. This trial was stopped prematurely before there was a large enough sample size to assess the predetermined clinically important outcome, so the conclusions are premature. There was, however, a trend towards lower mortality in the group receiving full maintenance fluids.

Conclusions and the argument for a controlled trial

Despite many descriptive clinical studies and years of research into the mechanisms of fluid and electrolyte changes in meningitis, there is still insufficient data to make recommendations about the empirical fluid management of children with bacterial meningitis. We do not know the volumes of fluid that should be administered, if intravenous fluids are optimum, or whether nasogastric fluids are adequate. Evidence from other brain injuries suggests that hypotonaemic solutions exacerbate cerebral oedema. We do not know, however, if isonotic intravenous fluids in children with impaired blood-brain barrier permeability will result in the maintenance of adequate cerebral perfusion and improve outcome, or lead to increased cerebral oedema and a worse outcome. It may be that the recommendation for fluid restriction was based on an incomplete understanding of the pathophysiology of hypotonaemia and cerebral oedema in meningitis; however, it is also a pragmatic policy reflecting what is possible in most developing countries. For another policy of fluid management to be recommended there would have to be proved improvements in clinically important outcomes at an affordable cost.

A randomised clinical trial would be justified under the following circumstances: if the answers to this simple management question could not come from existing data; if there was a real dichotomy of opinion regarding appropriate management; and if one or the other strategy of management was likely to make a difference to clinically important outcomes. The evidence that either fluid restriction to limited intake by mouth alone, or intravenous fluids given at maintenance rates, may make a real difference to mortality is provided by the respective opposing findings of Shann and coworkers and Singhi et al, each of whom showed a trend towards mortality differences, but in studies with low power and other methodological flaws. To assess the true effect of the two types of current practice a randomised trial of fluid restriction vs full maintenance fluids is required. The study must have adequate power to consider important clinical outcomes.

We propose a randomised trial of two fluid regimens for the first 48 hours of treatment: (1) fluid restriction using breast milk alone (or expressed breast milk at 60% of normal maintenance volumes, given by nasogastric tube in the unconscious child); (2) 100% of normal maintenance volumes with intravenous or nasogastrically administered half normal saline plus 5% dextrose plus 10 mmol/l KCl, plus breast milk if the child is not deeply unconscious or fitting. Mortality and severe neurological sequelae should be the principal outcome measures.

Other issues that require further study are: the role of hypertonic saline solutions; enteral hydration with high (90 mmol/l) sodium containing rehydration solution given by mouth, as a less expensive, practical alternative to intravenous fluid in developing countries; and the contribution of hypoglycaemia to seizures and mortality in young infants with meningitis.