Witness Statement Ref. No. 178/2

NAME OF CHILD: Claire Roberts

Name: Ian Young

Title: Professor

Present position and institution:

Professor of Medicine and Director of The Centre for Public Health, Queen's University Belfast

Previous position and institution:
[As at the time of the child's death]

Membership of Advisory Panels and Committees:
[Identify by date and title all of those between January 1995-August 2012]

Previous Statements, Depositions and Reports:
[Identify by date and title all those made in relation to the child's death]

OFFICIAL USE:
List of previous statements, depositions and reports attached:

Ref:	Date:	
096-007-039		Statement to the PSNI
091-010-060	4th May 2006	Deposition to the Coroner
WS-178/1	14th Sep 2012	Inquiry Witness Statement

Response to reports of Dr.R MacFaul on Claire Roberts

Professor Ian S.Young

The purpose of this report is to respond to incorrect statements made by Dr MacFaul in relation to fluid management of Claire in 1996, which subsequently translate through to criticisms of the information given to Claire's parents in 2004. I wish to highlight major factual errors in his original report, repeated throughout, which he corrects inadequately and to a limited extent in his supplementary report. Despite this limited correction, Dr MacFaul fails to withdraw criticisms based on the major factual errors which he has made.

Factual errors in Dr.MacFaul's report:

Throughout his report Dr MacFaul repeatedly refers to the following information from the major paediatric textbook (Forfar and Arneil) in support of his statements and criticisms. This first occurs at **238-002-044** and the text in bold is then cited repeatedly in the remainder of his report:

"206. The management of coma and encephalopathy relevant to the time has been included in the Advanced Paediatric Life-Support curriculum and its associated manuals. One important example is from the standard Textbook widely used in United Kingdom containing advice which would have been relevant and updated by the mid-1990s. Textbook of Paediatrics. Forfar & Arneil Third edition 1984 Page 791 et seq. which includes :

b. ***In many cases treatment of cerebral oedema is required to be presumptive. Fluid should be restricted to 60% of estimated daily requirements; low sodium containing infusions like 5% dextrose or 0.18% saline in 5% dextrose are contraindicated……"***

At the time of Claire's treatment, the 1984 third edition of Forfar and Arneil was 12 years old. In many respects it was completely out of date and had been replaced by the fourth edition of the textbook, published in 1992 and reprinted in both 1994 and again in 1996. The section of the textbook which Dr MacFaul relies on and reproduces in annex A of his report had been re-written. The sentences highlighted above in bold by Dr MacFaul and referred to repeatedly throughout his report had been completely removed from the updated edition of the textbook and no comparable sentences or warnings are to be found.

I am astounded that someone appointed to provide expert advice to a major enquiry of this importance would rely for a key aspect of his report on a 12-year-old textbook which had been out of date for at least four years before the critical period and would then proceed to criticise aspects of management and information provided on this basis. Any doctor providing treatment based on a recommendation in an out of date textbook, subsequently removed in the current edition, would, in my opinion, be subject to severe criticism.

I include as an attachment the relevant pages from the fourth edition of the textbook (1996 reprint) which was the current edition at the time of Claire's admission (page 771-778). These pages are completely different to the 1984 edition pages cited and used by Dr.MacFaul. The 1996 edition (valid since 1992) makes no reference to the need to restrict intravenous fluids in the management of encephalopathy or to the need to avoid 0.18% saline.

In addition I attach a key section from earlier in the textbook (479-480) dealing with the syndrome of low sodium and water intoxication, including the syndrome of inappropriate antidiuretic hormone secretion, which does not mention encephalopathy at all.

The inquiry throughout has been keen to establish the knowledge which various doctors had of Forfar & Arneil and clearly views this as an authoritative source reflecting current practice in paediatric management at the time of Claire's admission. It is therefore crucial that there is no suggestion from 1992 onwards that fluid should be restricted to

60% of daily requirements or that 0.18% saline in 5% dextrose in contraindicated in this setting. Sections of Dr MacFaul's report which state this and the criticisms which flow from his incorrect citation of an out of date textbook are simply wrong and should be corrected or withdrawn.

Dr MacFaul addresses his error in a very incomplete way in his supplementary report: "wording as specific and direct as in the 1984 textbook has not appeared in publications since then". However, this correction is totally inadequate. The truth is that words to this effect are completely absent from the 1996 contemporary edition of Forfar & Arneil. They have been removed and nothing comparable is included.

In reality, in 1996 there simply was not any general or widespread understanding that there was a routine need to restrict fluid intake in encephalopathy and to use fluid with a higher sodium content than 0.18%. Dr Scott-Jupp comments at **234-002-012** "As late as 2003 standard paediatric textbooks and pocket handbooks in both the UK and the US were still recommending hypotonic saline (0.18% or 0.25%) as a possible choice of standard IV fluid management." There may have been occasional units (such as Dr MacFaul's own) where this formed part of a local protocol. However, this guidance was not part of the recommended treatment in major textbooks of the time having, in the case of Forfar & Arneil, been removed as a recommendation in 1992.

At **238-002-044** Dr.MacFaul indicates that the Pinderfields' protocol had been in use since the middle of the 1980s. Therefore, this may have been drawn up based on the 1984 edition of Forfar and Arneil, and not modified following the publication of the 1992 edition of the textbook. Indeed, it seems that until recently Dr.MacFaul was simply unaware of contemporary guidance on management in 1996 as stated in the textbook, since this has only been drawn to his attention after he compiled his initial report.

Dr MacFaul at **238-002-090** comments "Neither of the Coroner's experts seem aware of guidance on fluid management of acute encephalopathy which related to 1996 and before aiming to prevent hyponatraemia". At **238-002-086** he comments **"**Prof Young does not

seem aware of guidance on fluid management of acute encephalopathy which related to 1996 and before.“ However, the guidance to which Dr.MacFaul refers related to an out of date textbook. As stated by Dr.Bingham (Great Ormond Street) to the Coroner in 2005 and recorded at **238-002-090** in reference to the initial intravenous fluids provided to Claire: “This is a fluid prescription was in line with the practice of the time and although current guidance would be to use fluid with a higher sodium content in this situation this advice did not exist in 1996." The person who was unaware of guidance on fluid management of acute encephalopathy which related to 1996 is Dr.MacFaul.

As indicated by Dr MacFaul in his supplementary report, by 2001 there was some recognition of the problem of hypotonic fluids in contributing to cerebral oedema which was beginning to gain more widespread traction. MacFaul refers to *Kirkham FJ.Non-traumatic coma in children. Arch Dis Child 2001;85:303-312,* where it was stated that hyposmolar fluids such as 5 % dextrose are contra-indicated, although even then it did not specifically highlight hypotonic fluids (0.18 % saline in 4 % dextrose is hypotonic not hyposmolar). However, this is five years after Claire’s hospital admission and does not represent relevant contemporary evidence, which is considered below.

Guidance on fluid management before and after 1996:

The purpose of this section is to indicate with reference to contemporary literature the level of awareness of hyponatraemia and its management before 1996 and up to 2004.

Arieff et al. in the BMJ in 1992 described 16 cases of hyponatraemia in children undergoing surgery, 15 fatal (BMJ 1992;304:1218-22). This was not the first description of fatal hyponatraemia in children, but was the first paper which may have been noticed by a wide readership as it was published by a significant UK journal. They concluded that “*The hyponatraemia in these children seems to have been caused by extensive extrarenal loss of electrolyte containing fluids and intravenous replacement with hypotonic fluids in the presence of antidiuretic hormone activity*”. This was undoubtedly a key observation, though not of direct relevance to the management of Claire Roberts, but a considerable period elapsed before this significantly influenced routine practice, as demonstrated below.

Arieff went on to publish a review of the management of hyponatraemia in 1993

(BMJ1993;307:305-8). This review again highlighted the increased risk of hyponatraemic brain damage in children, and indicated the following contributory factors: *"Recent evidence suggests that contributory factors to hyponatraemic brain injury may also include (a) systemic hypoxaemia; (b) a direct vasoconstrictive effect of antidiuretic hormone on cerebral blood vessels; (c) female sex; (d) physical factors; and (e) pre-existing liver disease, alcoholism, or structural lesions in the central nervous system."* The only caution given against the use of hypotonic fluids relates to the post-operative period, and there was no mention of the need to restrict hypotonic fluids in other settings such as encephalitis/encephalopathy.

This remained the most commonly articulated position about at risk patients over the next few years. In 1997 Fraser and Arieff published a further review of epidemiology, pathophysiology and management of hyponatraemia encephalopathy in the American Journal of Medicine (Am J Med. 1997;102:67–77) where they state: *"Clinical evidence suggests that the vast majority of brain damage from hyponatremia is associated with untreated hyponatremic encephalopathy, and occurs primarily in a limited number of clinical settings. These include (a) the postoperative state, (b) polydipsia-hyponatremia syndrome, (c) pharmacologic agents, (d) congestive heart failure,and (e) adult immunodeficiency syndrome (AIDS)."* Again, there is no mention of particular risk in the presence of unspecified encephalopathy or of the need to restrict hypotonic fluids in this setting.

In 1999 Bhalla et al. published a report from Liverpool under the heading "Lesson of the week" in the British Medical Journal entitled "Hyponatraemic seizures and excessive intake of hypotonic fluids in young children" (*BMJ* 1999;319:1554–7). In their introduction they highlight the fact that *"Afebrile seizures caused by hyponatraemia associated with excessive intake of hypotonic fluids was first reported in 1967. This is a common problem in the United States,but it has rarely been reported in the United Kingdom."* In each of the four cases, the excessive intake of hypotonic fluids was via the oral route and when a seizure developed initial treatment was by fluid restriction alone. In their discussion they comment *"There is controversy about management"* and

"For more difficult cases, opinions differ on whether to give physiological (sodium 150 mmol/l) or 3% hypertonic (sodium 513 mmol/l) saline."

In 2001 a further "Lesson of the Week" was published in the British Medical Journal entitled "Acute hyponatraemia in children admitted to hospital:retrospective analysis of factors contributing to its development and resolution", indicating a continuing need to address the problem (*BMJ* 2001;322:780–2). The authors (from Toronto) highlight *"23 patients in the study group. The median age was five years (range one month to 21 years), with males predominating (18 of 23); 13 developed hyponatraemia in the postoperative period. Fifteen patients were referred to the critical care unit after the development of symptomatic hyponatraemia while receiving intravenous fluids—11 were from the hospital wards and four were transferred from other institutions."* Five of these children died and one suffered severe brain damage. All the children had received hypotonic fluids while their plasma sodium concentration was less than 140 mmol/l, *"because of the wide belief in paediatric practice that "maintenance fluids" should be hypotonic."* In this paper the authors, in contrast to earlier publications highlighted above, identify as a risk factor *"Disturbances of the central nervous system (meningitis, encephalitis)".* In their conclusion they recommend *"The currently used guidelines for maintenance fluids in children admitted to hospital must be changed because they do not take into account the unpredictability of vasopressin secretion"* highlighting the fact that in 2001 use of hypotonic fluids remained routine even in acutely unwell children with encephalitis.

