

What is the most appropriate fluid therapy for acute bacterial meningitis for children in developing countries?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at: http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *What is the most appropriate fluid therapy for acute bacterial meningitis for children in developing countries?*

The **WHO Pocketbook of Hospital Care for Children** recommends that there is no good evidence to support fluid restriction in children with bacterial meningitis, and to give them their daily fluid requirement but not more because of the risk of cerebral oedema. IV fluids should be monitored very carefully and examination for signs of fluid overload performed regularly. (Pocketbook chapter 6.3, page 152).

Introduction:

Acute bacterial meningitis is a major cause of paediatric morbidity and mortality in the developing world. Early recognition and prompt and adequate antimicrobial and supportive therapy can improve the chances of survival. Bacterial meningitis is an infection of the fluid in the spinal cord and surrounding the brain. The secondary symptoms of brain swelling and shock require treatment with medications and intravenous fluids, though the volume of fluid administered is a matter for debate - both under or over hydration may result in serious neurological sequelae.

Over 50% of meningitic children are reported to have hyponatraemia (lower than normal concentration of sodium in the blood /

extracellular fluid) on admission attributed to an increased concentration of circulating antidiuretic hormone (ADH) [1]. It is promulgated that this ADH secretion works to maintain intravascular volumes by reducing kidney water excretion, ensuring adequate cerebral perfusion and preventing ischaemia [2], but resulting in a dilutional hyponatraemia. This water retention may exacerbate cerebral oedema, which has been associated with the presence of seizures, herniation and adverse neurodevelopmental outcomes [3,4,5,6,7]. Consequently, some researchers advocate fluid restriction in acute bacterial meningitis to avoid exacerbating cerebral oedema and improve neurological outcome [3,5,8].

Other studies have found clinical dehydration present in children admitted with meningitis [9,10]. The physiological response of ADH secretion helps conserve fluid and combat dehydration, however dehydration itself results in hyponatraemia. If dehydration is the cause of hyponatraemia, this questions the rationale of fluid restriction. Furthermore, children receiving maintenance fluid plus replacement of volume deficits had normalised ADH levels within 24 hours, whereas those restricted to two-thirds maintenance fluids ADH concentrations remained high [9]. Hence the high ADH levels may be due to hypovolaemia, and can be rectified when sufficient sodium and fluid are administered.

Though widely accepted that hyponatraemia is linked to the severity of childhood meningitis, there is controversy as to the cause of this imbalance. The current management of fluid restriction is questionable should dehydration rather than inappropriate secretion of ADH be the major factor in the pathogenesis of meningitic hyponatraemia. This current review attempts to evaluate treatment of acute bacterial meningitis with differing volumes of fluid administration with regards to clinical outcomes.

Methodology

The MeSH terms ‘meningitis’ and ‘infusions, intravenous’ were utilised, as were the free text terms ‘fluid restriction’, ‘fluid therapy’ and ‘fluid maintenance’.

Initially, the Cochrane Library was searched with the simple search strategy ‘meningitis and fluid’. 59 Cochrane Reviews were retrieved, of which one looked specifically at fluid therapy for acute bacterial meningitis [11]. The Cochrane Central Register for Controlled Trials (CENTRAL) was searched concurrently.

The PubMed ‘Clinical Queries’ framework was utilised to search for more recent studies on fluid therapy for acute bacterial meningitis. The search strategy employed was as follows: (meningitis AND fluid restriction) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])). Clinical filters for both ‘therapy’ and ‘narrow, specific’ were used, and no new relevant papers were identified. MEDLINE and EMBASE were searched using a similar strategy, yielding no new papers. Articles were restricted to the English language. When searching on PubMed, papers older than the most recent update to the Cochrane Review were excluded to prevent duplication of findings. Methodological quality of selected articles was assessed using the Oxford Centre for Evidence-Based Medicine Levels of Evidence.

The recommendations have been summarised below.

Results

The evidence behind treatment of acute bacterial meningitis with differing volumes of initial fluid administration was the topic of a Cochrane Review last updated in August 2005 [11]. This systematic review was evidence level 1a, and identified three trials eligible for inclusion examining a total of 415 infants [9,12,13]. Data were combined using meta-analysis using relative risks for the dichotomous data or weighted mean difference for continuous data. A fixed-effect statistical model was used as there was no significant heterogeneity.

The meta-analysis of the three studies for death found no significant difference between deaths in the maintenance and fluid-restricted groups (RR 0.82, 95% CI 0.53 to 1.27). One study reported

no fatalities [9]. One study subdivided groups into children with or without hyponatraemia, finding no significant difference in death rates between the groups [13].

No significant difference was found on meta-analysis between the maintenance-fluid and fluid-restricted groups in acute severe neurological sequelae (2 studies, 407 children: RR 0.67, 95% CI 0.42 to 1.08) or in mild to moderate sequelae (1 study, 357 children: RR 1.24, 95% CI 0.58 to 2.65). No significant difference in acute neurological sequelae was found between those children with or without hyponatraemia. On further specification of neurological sequelae, a statistically significant difference in favour of the maintenance-fluid group was found in regard to spasticity (1 study, 357 children: RR 0.50, 95% CI 0.27 to 0.93), seizures at both 72 hours (1 study, 357 children: RR 0.59, 95% CI 0.42 to 0.83) and 14 days (RR 0.19, 95% CI 0.04 to 0.88) and chronic severe neurological sequelae at 3 months follow up (1 study, 351 children: RR 0.42, 95% CI 0.20 to 0.89) [11].

Discussion

The Cochrane Review only identified three eligible studies and found no statistically significant difference in mortality from restricting fluids [11]. Of the two studies reporting neurological sequelae, meta-analysis demonstrated statistically significant reductions in the rates of early spasticity and seizures, and later overall neurological sequelae in children receiving maintenance fluids rather than fluid-restriction. No overall statistical differences were seen in overall short-term neurological sequelae, risk of hemiparesis, visual or hearing impairment. Two of the studies in the Cochrane Review were small using children from single centres [9,13], and thus the far larger Duke et al [12] study dominates morbidity and mortality. The long delays before presentation and a high prevalence of malnutrition may be implicated in the high rate of dehydration at presentation, and thus inadequate fluid treatment of dehydration may explain the higher rate of neurological sequelae in the fluid-restricted group.

Summary

This review has found some evidence favouring intravenous fluid maintenance volumes rather than restricted fluid intake for the treatment of

acute bacterial meningitis. This should be within the first 48 hours, and applies to settings where patients present late and there is a high mortality rate. Where children present early and mortality rates are lower, there is insufficient evidence to guide practice. Further large, good-quality studies need to be performed in these fields, preferably in a multi-centre randomised controlled trial. Ideally, fluid regimes should be tailored to the individual patient whilst monitoring for signs of fluid overload or dehydration.

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