Kirkham review non-traumatic coma in children in *Arch Dis Child* 2001;**85**:303–312. Addressing the use of intravenous fluids Kirkham says the following: *"salt wasting is an important association with conditions such as meningitis; initial fluid therapy should aim to slowly replace salt and water losses as well as maintain adequate nutrition. Resuscitation and maintenance of systemic homoeostasis are the priorities in the acute situation and there is no case for fluid restriction; however hypo-osmolar fluids such as 5 or 10% dextrose are contraindicated because of the risk of delayed cerebral oedema."* Kirkham then goes on: *"Fluid management can be very difficult and should*

be tailored for the individual patient's needs. There is considerable controversy over fluid restriction, which has been shown to be potentially harmful in patients with subarachnoid haemorrhage and meningitis. The syndrome of inappropriate secretion of ADH, for which fluid restriction is indicated, is relatively rare; instead cranial diabetes insipidus may require careful management. It is essential that the systemic circulation is well filled and that large volumes of hypo-osmolar fluids are not given." There is no suggestion that fluids should be routinely restricted to 60% of daily requirements or that the use of 0.18% saline in 5% dextrose is prohibited.

Also writing in 2001, Albanese et al. discussed Management of hyponatraemia in patients with acute cerebral insults (*Arch Dis Child* 2001;**85**:246–251). Their main focus was on distinguishing syndrome of inappropriate ADH production from cerebral salt wasting. However, of note there was no recommendation to routinely restrict fluids or avoid 0.18% saline in 5% dextrose.

In 2004, Hoorn et al. from Toronto reported a retrospective review of all children presenting to an emergency department over a three-month period in a major teaching hospital (*Pediatrics* 2004;113:1279 –1284): "Acute Hyponatremia Related to Intravenous Fluid Administration in Hospitalized Children: An Observational Study". They identified 96 patients who were hyponatremic on presentation, but focussed on 40 patients who developed hyponatremia in hospital. One died and two suffered major neurological sequelae in this three month period. They identify patients with encephalitis as at risk group, but reference this to papers published in 1999 and 2001. They identify a clear need for a change in practice in terms of routine fluid use*: "We believe that hospital acquired hyponatremia unnecessarily puts children at risk for the development of adverse neurologic events and is largely preventable. We suggest that the current recommendations for intravenous fluid therapy in hospitalized children be revised. Hypotonic fluids should not be used routinely in the intraoperative or postoperative period or when a patient has a PNa in the low-normal or distinctly hyponatremic range (<138 mmol/L)."*

In an accompanying editorial, indicating that the issue was now being seen as an important one, Moritz and Ayus argued that 0.9% saline should be used in maintenance fluids routinely to prevent avoidable deaths in hospitalised children (Hospital acquired hyponatraemia: why are there still deaths? *Pediatrics* 2004;113;1395).

The first systematic review of evidence related to routine use of hypotonic versus isotonic fluids in children was published by Choong et al. in Arch Dis Child 2006;91:828–835. They identified a limited amount of evidence but their conclusions were important, given the priority assigned to the evidence from systematic reviews rather than observational studies: *"The current practice of prescribing IV maintenance fluids in children is based on limited clinical experimental evidence from poorly and differently designed studies, where bias could possibly raise doubt about the results. They do not provide evidence for optimal fluid and electrolyte homoeostasis in hospitalised children. This systematic review indicates potential harm with hypotonic solutions in children, which can be anticipated and avoided with isotonic solutions. No single fluid rate or composition is ideal for all children. However, isotonic or near-isotonic solutions may be more physiological, and therefore a safer choice in the acute phase of illness and perioperative period."*

However, routine use of normal saline as a maintenance fluid remained controversial. Holliday et al. discussed the issue in Arch Dis Child 2007;92:546–550. Under the title "Fluid therapy for children: facts, fashions and questions" – *"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."*

Auditing practice in 2007 in Glasgow prior to the NPSA alert, Snaith et al. (Pediatric Anesthesia 2008 18: 940–946) reviewed 100 appendectomy patients between February

2004 and March 2007. No patient had daily plasma electrolyte measurements whilst administered i.v. fluid. Twenty-seven patients had recorded hyponatremia ([Na] <135 mmol/l); 21 at presentation, six subsequently after admission). Hypotonic maintenance fluid was continued in 26/27 patients with hyponatremia, indicating continuing lack of awareness of how to manage hyponatraemia in the UK in this era.

In summary, therefore, it is clear that widespread variation in practice in relation to fluid management in children persisted between 1996 and the NPSA safety alert in 2007. There was, however, increasing recognition of the dangers of the routine use of hypotonic fluids for maintenance over this period and it is likely that in some areas, as in Northern Ireland, practice began to change.

Response to criticisms made by Dr.MacFaul of information provided to Claire's parents in 2004:

I would therefore like to deal with the specific criticisms which Dr MacFaul makes in relation to the information provided to Claire's parents in 2004. Many of these criticisms flow from his earlier error highlighted above, acknowledged to a limited extent in his supplementary report, and therefore having no basis in fact.

"354. From the notes of the meeting incorrect information was given to the parents

as follows.

355. "Treatment today differs from that used eight years ago".

356. This is not correct in that the treatment of acute encephalopathy in terms of

fluid management and in particular in selection of the sodium content of the fluid did

not differ in 2004 from 1996."

As discussed above, there was no recommendation which was widely understood or

included in major textbooks current in 1996 to use fluid with a higher sodium content than 0.18%. A number of other experts reviewing the case for the coroner and inquiry have not challenged the initial choice of fluid therapy.

Indeed, at **238-002-034** Dr.MacFaul admits himself that even more recently there was not general recognition of a requirement for fluid restriction in encephalopathy: “it is of note that guidance published in 2006 on management of children with reduced level of consciousness, endorsed by the RCPH and used as a basis of multi site audit reported in 2011, does not address the issue of IV fluid to be used.”

By 2004 recommendations with regard to routine fluids had been made, and these had been implemented in the Children’s Hospital. Therefore, information given to Claire’s parents was correct in 2004 and Dr MacFaul’s criticism is not valid.

This is confirmed by Professor Neville in his expert report at **232-002-008**, commenting on the nature and volume of intravenous fluids prescribed in 1996 “What was given was routine, but should have been carefully monitored in the circumstances” compared with the current time “Now I think a higher sodium content and fluid restriction would be routine”.

Furthermore, at **234-002-002** Dr. Scott-Jupp says, in relation to the choice of intravenous fluids for Claire, “The IV fluid given was 0.18% Sodium Chloride in 4% Dextrose. This was absolutely the standard IV fluid given to most children needing fluids for any reason in 1996. This policy has changed over the last few years. Although now policy is universally to give either 0.45% or 0.9% Sodium Chloride, there would have been no reason in these circumstances to have deviated from the normal policy. Even when the results of the electrolytes were available and the low sodium of 132 was noted, I believe at the time most practitioners would have continued with 0.18% Saline. The quantity prescribed was 65mls per kg per 24 hours. I believe that this was appropriate as at the time there was no particular reason to impose fluid restriction as a means of preventing Cerebral Oedema.”

"357. "The doctor gave her standard fluid intravenously-which is the textbook recommendation".

358. I have provided the information in relation to fluid management in acute encephalopathy. The textbook recommendation is not to use 0.18% saline. Consequently the statement is incorrect."

As discussed above, Dr MacFaul has provided incorrect and out of date information in his report. This has resulted in significant criticism which is completely unwarranted. His statement in 358 is simply wrong. It needs to be withdrawn.

"359. "… With the sodium level at 121, the doctor had responded appropriately."

360. This is not correct. The correct action was to change the sodium level of the intravenous fluid and to reduce the rate of infusion. Neither was done."

In his original report at **238-002-036** Dr.MacFaul quotes the Paediatric Vade Mecum. I wish to highlight the following sections describing the treatment of hyponatraemia and extracted from that page of his report:

Treatment In an acutely ill child with Na^+ <125 mmol/L and:
inappropriate ADH secretion – restrict fluids ± diuretics;
congenital adrenal hyperplasia – *see* page 31;
renal tubular acidosis – replace fluids initially with 0·9 per cent saline i.v. and then orally with electrolyte mixture.

When Na^+ <120 mmol/L and the child is symptomatic (pale and hypotensive, with falling urinary output, but well hydrated), 30 per cent NaCl injection BP (5000 mmol/L of Na^+) can be infused initially to replace *half* the estimated Na^+ deficit over 4–6 hours. Then repeat plasma electrolytes and recalculate needs. For the composition of solutions for intravenous use, *see* Table 2.4 page 17.

The relevant section from Forfar & Arneil (page 480) simply states in relation to SIADH:

"Treatment of this condition involves water restriction.....". There is no reference to any need to change the sodium level of the intravenous fluid.

There was certainly a body of contemporary literature which supported the use of hypertonic saline in hyponatraemia associated with significant neurological symptoms. However, this is not reflected in the contemporary edition of Forfar and Arneil and the Paediatric Vade Mecum referenced by Dr MacFaul, which recommends hypertonic saline only in a symptomatic child with serum sodium of < 120 mmol/l.. Where hyponatraemia is not believed to be the cause of clinical symptoms, then treatment by fluid restriction and management of the underlying cause was the contemporary recommendation which remains the recommendation today.

In light of this information, it is clear that, as indicated to Claire's parents, an appropriate response was made in terms of fluid restriction. The doctors made a judgement that her neurological symptoms were attributable to status epilepticus or encephalitis/encephalopathy rather than to hyponatraemia. In this case, fluid restriction was an appropriate response and in line with the recommendations highlighted above. I accept that while intake of intravenous 0.18% saline was appropriately reduced, due to the administration of other drugs additional 0.9% saline was given, meaning that the overall fluid restriction was not as great as intended. This was not fully recognised at the time of the meeting with Claire's parents.

"361. Prof Young confirmed that Claire's sodium level had not been monitored

between arriving at the hospital and 24 hours later but stated this was not unusual at

the time. This is also incorrect in the sense that it is usual to repeat blood sample if

one has been found abnormal generally but in a child with persistent reduction of

the

level of consciousness, it was essential to monitor the blood sodium level the following morning or at latest when the paediatric neurologist reviewed when further

investigations should have been carried out."

There is no doubt that in 1996 it was unusual to carry out repeat blood samples more often than once per day outside of an intensive care setting. However, I agree and have said elsewhere that Claire's sodium should have been checked during the day following her admission to hospital.

Forfar & Arneil in 1996 recommended that urea and electrolytes should be checked twice per day in the setting of encephalopathy. This was not part of routine practice in the Children's Hospital in 1996 and this was the information which was conveyed to Claire's parents. Furthermore, the Pindersfield Hospital Paediatric Unit Protocol (1999) for Coma and Acute Encephalopathy provided by Dr.MacFaul at **238-002-166** does not specify any frequency for monitoring of urea and electrolytes. In addition, this requirement has not to my knowledge been highlighted by the other expert witnesses in this case. I am therefore extremely doubtful that this could be described as a routine standard of care at that time, and certainly that would have been my opinion at the time of my meeting with Claire's parents.

Dr.MacFaul himself cites the following at **238-002-039: "**In a survey of 17 hospitals in 2004 on Hyponatraemia in children on IV fluids serum electrolytes had been measured in the preceding 24h for only 54% and between 24 and 48 h earlier in an additional 25 % of children. (*Armon K et al Arch Dis Child 2008;93:285-287*)." This clearly indicates that monitoring of electrolytes was not routinely done in children with hyponatraemia as recently as 2004.

Dr.Scott-Jupp in his expert report says the following at **234-002-003** "standard practice

at that time was to check serum electrolytes on children receiving IV fluid as a routine only once every 24 hours. Even now, following the National Patient Safety Authority (NPSA) alert about the use of hypotonic IV fluids in children which was issued in 2007, the advice is to check electrolytes four to six hourly only if the serum sodium level is below 130".

"362. It was stated that Claire's CNS observations had remained stable over a period of time and no clinical signs of further deterioration were noted. This is not correct, the GCS reduced over the evening and had done so by the time the blood sodium level was available"

Between 3pm on 22/10 and 2am on 23/10 Claire's GCS score remained between 6 and 8 with no consistent pattern of deterioration. It was in this context that the above statement was made and I would hold that this remains correct when the overall pattern of results is considered, in particular given the known significant inter-observer variability using the GCS.

"363. In a letter from Ms Rooney responding on behalf of the Trust to parents further requests after the meeting, (dated 12/1/2005) further incorrect statements were made as follows

"364. The letter reiterated that treatment has now changed (it has not for acute encephalopathy in respect of fluid volume and sodium content)."

As discussed above, this point is simply wrong and reflects Dr. MacFaul's inppropriate citation of out-of-date evidence. It should be withdrawn.

Professor IS Young

30/10/11

PERSONAL PRACTICE

Management of hyponatraemia in patients with acute cerebral insults

A Albanese, P Hindmarsh, R Stanhope

Abstract
Hyponatraemia is a common finding in patients with acute cerebral insults. The main differential diagnosis is between syndrome of inappropriate ADH secretion and cerebral salt wasting. Our aim is to review the topic of hyponatraemia in patients with acute cerebral insults and suggest a clinical approach to diagnosis and management.
(*Arch Dis Child* 2001;**85**:246–251)

Keywords: hyponatraemia; SIADH; cerebral salt wasting; diabetes insipidus

Hyponatraemia is a common finding in patients with acute cerebral insults, especially after neurosurgical procedures for hypothalamic-pituitary tumours. It can be associated with the syndrome of inappropriate ADH secretion (SIADH), cerebral salt wasting (CSW), treatment of transient/permanent diabetes insipidus (DI), and excessive fluid administration in patients with adipsia. These conditions may occur in isolation or may coexist. For instance, after neurosurgical procedures involving the hypothalamic-pituitary area, an initial transient DI phase can be followed by transient remission or excessive SIADH and then followed by permanent DI. The initial treatment of DI with desmopressin (vasopressin analogue) can be challenging and hyponatraemia may occur either following an excessive dose of desmopressin or during an SIADH phase.

Impairment of thirst can arise following the destruction of hypothalamic osmoreceptors, and its coexistence with DI makes the fluid management extremely complex. In these circumstances avoidance of wide swings in serum sodium concentration can be challenging, even when high expertise among medical and nursing staff is available. CSW is another cause of hyponatraemia, which can be difficult to differentiate from SIADH. It has been proposed that CSW represents the commonest cause of hyponatraemia in neurosurgical patients.[1 2] It can also coexist with DI and in this case the excessive polyuria secondary to natriuresis can be easily misinterpreted as poor control of DI. An increase in desmopressin dose will only cause a further deterioration in the degree of hyponatraemia. Overall, a clear understanding of the underlying cause of hyponatraemia is required so that the appropriate therapeutic approach can be taken.

The aim of this review is to clarify the different pathogenic mechanisms responsible for hyponatraemia in patients with cerebral insults, in particular after neurosurgical procedures involving the hypothalamic area, to raise the level of awareness of CSW and to suggest a practical approach to the diagnosis and treatment of hyponatraemia in this cohort of patients. Finally, we describe an adipsic child with a hypothalamic brain tumour who developed DI and intermittent CSW to illustrate the practical difficulties encountered in the management of hyponatraemia and fluid balance.

Background

DIABETES INSIPIDUS

Central DI[3] is caused by a deficiency of antidiuretic hormone (ADH), caused by destruction or degeneration of the neurones that originate in the supraoptic and paraventricular nuclei of the hypothalamus. Hypothalamic tumours (craniopharyngioma and germinoma) represent the commonest causes of DI in childhood, followed by Langerhans' cell histiocytosis or other infiltrative processes such as leukaemia, lymphoma, and sarcoidosis. DI is caused by the destructive lesion, or more often the neurosurgery for removal of the hypothalamic-pituitary tumour. Postsurgery a triple response is also described and it is characterised by initial DI followed, after 4–8 days, by a transient remission or excessive release of ADH lasting 1–14 days and then reoccurrence of often permanent DI. Cerebral insults resulting from head trauma or hypoxic brain injury involving the hypothalamic-pituitary area are also well known causes of transient/permanent DI. Cerebral malformation and familial cases of ADH deficiency are less common causes of DI. An idiopathic form of DI is rare and always requires regular neuroimaging to rule out an evolving organic lesion.

ADH deficiency normally leads to polyuria with excessive urine free water loss that in the presence of intact thirst sensation will be compensated by an excessive drinking: plasma osmolality should be maintained if adequate replacement of fluid losses occurs. Fluid restriction, inadequate intravenous fluid replacement, impaired thirst sensation, and

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inability to obtain water because of young age will all result in hypernatraemic hypovolaemia. The laboratory findings of ADH deficiency will be an inappropriate low urine osmolality compared to the high plasma osmolality (urine to plasma osmolality ratio < 1.5). Coexistence of ACTH and partial ADH deficiency may clinically mask polyuria as cortisol is required for free water excretion and following corticosteroid treatment (for instance high dose dexamethasone used for cerebral oedema), partial DI may clinically become manifest. To confirm the diagnosis of partial forms of DI a water deprivation test with urinary ADH measurements[4] may be required; if cortisol deficiency is suspected, the patient should be given cortisol replacement.

SYNDROME OF INAPPROPRIATE ADH SECRETION

Many conditions affecting the brain (postneurosurgery, head injury, haemorrhage, infections, etc) can cause SIADH. The syndrome may also occur as a result of the interaction/enhancement of ADH action induced by anticonvulsant drugs, especially carbamazepine and lamotrigine.[5 6] An excess of ADH, exogenous or endogenous, acts on the distal renal tubules and causes free water retention. This is often associated with stimulation of thirst. The excess free water is evenly distributed throughout the body, leading to hypo-osmolar expansion of extracellular fluids and consequent swelling of cells without clinical signs of peripheral oedema.

The counteractive mechanism to volume expansion is urine sodium loss via an increased glomerular filtration and decreased proximal tubular sodium reabsorption. Plasma renin activity is always low, even though aldosterone might not be suppressed. Natriuresis will progress until a new steady state is reached when, in the presence of low plasma sodium, the urine sodium loss may decrease. Furthermore, water retention will reach a plateau and the urine will then be less concentrated. Plasma ADH concentration is usually within the normal range but at an inappropriately high concentration for the low plasma osmolality. The biochemical characteristics will be: low plasma osmolality with inappropriate high urine osmolality (urine to plasma osmolality ratio >1), hyponatraemia with urine sodium loss more than 20 mmol/l, suppressed plasma renin activity, low haematocrit, and low plasma urea and uric acid. Clinical manifestations such as anorexia, confusion, headache, weakness and muscular cramps, followed by nausea, vomiting, and progressive neurological abnormalities may develop. They will depend on the rate of development of intracellular hypo-osmolality as cells can compensate by decreasing the intracellular solute concentration and thus correct the primary swelling. In the most severe cases a rapid decline in plasma sodium can precipitate seizures, lethargy, coma, and death.

Table 1 Biochemical and clinical findings helpful in differentiating CSW from SIADH

	SIADH	*CSW*
Creatinine clearance	Normal or increased	Normal or decreased
Blood urea	Normal or decreased	Normal or increased
Plasma renin	Suppressed	Normal or raised, or occasionally suppressed
Urine volume	Normal or decreased	Normal or increased
Body weight	Stable or increased	Stable or decreased

CEREBRAL SALT WASTING

CSW was initially described[7] in patients with cerebral diseases in 1950. It has been reported in cases with subarachnoid haemorrhage,[8] infections,[7] head injury,[9] brain tumours,[10] trans-sphenoidal pituitary surgery,[11] and neurosurgery.[12] It is characterised by extracellular fluid depletion and hyponatraemia caused by progressive natriuresis with concomitant diuresis. It has been hypothesised that one or more salt losing factors, such as atrial natriuretic peptide[13] or hypothalamic secretion of ouabain like factors,[14] can cause CSW. Current evidence[15–20] suggests that even though atrial natriuretic peptide and brain ouabain like factors might have a role in CSW, several other factors can also be implicated.

The main biochemical findings of CSW will be low plasma osmolality with inappropriate high urine osmolality (urine to plasma osmolality ratio >1), hyponatraemia with urine sodium loss more than 20 mmol/l, normal/high haematocrit, and plasma urea. Plasma renin activity can be raised or in the high normal range; occasionally it may be depressed or in the normal range.[21] The clinical presentation of hyponatraemia will depend on the rate of development of hyponatraemia.

Differential diagnosis

Identical acute cerebral insults may cause either SIADH or CSW. The clinical and biochemical manifestation of both conditions can be virtually identical and the only discriminative feature is the status of extracellular volume: it tends to be expanded in SIADH and low in CSW. Clinical and biochemical findings helpful to differentiate CSW from SIADH include fluid intake and urine output monitoring, daily body weight, blood urea, creatinine clearance, and plasma renin activity (table 1). However, none of these are pathognomonic for either condition. At presentation, changes in extracellular volume can be subtle and neither clinical or biochemical estimations are able to ascertain them with consistent accuracy. For this reason, in any hyponatraemic patient with deteriorating clinical status, in the absence of clinical signs of hypovolaemia such as hypotension, a practical approach (fig 1) would be to perform a formal measurement of blood volume using either central venous pressure or radioisotope dilution techniques (labelled red blood cell studies) to differentiate between SIADH and CSW.[1 2] An echocardiogram may also be required[22] to rule out cardiac compromise which might cause discrepancy between central venous pressure and volume status. Other causes of hypo-osmolar hypovolaemia secondary to non-renal losses, renal tubulopathy, mineralcorticoid deficiency, cardiac or liver failure, and use of diuretics should be excluded at the onset of hyponatraemia.

Hyponatraemia in a patient with DI (fig 2) can be caused by water intoxication secondary to excessive desmopressin replacement, to

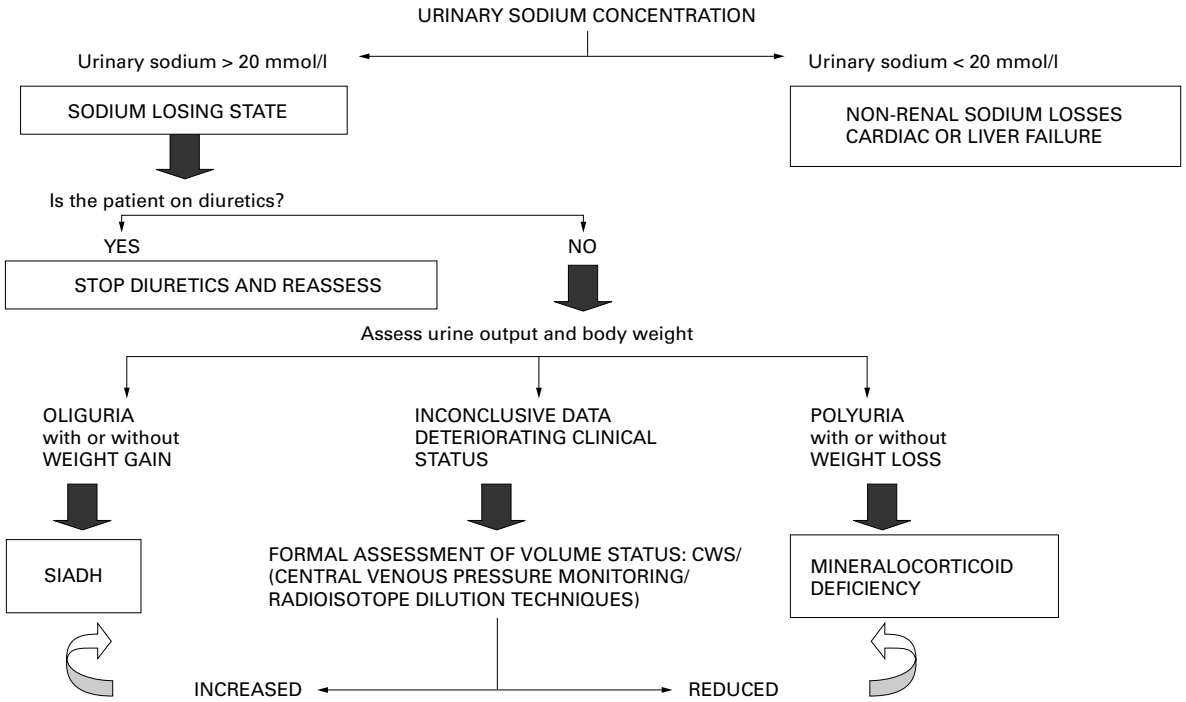

Figure 1 Algorithm for the differential diagnosis between CSW and SIADH in hyponatraemic patients with acute cerebral insult.

coexistent CSW, to concurrent untreated or undertreated cortisol deficiency,[23] anticonvulsant treatment,[6] or to a different source of sodium loss. In the case of excessive desmopressin replacement, the diagnosis will be confirmed by documented improvement of the hyponatraemia following desmopressin withholding. The presence of hyponatraemia and natriuresis in urine samples collected while the patient develops polyuria (prior to desmopressin dose) will point towards a coexistence of CSW and DI.

In hyponatraemic patients with brain tumours receiving nephrotoxic chemotherapeutic agents, it can be very difficult to differentiate CSW from renal tubulopathy. The excessive degree of natriuresis compared to the degree of altered renal tubular threshold for phosphate,

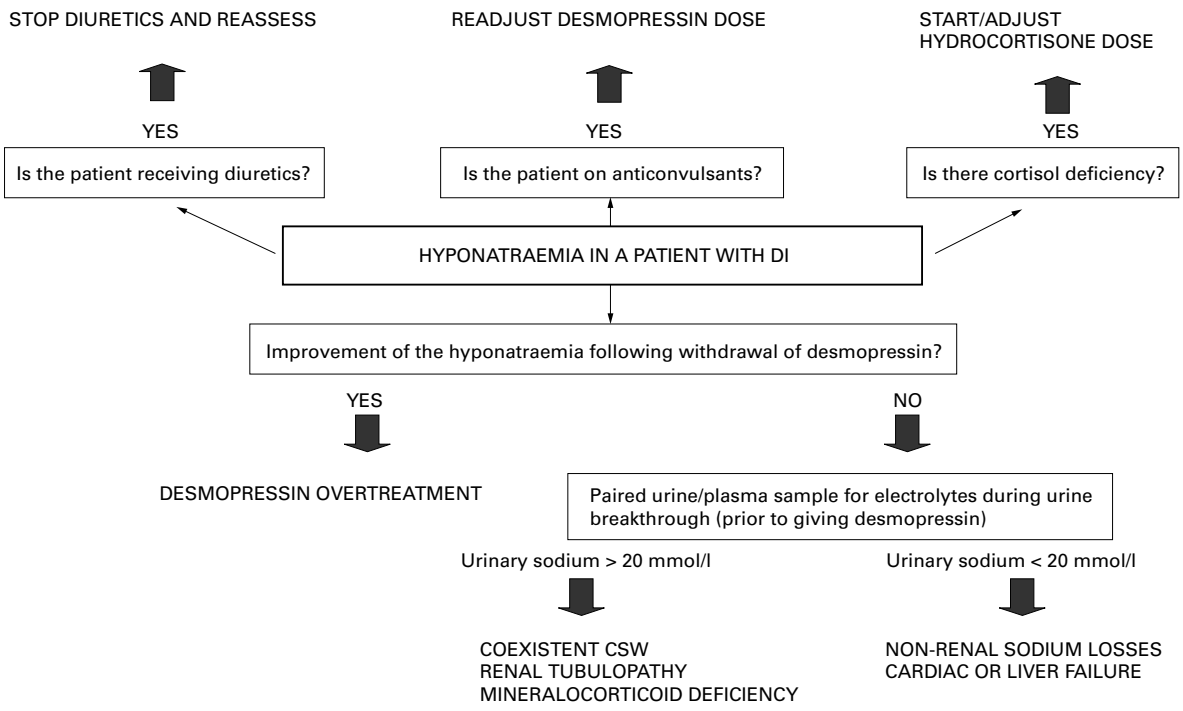

Figure 2 Algorithm for evaluation of hyponatraemia in patients with cerebral insult and DI.

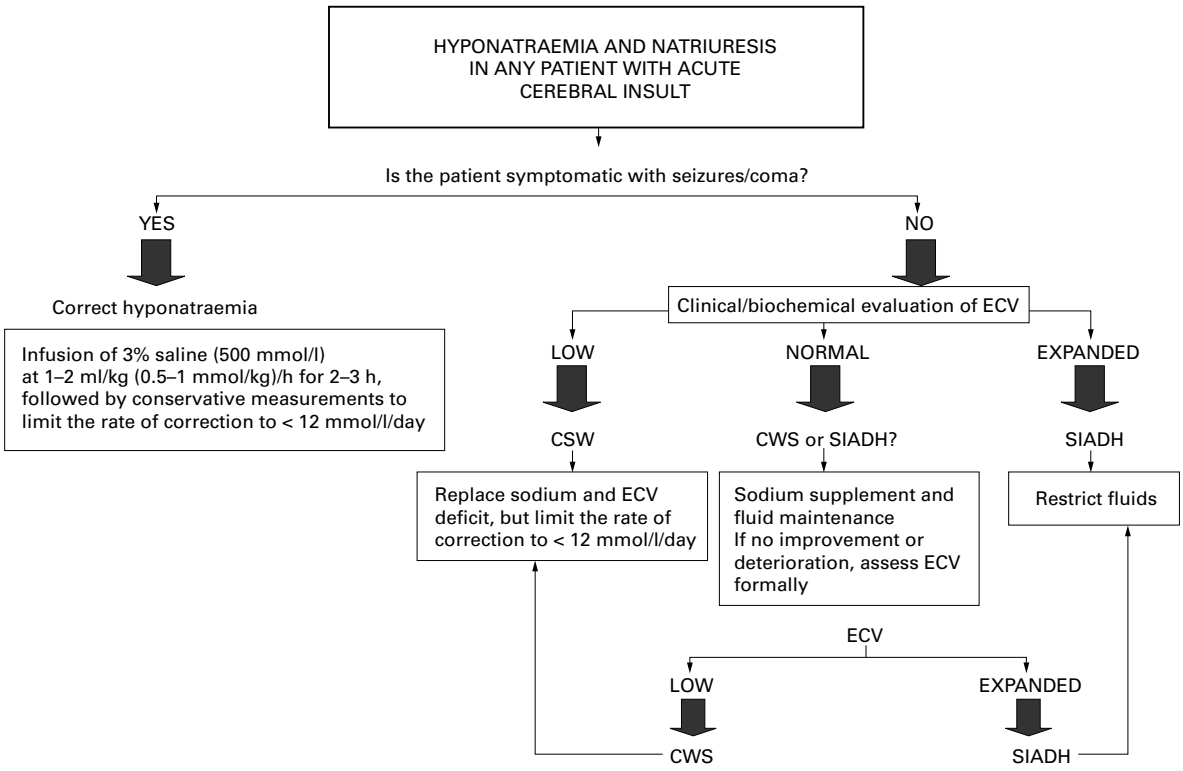

Figure 3 Algorithm for therapeutic approach to hyponatraemia in CSW and SIADH.

hypokalaemia, and tubular protein leak should suggest CSW.

Therapeutic approach

In SIADH, therapeutic interventions should include water intake restriction; only in advanced SIADH with total body sodium depletion, should the sodium be replaced. In severe hyponatraemia, treatment with diuretics can be attempted. Severe symptomatic hyponatraemia (associated with seizures and/or coma) should be partially corrected by infusion of hyperosmolar sodium solution—that is, infusion of 3% saline (500 mmol/l) at 1–2 ml/kg/h (0.5–1 mmol/kg/h) for two to three hours, followed by conservative measurements to limit the rate of correction to less than 12 mmol/l per day. Rapid correction of hyponatraemia can be associated with pontine myelinolysis.

In CSW, therapeutic intervention will include replacement of both sodium and extracellular volume deficit, avoiding rapid corrections. High dose fludrocortisone (0.2–0.4 mg/day) has been found to be beneficial in some patients with CSW,[24–27] but its use requires close monitoring of plasma potassium concentrations as notable hypokalaemia may occur, especially in childhood.

In situations where any hyponatraemic patient with acute cerebral insults/ postneurosurgery and inappropriate urinary sodium loss is clinically euvolemic, a practical approach[2] is to administer sodium supplement and maintain normal fluid intake first. If no improvement or further deterioration occurs within 72 hours, the volume status should be formally assessed (central venous pressure monitoring and/or dilutional studies) to confirm the diagnosis and institute appropriate fluid treatment. Figure 3 illustrates the suggested therapeutic approach for patients with hyponatraemia.

Postneurosurgery patients with suprasellar tumours require close monitoring of fluid and electrolyte balance. The onset of polyuria (urine output > 5 ml/kg/h) in the presence of urine/plasma osmolality ratio < 1.5 is suggestive of DI, and desmopressin should be administered. Low doses should initially be used and according to the clinical response, dose adjustments made. Initially, desmopressin should be given as required (waiting for the onset of polyuria before giving a further dose of desmopressin), as prediction of desmopressin requirement is impossible because of the evolving nature of DI in these patients. An alternative regimen in the acute onset of DI is to use intravenous vasopressin infusion titrated against plasma and urine biochemistry and urine output. It requires frequent blood and urine electrolyte monitoring, and urethral catheterisation, which is not always feasible in children. As soon as a pattern of desmopressin requirement becomes clear, regular desmopressin should be prescribed. The aim is to achieve an appropriate 24 hour urine output for the child's weight and to allow urine breakthrough once a day prior to desmopressin dose, to avoid the risk of water intoxication. When DI becomes stable and regular treatment is required, desmopressin is the drug of choice because of the longer duration of action and lack of vasoconstriction. In hypodypsic patients, fixed daily fluid intake appropriate for weight and target

weight, at which the patient is known to be eunatraemic and euvolaemic, should be established, and desmopressin dose adjusted accordingly.

In patients with coexistent DI and CSW, it should be considered that natriuresis contributes to the increased urine output and is not an index of poor controlled DI. An increase in desmopressin dose will be inappropriate because it will lead to an increase in renal free water reabsorption and therefore to a further deterioration of hyponatraemia. Therapeutic intervention should include sodium and fluid replacement, and administration of desmopressin, with close monitoring of plasma electrolytes and osmolality. If the patient deteriorates clinically, central venous pressure monitoring is mandatory to guide fluid replacement.

Key messages

- Careful adjustment of dose of desmopressin, cortisol, and some anticonvulsants, as all three interact
- Provided that fluid replacement is maintained. DI is not life threatening
- Excessive administration of desmopressin can result in hyponatraemia with fatal fluid overload and may require dialysis
- The only biochemical difference between CSW and SIADH is the extracellular volume, decreased in the former and increased in the latter
- In euvolaemic and hyponatraemic patients with cerebral insults: give sodium supplement and maintenance fluid intake first. If no improvement or deterioration, assess volume state with central venous pressure monitoring
- Limit the rate of correction of plasma sodium to less than 12 mmol/l/day

Case history

A 2.5 year old girl underwent partial surgical resection of a suprasellar ependymoma. She presented with symptoms of severe hypernatraemia, secondary to DI and acute obstructive hydrocephalus while holidaying abroad. Her fluid/electrolytes balance proved to be very difficult to manage. Initially she was on free water replacement to correct the hypernatraemic dehydration secondary to DI. She subsequently developed symptomatic water intoxication with a seizure following commencement of vasopressin infusion. Postsurgery, CSW was suspected because of inappropriate urine sodium loss despite hyponatraemia. Her urine output was very high (6–16 ml/kg/h), as was her urine Na concentration which varied between 130 and 300 mmol/l; serum Na ranged between 130 and 180 mmol/l and vasopressin requirement was 0.05–2.0 mU/kg/h. In addition to DI, she had panhypopituitarism and was treated with replacement thyroxine and glucocorticosteroids. She was subsequently transferred to London. On admission the major problems encountered were:

- Poor response to intravenous infusion of vasopressin, with persistent high urine volume output
- Fluctuating excessive natriuresis, resulting in hyponatraemia
- Excessive fluid intake as, to avoid dehydration, urine losses had to be replaced intravenously when exceeding the fixed oral maintenance
- Difficulties with fluid replacement, because of the coexistence of adipsia and polyuria (secondary to excessive fluid intake, under treated DI, and natriuresis).

Our management plans included:

- Exclusion of other causes of excessive urine sodium losses, such as inappropriate cortisol replacement or renal tubulopathy
- Exclusion of other causes of exacerbating CSW, such as CNS infection or reoccurrence of obstructive hydrocephalus. The latter was documented on repeat brain imaging and a ventricular-peritoneal shunt was inserted. This was followed by an improvement in natriuresis and polyuria
- Keeping accurate fluid/sodium balance charts, with daily body weight and paired urine/plasma osmolality and electrolytes, taken before administering desmopressin
- Slowly reducing excessive urine output by tackling the different exacerbating factors:
  - Undertreated DI: changing from parenteral to oral desmopressin, but given as required, allowing urine breakthrough (increase in urine output to more than 5 ml/kg/h for two consecutive hours) before repeat administration, to avoid water overload
  - Excessive fluid intake: slow reduction in urine loss replacement, aiming to give fixed oral maintenance appropriate for body weight, age, and insensible losses
  - Fluctuating plasma sodium concentrations: prompt recognition of incoming natriuresis and treatment with saline replacement, avoiding rapid changes in plasma sodium and osmolality.

With the above regimen a progressive improvement occurred in the fluid/electrolyte management but, unfortunately, in view of her neurological impairment and a rapid growth in the hypothalamic tumour, palliative care was instigated. She died nine months after initial diagnosis but her DI was easily controlled with small doses of oral desmopressin, and her electrolytes remained normal.

Conclusions

Hyponatraemia in patients with cerebral disorders is a common finding. Close monitoring of body weight and both fluid and sodium balance with paired urine and plasma electrolytes and osmolality is required. The initial differential diagnosis should include both CSW and SIADH when other causes of hyponatraemia—that is, hypo-osmolar dehydration secondary to non-renal losses, renal tubulopathy, mineralocorticoid deficiency, cardiac or liver failure, anticonvulsants, and use of diuretics, have been excluded. The coexistence of DI and CSW

should be considered in hyponatraemic patients who undergo hypothalamic neurosurgery. When both coexist, and high sodium intravenous infusion rates are required, great care is necessary with vasopressin/desmopressin treatment in order to avoid exaggerated plasma sodium fluctuation which can easily produce cerebral damage. Of course there is an interaction between cortisol and ADH and allowance in the dose of the latter must be made for changes in the former. When it is clinically not possible to differentiate between CSW and SIADH, monitoring of central venous pressure or isotope dilution techniques are required to be able to define the degree of volume expansion and undertake the correct treatment.

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THE SCIENCE OF MEDICAL CARE

Epidemiology, Pathophysiology, and Management of Hyponatremic Encephalopathy

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Hyponatremia can be succinctly defined as an abnormally low plasma sodium concentration. Clinical descriptions have been plentiful since the popularization of flame photometry for the measurement of sodium in body fluids (about 1950).[1] Prior to 1960, symptoms frequently attributed to hyponatremia in the absence of other concomitant disease processes were anorexia, apathy, weakness, muscular cramps, nausea, vomiting, and headache,[1–3] although more serious symptoms such as seizures, ataxia, and even death were induced in water-intoxicated laboratory animals.[3] Although the kidney is important in the pathogenesis of hyponatremia, the target organ for changes that produce morbidity and mortality is the brain. Hyponatremia has few important sequelae or clinical manifestations other than those associated with the central nervous system. Additionally, brain edema associated with hyponatremia can lead to several secondary but devastating clinical entities, such as pulmonary edema, central diabetes insipidus and mellitus, cerebral infarction, cortical blindness, persistent vegetative state, respiratory arrest, and coma.[4–7] By contrast, patients with hyponatremia associated with systemic disorders such as heart failure, hepatic cirrhosis, tuberculosis, and lung cancer may have major sequelae that are often unrelated to hyponatremia.[8–11]

Multiple reports from 1933 to 1966 described seizures, coma, or death in patients with symptomatic hyponatremia.[3,12–16] Complete recovery in many instances was possible following prompt treatment with hypertonic NaCl.[12–14] Despite the continuing reports after 1966 of brain damage or death in patients with hyponatremia,[10,17,18] until the last decade there was a perception that such deaths were often related to underlying medical conditions.[19,20] However, over the last 10 years it has become evident that symptomatic hyponatremia can lead to death or permanent brain damage in otherwise healthy adults[4,6,21,22] and children.[23–25] In this review, we will discuss the epidemiology, clinical manifestations, pathophysiology, management, and clinical complications of hyponatremic encephalopathy.

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PATHOGENESIS OF HYPONATREMIA AND HYPONATREMIC ENCEPHALOPATHY

To understand the pathophysiology of hyponatremic encephalopathy, there are some basic concepts relating to sodium and water homeostasis that must be understood. These include concepts of free water clearance, osmolality, tonicity, and thirst regulation, and their relationships to the release of antidiuretic hormone (ADH). It is also important to understand the role played by osmolality, tonicity, and thirst in the regulation of cell volume and the distribution of body water.

Free Water Clearance

Hyponatremia occurs (a) when the intake of free water is in excess of the ability of the kidney to excrete it, or (b) when there is urinary loss of monovalent cation (sodium + potassium) at a concentration that exceeds the intake. Free water clearance can be conceptualized by dividing the urine volume (V) into two fractions. The first fraction, osmolar clearance (Cosm), represents the volume of urine (liters/day) that is necessary to excrete all of the daily solute load at an osmolality equivalent to plasma. The second fraction, free water clearance (C_{H_2O}), represents the difference between the total urine volume (liters/day) and the osmolar clearance ($C_{H_2O} = V - Cosm$). This represents the volume of urine from which solute has been completely removed during formation of a dilute urine. To maintain a normal plasma osmolality it is necessary that the C_{H_2O} equal the intake of free water minus insensible losses (normally about 600 mL/day). If the free water intake exceeds C_{H_2O}, then plasma osmolality (and sodium) must fall. The ability to generate free water clearance and thereby dilute the urine (below isotonicity) depends on three factors: (a) delivery of solute must be adequate to the distal diluting segments in the loop of Henle and distal convoluted tubule; (b) the distal diluting segments must be functional so that sodium and chloride can be removed,

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thereby generating free water; (c) ADH must be suppressed so that the free water generated at the distal diluting sites is not reabsorbed in the collecting system. Although urinary loss of sodium at a concentration greater than that of plasma can lead to hyponatremia, such clinical circumstances are quite rare, occurring primarily in patients with adrenal insufficiency or those who have an idiosyncratic reaction to thiazide diuretics.

Antidiuretic Hormone

Antidiuretic hormone is the principal hormone responsible for the regulation of body water. It is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and stored for release at sites in the posterior pituitary.[26] There are two primary stimuli for the release of ADH: (a) increased plasma osmolality, and (b) decreased intravascular volume.[26] With ADH release, ingested water is retained, which lowers plasma osmolality, alleviates thirst, and repletes plasma volume. As these parameters are satisfied, ADH release is inhibited and any excess water taken in is eliminated as urine. If patients with normal kidneys take in a normal daily solute load (1,000 mOsm) and are able to produce a maximally dilute urine (50 mOsm/kg), they will theoretically be able to ingest up to 20 L of water per day without becoming hyponatremic. However, in patients with poor nutrition (solute load of 250 mOsm/day) as in the case of beer potomania,[25] water intake in excess of 5 L could lead to the development of hyponatremia. A number of factors other than elevated plasma osmolality and hypovolemia can cause ADH release, and override the effects of osmolality and volume. These include many medications, tumors, pulmonary lesions, intracranial processes, emesis, nausea, stress, hypoxia, and even anxiety and fear. Elevation in ADH levels secondary to these entities are referred to as the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Patients with SIADH may develop a clinical condition consisting of a normal to increased intravascular volume, with hypo-osmolality, urine osmolality above 100 mOsm/kg, and decreased plasma levels of sodium, urea, uric acid, and creatinine. The patient must have no other reason for increased ADH, such as volume depletion or hyperosmolality.

Osmolality

Osmolality is defined as the total number of solute particles in a given volume of solvent and is unaffected by the molecular weight of the particles. It is generally expressed as the number of milliosmoles of solute per 1 kg (liter) of water, and is usually determined by freezing point depression. An increase in extracellular osmolality by solutes that diffuse freely into cells (urea, ethanol) leads to rapid osmotic equilibrium between extracellular and intracellular compartments because of solute diffusion across the plasma membrane. However, when extracellular fluid osmolality is increased by solutes that are impermeable to cell membranes (sodium, glucose, mannitol, glycerol, and radiocontrast agents), intracellular osmolality will increase only because of the shift of water from the intracellular to the extracellular compartment. Solutes that freely penetrate cell membranes are called ineffective osmoles and those that do not are called effective osmoles. The total osmolality of any solution is the sum of both the effective and ineffective osmoles.

Tonicity

Solutes that contribute to effective osmolality determine tonicity, and the body strives to regulate tonicity and not osmolality. Thus, thirst and ADH release respond only to tonicity and not to total plasma osmolality. Extracellular fluid is said to be hypertonic if the effective osmolality is greater than that which is physiologically normal (ie, greater than 287 mosmoles/kg water). It is said to be hypotonic when effective osmolality is less than normal. Thus, hypertonic fluid is one that causes cellular dehydration by pulling water from cells, while hypotonic fluid causes cell swelling as a result of intracellular water movement to produce osmotic equilibrium.

Thirst

Afferent stimuli for thirst sensation include both increase in plasma osmolality and decrease in extracellular volume. Also, increases in either plasma or CSF sodium concentrations will stimulate thirst and cause ADH to be released. At a normal plasma osmolality of approximately 285 mOsm/kg water, circulating plasma ADH level is approximately 2 pg/mL, which is the level needed to produce a half maximal urine concentration of approximately 600 mOsm/kg. Normal individuals do not usually experience thirst at this level of plasma osmolality. With dehydration, thirst is first expressed only when plasma osmolality reaches approximately 294 mOsm/kg water. This level of plasma osmolality represents a 2% increase above normal and is generally referred to as the "osmolar threshold" for thirst. At this level of plasma osmolality, ADH is maximally stimulated (usually above 5 pg/mL) and is sufficient to achieve a maximally concentrated urine (above 1,000 mOsm/kg in young adults). A number of pharmacologic agents increase thirst, including tricyclic antidepressants and antihistamines. Certain hormones increase thirst, including ADH and angiotensin-II.

A patient with defective thirst mechanism and intact osmolar regulatory center will appropriately re-

lease ADH in response to volume contraction and hypertonicity, but will become increasingly dehydrated because of the lack of thirst sensation. Such patients will not have the desire to drink, and have to be taught to drink water on a routine basis. They also have to learn to increase water intake with increased ambient temperature and increased physical activity. Such patients are classically described as having essential hypernatremia, as their ability to normalize their serum sodium depends entirely on the ability to take in sufficient amounts of oral fluids. On the contrary, patients with intact thirst mechanism and decreased circulating ADH (diabetes insipidus) can often exist quite normally because of voluntary water intake stimulated by thirst. These patients may get into trouble only if access to water is prevented, as in the case of physical or mental incapacitation.

Cellular Response to Hyponatremia

When plasma osmolality falls as a result of hyponatremia, osmotic equilibrium between cellular compartments is maintained either by the extrusion of intracellular solutes or by the dilution of intracellular solutes by the influx of water from the extracellular space.[27] However, recent studies have cast doubt on the stimuli for cell volume regulation, and it is likely that alterations of cellular metabolism are the primary signal.[28] Complications from hyponatremia generally arise only when osmotic equilibrium is achieved by the intracellular influx of water. Even when cell volume regulation is achieved by the latter mechanism, no significant long-term complications are observed in most organ systems. Unfortunately, small increases in brain volume (above 5%) can lead to substantial morbidity and mortality,[29] thus, all efforts must be made to prevent the development of brain swelling from hyponatremia.

When plasma sodium and hence osmolality start to fall, water immediately starts to move into cells to achieve osmotic equilibrium. In brain, this initial swelling starts the process of extrusion of intracellular solutes to decrease brain osmolality to match that of plasma. If solute extrusion is successfully achieved, osmotic equilibrium will be maintained between brain and plasma, and the patient will remain asymptomatic despite having a low plasma sodium and osmolality. However, if adequate solute extrusion is not accomplished, water will continue to move into the brain until osmotic equilibrium between brain and plasma is reached. The mechanisms for water movement in brain have not been thoroughly investigated until very recently.

Aquaporin CHIP (channel-forming integral membrane protein) is found in many water-permeable epithelia,[30] and water channels have been identified in a number of different tissues, including renal tubular epithelium. Water channels are necessary for ADH to concentrate the urine[31] and appear to play an important role in renal water retention in a number of pathological states, such as cirrhosis.[32] The movement of water into brain cells (both neurons and astroglia) appears to be mediated by a specific type of water selective channel, the aquaporin AQP4, which has been identified in the brain.[33] In the brain, AQP4 is found in ependymal cells, glial cells, Purkinje cells, and neurons, and may be important in the mediation of water flow.[33] Whereas the action of ADH on aquaporin in the kidney is mediated via the V2 receptors,[31] its actions on brain are mediated via V1 receptors, and the mechanisms for interaction with aquaporin have not yet been elucidated.[34] Vasopressin (ADH) is synthesized in hypothalamic nuclei and released as a function of increases in plasma osmolality, which depolarizes supraoptic neurons.[35] Decreases of plasma osmolality lead to astroglial swelling, activating a regulatory volume decrease (RVD). However, ADH blocks the RVD, increasing water movement into astroglia.[36] The effect may be mediated via mechanosensitive cation channels in brain,[35] where ADH has been shown to inhibit calcium-coupled sodium efflux.[37] Another mechanism for osmotic water movement in brain cells appears to be sodium transport by the Na^+-K^+ ATPase system.[38] The Na^+-K^+ ATPase is found in choroid plexus epithelium, providing for release of sodium into the subarachnoid space, driving the passive movement of water from brain into cerebrospinal fluid.[30]

If solute extrusion is not adequate to prevent cell swelling, there will be increased intracranial pressure, cerebral edema, and eventual tentorial herniation if water influx into the brain is allowed to continue. In brain, this initial swelling starts the process of extrusion of intracellular solutes to decrease brain osmolality toward that of plasma. If solute extrusion is successfully achieved, osmolar equilibrium will be maintained between brain and plasma, and the patient will remain asymptomatic despite having a low plasma sodium and osmolality. There are many mechanisms by which osmoticly active solutes are extruded from brain during hyponatremia to avoid complications.[38,39] However, it appears that the extrusion of sodium from brain by the Na^+-K^+ ATPase pump and sodium channels are the first pathways to be activated by water influx.[38,39] Other osmoticly active solutes such as potassium appear to be extruded later in the process. In particular, potassium extrusion only occurs after calcium-mediated stretch receptors are activated.[40] If sodium extrusion is not adequate to lower brain osmolality, then potassium extrusion will be stimulated to assist brain adaptation. Other intracellular solutes such as amino acids

may also play a role in this adaptive process but their role is less clear.[41,42]

Role of Sex Hormones and ADH in Brain Adaptation to Hyponatremia

Over the last decade, many clinical studies have shown that premenopausal women are at a substantially greater risk of dying or developing permanent brain damage from symptomatic hyponatremia than are either postmenopausal women or men of any age.[4,6,21,43] Although a number of mechanisms have been proposed, it appears that the inhibitory effect of the female sex hormones on brain Na^+-K^+ ATPase pump function is of paramount importance.[29,44] Both estrogen and progesterone have been shown to inhibit the function of the Na^+-K^+ ATPase pump in brain and in many other tissues.[38,44] Differences in sodium pump function have also been shown to exist between the sexes, with pump function being less in females than in males.[38] Since both female sex hormone and ADH levels vary with the menstrual cycle,[26] the ability of premenopausal females to appropriately adapt to hyponatremia may depend in large part on the time of the menstrual cycle at which hyponatremia develops.

Sex hormones have also been shown to affect plasma levels of ADH. Circulating levels of ADH in rats have been shown to vary with stages of the female cycle.[26] Additionally, orchiectomy in male rats was found to be associated with increased ADH levels, while testosterone administration to orchiectomized rats decreased circulating ADH levels. Using magnetic resonance spectroscopy (MRS), an earlier study in rats showed that high concentrations of ADH will decrease brain ATP production in females but not in males.[45] Although the mechanism responsible for this observed decrease in brain ATP production was not clear at the time, subsequent studies have shown that ADH significantly increased vascular smooth muscle contractility and decreased cerebral blood flow in female rats.[46,47] Thus, ADH-associated vascular contractility may lead to hypoperfusion, tissue hypoxia, and decreased ATP production.

The effect of female sex hormones on brain adaptation to hyponatremia could be quite devastating. Firstly, the hormones inhibit the Na^+-K^+ ATPase pump, which plays an important role in extrusion of sodium from cells during the development of hyponatremia.[39] This effect of the hormones on the sodium pump will result in brain edema and increased intracranial pressure with all its sequelae. Secondly, these hormones also appear to increase circulating levels of ADH, which are responsible for the water retention that causes hyponatremia. There is also evidence to suggest that ADH directly increases water movement into brain.[36] The net effect of the female sex hormones, then, is to prevent brain adaptation while stimulating water influx into the brain.

CLINICAL MANIFESTATIONS OF HYPONATREMIA

The clinical signs and symptoms of hyponatremia are directly related to the development of cerebral edema, increased intracellular pressure and cerebral hypoxia (**Table**). Early symptoms of hyponatremia from any cause may include apathy, weakness, muscular cramps, nausea, vomiting, and headache.[1–3] More advanced clinical manifestations include impaired response to verbal and painful stimuli, hallucinations, urinary incontinence, and pulmonary edema. As edema worsens, clinical manifestations of hyponatremia are related to the degree of increased intracranial pressure and brain herniation. These manifestations may include decorticate posturing, hypothermia and hyperthermia, central diabetes insipidus and mellitus, seizures, respiratory arrest, coma, permanent brain damage, and death (Table).

CLINICAL SETTINGS ASSOCIATED WITH BRAIN DAMAGE FROM HYPONATREMIA

The incidence of hyponatremia is similar among men and women, but brain damage occurs predominantly in young (menstruant) females and prepub-

TABLE
Clinical Manifestations of Hyponatremic Encephalopathy

Early*	anorexia
	headache
	nausea
	emesis
	muscular cramps
	weakness
Advanced*	impaired response to verbal stimuli
	impaired response to painful stimuli
	bizarre (inappropriate) behavior
	hallucinations (auditory or visual)
	asterixis
	obtundation
	incontinence (urinary or fecal)
	respiratory insufficiency
Far Advanced*	decorticate and/or decerebrate posturing
	bradycardia
	hyper- or hypotension
	altered temperature regulation (hypo- or hyperthermia)
	dilated pupils
	seizure activity (usually grand mal)
	respiratory arrest
	coma
	polyuria (secondary to central diabetes insipidus)

*Any manifestation may be observed at any stage, and some patients will have only minimal symptoms.

ertal individuals of either gender.[4,21,24] Brain damage from hyponatremia is generally uncommon in men and older (postmenopausal) women (**Figure 1**).

It is now clear that brain damage from hyponatremia can be associated with either hyponatremic encephalopathy or improper therapy of symptomatic hyponatremia. Clinical evidence suggests that the vast majority of brain damage from hyponatremia is associated with untreated hyponatremic encephalopathy, and occurs primarily in a limited number of clinical settings. These include (a) the postoperative state, (b) polydipsia-hyponatremia syndrome, (c) pharmacologic agents, (d) congestive heart failure, and (e) adult immunodeficiency syndrome (AIDS).

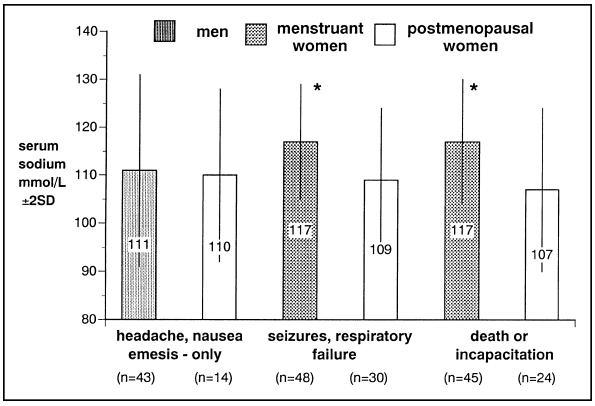

Figure 1. Plasma sodium in 136 patients with hyponatremic encephalopathy. The men and postmenopausal women with headache, nausea, and emesis only did not progress to respiratory failure. We have observed fewer than 10 menstruant women with headache, nausea, and emesis who did not progress to respiratory failure, and these are not included because of the small sample. Plasma sodium in menstruant women who progressed to respiratory failure or permanent brain damage was significantly higher ($P < 0.001$) than that of postmenopausal women who progressed to respiratory failure or permanent brain damage. The plasma sodium in menstruant women who progressed to respiratory failure or permanent brain damage was also significantly higher ($P < 0.001$) than that of either men or postmenopausal women who had headache, nausea, and emesis only ($P < 0.01$). We have observed fewer than 10 men (all age groups) with headache, nausea, and emesis who progressed to respiratory failure, death, or permanent brain damage, and these are not included because of the small sample size. Of the 136 patients, 127 have previously been published in other contexts.[4–6,10,21,56,58] The data are presented as the mean ± two standard deviations (±2SD).

Postoperative Hyponatremia

Postoperative hyponatremia is a common clinical problem in the United States and Western Europe, with an occurrence of about 1%,[19–21,48] or about 250,000 cases per year, with an overall morbidity of approximately 5%.[48] In virtually all cases, the patients tolerated the surgery without complications, being able to walk, talk, and eat after surgery before symptoms of encephalopathy developed. Initial symptoms are usually quite mild (Table). Because these symptoms are somewhat nonspecific, they are often mistakenly attributed to routine post-operative sequelae. However, if the symptoms are due to hyponatremia and left untreated, the patient may progress to more advanced manifestations (Table).[4–6] Thus, symptomatic hyponatremia in post-operative patients is particularly dangerous and should be promptly treated. In this setting, premenopausal women are particularly at risk of developing hyponatremic encephalopathy and respiratory insufficiency (Figures 1 and **2**). Men and postmenopausal women are far less likely to develop respiratory insufficiency from hyponatremia (Figures 1 and 2).[21] Additionally, respiratory arrest occurs at a significantly higher plasma sodium (±SD) in menstruant women (117 ± 7 mmol/L; range 104 to 130 mmol/L) than in postmenopausal women (107 ± 8 mmol/L; range 92 to 123 mmol/L) (Figure 1). Although the frequency of permanent brain damage from hyponatremia following elective surgery is not known, recent studies suggest a morbidity of about 20% in patients with encephalopathy.[48]

Polydipsia

Another common setting in which symptomatic hyponatremia can occur is with the polydipsia-hyponatrermia syndrome (usually known as psychogenic polydipsia), which occurs primarily in individuals who have either schizophrenia or bipolar disorder.[49] The average daily solute intake is about 1,000 mmoles/day, and if the kidney can elaborate a maximally dilute urine (below 100 mOsm/kg), the normal individual should theoretically be able to excrete in excess of 20 liters per day. To lower plasma sodium below 120 mmol/L requires retention of more than 80 mL/kg of water, so that to develop hyponatremia in the absence of elevated plasma levels of ADH requires ingestion of over 20 liters per day in a 60-kg adult. Most patients with polydipsia-hyponatrermia syndrome have actually ingested less water than that theoretically required. Instead, they have less fluid intake but both abnormal urinary diluting capacity and elevated plasma ADH levels.[49,50] Beer potomania is a variation of polydipsia-hyponatrermia syndrome, where the hyponatremia is associated with poor nutrition and massive ingestion of beer instead of water.[25]

Congestive Heart Failure

The most common cause of hyponatremia in the United States is congestive heart failure,[51] with an incidence of about 400,000 cases per year. The pathogenesis of the hyponatremia is complex and may include activation of vasoconstrictor hormones, thirst stimulation, diuretic therapy, impaired renal water excretion, high plasma ADH levels, and elevated plasma renin activity.[8] The 1-year mortality among patients with congestive heart failure ex-

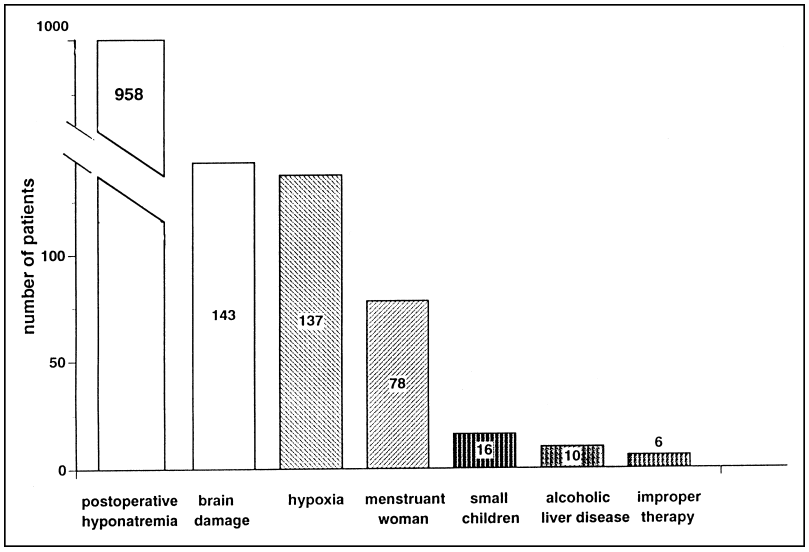

Figure 2. Major risk factors associated with permanent brain damage among hospitalized patients with hyponatremia (serum sodium below 128 mmol/L). Most patients (96%) suffered an hypoxic episode because of failure to initiate active therapy in a timely manner. In only 4% of patients suffering permanent brain damage could improper therapy for hyponatremia be implicated in the outcome. The incidence of hyponatremic encephalopathy in 11 published series from our laboratory comprising 958 hospitalized patients with hyponatremia was 23% (143 of 958). Among patients with hyponatremic encephalopathy, the overall morbidity was 15%. The data are extracted from Arieff,[4] Ayus and Arieff,[5] Fraser and Arieff,[6] Arieff et al,[10] Ayus et al,[21] Arieff et al,[24] Ayus and Arieff,[48] Ayus et al,[56] and Ayus and Arieff.[58]

ceeds 50%,[8] although an undetermined number of these actually die from hyponatremia. Although the mortality from hyponatremia among patients with heart failure is thus difficult to estimate, there are many reported deaths,[10] and a low plasma sodium is of major prognostic importance.[8] Recent studies suggest that the renin-angiotensin system is of major importance in the pathogenesis of hyponatremia in patients with heart failure,[51] and that both the hyponatremia and long-term outcome can be improved by converting-enzyme inhibition.[8]

Pharmacologic Agents

A number of pharmacologic agents may interfere with the ability of the kidney to excrete free water. Included are large numbers of sedatives, hypnotics, analgesics, oral hypoglycemic agents, tranquilizers, narcotics, antineoplastic drugs, antidepressant agents, and diuretics.[52] In most such instances, there is excessive net retention of ingested or infused free water. Those diuretics most commonly associated with hyponatremia are thiazides and "loop" diuretics (furosemide). In patients with thiazide-associated hyponatremia, there may be an idiosyncratic reaction to the drug, resulting in massive acute losses of sodium and potassium in the urine, often with associated polydipsia.

Acquired Immune Deficiency Syndrome (AIDS)

AIDS is a major cause of hyponatremia in the United States.[53] The hyponatremia in patients with AIDS may be secondary to SIADH, volume deficiency with hypotonic replacement fluids, or adrenal insufficiency.[54] Even in the presence of mineralocorticoid deficiency, glucocorticold function may be intact, resulting in a normal ACTH stimulation test. Adrenal insufficiency is particularly suspect in hyponatremic AIDS patients who have disseminated cytomegalovirus or tuberculosis. Therapy with fludrocortisone acetate is indicated only if adrenal insufficiency is documented in hyponatremic patients with renal salt-wasting.[54] Current data strongly suggest that patients who have AIDS and hyponatremia have both a higher mortality and longer duration of hospitalization than those who are normonatremic.

HYPOXIA AND HYPONATREMIC ENCEPHALOPATHY

Hypoxemia is a major factor contributing to brain damage in patients with hyponatremia.[5,48] Hypoxia leads to a failure of homeostatic brain ion transport, which allows the brain to adapt to increases in cell water. The adaptive increase of Na^+-K^+-ATPase transport activity, which is initiated by hyponatremia, is severely blunted by hypoxia, thus

causing a net increase in brain sodium and resulting in brain edema.[39] Among patients with hyponatremic encephalopathy, the progression to death or brain damage is frequently associated with hypoxemia (Figure 2).[4,5] Hypoxia decreases the effectiveness of the compensatory changes by which the brain adapts to hyponatremia and is also a major stimulus for increased secretion of ADH. Plasma ADH levels are elevated in the vast majority of hyponatremic patients,[20] and ADH can directly increase water movement into the brain and thus worsen brain edema. ADH also decreases brain production of ATP and lowers brain intracellular pH, which may be contributory factors to the impaired Na^+-K^+-ATPase transport activity observed with hypoxia.[39]

In patients with symptomatic hyponatremia, respiratory arrest often occurs very abruptly, and patients who suffer an hypoxic event infrequently survive without permanent brain damage.[4,6] The possibility of hypoxia complicating symptomatic hyponatremia far exceeds that of brain injury due to inappropriate therapy (Figure 2). Thus, at the present time, there is essentially no rationale for failure to actively treat patients with symptomatic hyponatremia.

MANAGEMENT OF THE PATIENT WITH HYPONATREMIA

The Asymptomatic Patient

In patients with asymptomatic hyponatremia, aggressive therapy with hypertonic NaCl is not indicated. If the patient is volume depleted, isotonic (154 mM) NaCl is usually the fluid of choice. If there is a hormone deficiency (adrenal insufficiency, hypothyroidism), appropriate hormone replacement is indicated in addition to volume repletion. If the patient has received a drug that may interfere with renal handling of sodium or water, the drug should be discontinued whenever possible. Although water restriction can theoretically be of benefit in some of these disorders, practical considerations diminish its usefulness. If fluid intake can be restricted to less than 800 mL/day, there will be a negative free water balance (see above) and the plasma sodium will slowly rise. However, in patients who are not taking oral nourishment and are maintained on intravenous fluids, the net insensible water loss is close to zero.[52] With successful fluid restriction, the rate of correction of plasma sodium will rarely exceed 1.5 mmol/L per day. Thus, water restriction is only appropriate in a patient with asymptomatic hyponatremia.

There are several medical regimens for the long-term management of patients with stable asymptomatic hyponatremia. Demeclocycline, a tetracycline antibiotic, in doses above 600 mg/day can be effectively used to produce a state of nephrogenic diabetes insipidus and has been successful in treating patients with SIADH.[52] Both acute renal failure and renal tubular toxicity have been reported when patients have either heart failure or cirrhosis.[55] Other drug regimens of potential benefit in the treatment of chronic hyponatremia include urea and inhibitors of ADH or its receptors, the use of which are still experimental.[42]

The Symptomatic Patient

When the presenting symptoms of hyponatremic encephalopathy include respiratory arrest, therapy is unlikely to yield a viable result.[4,21] As previously mentioned, about 1% of all postoperative patients develop hyponatremia, and of these, more than 15% manifest hyponatremic encephalopathy.[48] Every postoperative patient should be considered at risk for the development of hyponatremia, and appropriate prophylactic measures undertaken. The most important of these measures include the avoidance of intravenous hypotonic fluid to postoperative patients (unless hypernatremic). Other important measures include monitoring daily electrolytes, strict input and output, and daily weights. The rationale for the use of hypotonic fluids in postoperative patients is difficult to discern, and has no place in the modern practice of medicine. Since the 1950s, there have been a number of articles in both the medical and surgical literature demonstrating the propensity of intravenous hypotonic solutions to cause permanent brain damage or death in the postoperative patient. Isotonic (154 mM) NaCl is virtually always preferable as the appropriate postoperative intravenous fluid.

Therapy for Symptomatic Hyponatremia

Symptomatic hyponatremia is a medical emergency, with a morbidity in excess of 15%.[48] In patients with hyponatremic encephalopathy, the preponderance of clinical evidence demonstrates that correction by water restriction alone leads to an unacceptable morbidity and mortality. Patients with hyponatremic encephalopathy should be constantly monitored, preferably in an intensive care unit. The first step in management of such patients is a secure airway, with assisted ventilation if required. Therapy should be initiated with intravenous hypertonic sodium chloride (514 mmol/L) using an infusion pump, with the infusion designed to raise plasma sodium at a rate of about 1 mmol/L per hour (**Figure 3**). If the patient is actively having seizures or has other evidence of increased intracranial pressure, then the rate of hypertonic

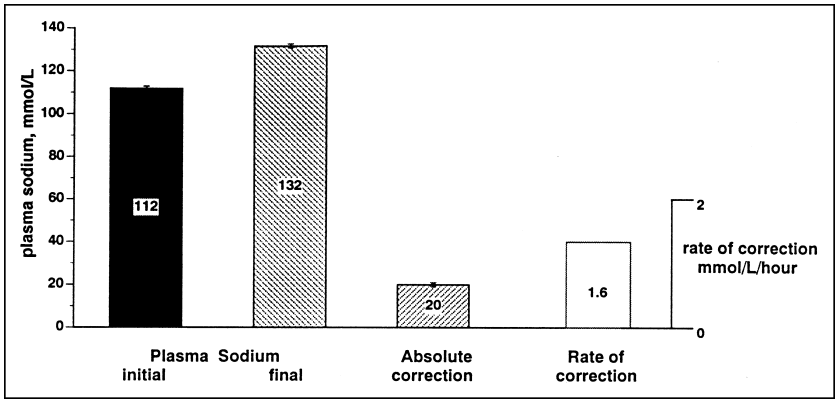

Figure 3. Summarized reports of 172 pediatric and adult patients from three countries and six states in the United States who underwent rapid correction (rate of correction above 0.6 mmol/L per hour) of severe symptomatic hyponatremia. None of the adults had respiratory arrest prior to the start of therapy, and children suffering respiratory embarrassment were intubated immediately. All were treated with hypertonic NaCl, isotonic NaCl, or hypertonic NaCl plus furosemide. The serum sodium was increased from an initial value (±SD) of 112 ± 8 mmol/L to a final value after 24 to 48 hours of 132 ± 5 mmol/L. The absolute change after 24 to 48 hours was 20 ± 5 mmol/L, and the rate of correction was 1.6 ± 0.8 mmol/L/hr. All patients survived without evidence of morbidity, regardless of whether the hyponatremia was acute or chronic. Modified from DeFronzo and Arieff.[52]

fluid administration should be adjusted so that the rise in plasma sodium is about 4 to 5 mmol/L per hour over the first hour, or until seizure activity has ceased.[18] Therapy with hypertonic NaCl should be discontinued when (a) the patient becomes asymptomatic; (b) the patient's plasma sodium has increased by 20 mmol/L; or (c) the plasma sodium reaches a value in the range of 120 to 125 mmol/L. These guidelines may be modified if patients are symptomatic at higher levels of plasma sodium (124 to 131 mmol/L). During the interval that active correction of symptomatic hyponatremia is being carried out, monitoring of plasma electrolytes should be carried out every 2 hours, until the patient has become neurologically stable. In addition to hypertonic sodium chloride, therapy may include endotracheal intubation and assisted mechanical ventilation, and administration of a loop diuretic (furosemide) when required. This regimen may require modification in patients with severe renal or cardiac disease. Owing to possible complications, the plasma sodium should never be acutely elevated to hypernatremic or normonatremic levels, and should not be elevated by more than 25 mmol/L during the initial 48 hours of therapy.[56]

In order to correct symptomatic hyponatremia, an initial estimate of the patient's total body water (TBW) should be made. Despite the belief that the TBW is about 60% of the body weight (kg), the percent of TBW varies widely as a function of age, sex, and body habitus, with a range of 42% (obese elderly women) to 75% (infants). Correction of the plasma sodium should be initially planned using intravenous 514 mM NaCl, often combined with a loop diuretic (furosemide).[52] The technique is as follows: For a 50-kg woman (assuming 25 L of total body water) whose plasma sodium is 105 mmol/L, the goal is to raise the plasma sodium to about 125 mmol/L in about 48 hours. This is accomplished by infusing (using an infusion pump) 514 mM NaCl at a rate calculated to increase plasma sodium at 1 mmol/L per hour, an infusion rate of 25 L × 20 mmol/L = 500 mmoles NaCl in 48 hours. Using 514 mM NaCl, this will be [(500 mmoles)/(514 mmoles/L) ÷ (48 hours)], or 20 mL/hour. The plasma sodium must be monitored at least every 2 hours, with appropriate adjustments in the infusion rate to reach the desired therapeutic goal.

Possible Complications of Therapy for Hyponatremia

Previous medical opinion suggested that the major factors that might lead to permanent brain damage were related to both the magnitude and duration of the hyponatremia, opinions supported largely by anecdotal evidence. Recent investigations have demonstrated that neither the magnitude nor duration of hyponatremia were the primary factors responsible for the development of brain damage.[21] Rather, the age, gender, and reproductive (hormonal) status of the patient, as well as the presence of encephalopathy, were the most important predictive factors (Figure 1). The most susceptible groups were menstruant women and prepubescent children.[4,6,21,24] Menstruant women

are 25 times more likely to suffer brain damage associated with hyponatremic encephalopathy than are either postmenopausal women or men of any age.[21] It has been suggested that patients with "chronic" hyponatremia are more likely to develop brain damage as a complication of therapy with hypertonic NaCl than are those with "acute" hyponatremia.[57] This supposition has not been supported by clinical evidence.[8,10,49] Therapy does not appear to be an important factor in the genesis of permanent brain damage in hyponatremic patients, because the vast majority of patients who have developed such complications have not been treated for their hyponatremia.[6,48] On the other hand, there is overwhelming evidence that treatment of symptomatic hyponatremia with hypertonic NaCl is associated with survival and recovery.[13,18,56,58]

HYPONATREMIA AND CEREBRAL DEMYELINATING LESIONS

There has been some controversy concerning the rate at which hyponatremia should be corrected. Some authors have suggested that the development of a rare neurologic syndrome, central pontine myelinolysis (CPM), is somehow related to the rapid correction of hyponatremia.[57] However, a number of studies have shown that cerebral demyelinating lesions develop only when patients with hyponatremia (a) are inadvertently made hyponatremic during treatment; (b) have an absolute increase in plasma sodium that exceeds 25 mmol/L in the first 24 to 48 hours of therapy; (c) suffer an hypoxic event; or (d) have severe liver disease.[7,11,56]

In the initial description,[59] central pontine myelinolysis (CPM) was described as "a single, sharply outlined focus of myelin destruction which indiscriminately affected all fiber tracts." Among patients with CPM, extrapontine demyelinating lesions were infrequent.[59] Using strict diagnostic criteria (either pathological or radiological), 85% of patients said to have CPM do not, and virtually all have had severe associated medical conditions.[7] These include alcoholism, advanced liver disease, extensive burns, sepsis, Hodgkin's disease, or other malignancies. If plasma sodium is increased in patients with liver failure, there is a substantial risk of developing cerebral demyelinating lesions.[11] Hyponatremia is not a prerequisite for these lesions to occur, as hyponatremia induced in normonatremic animals can result in cerebral demyelinating lesions.[60]

Currently, the diagnosis of CPM is frequently established using radiological criteria, employing either CT or MRI of the brain.[7] However, the diagnosis of CPM has often been suggested when radiological examination (CT and/or MRI) was either not carried out or disclosed only extrapontine cerebral demyelinating lesions. Since CPM is a distinct pathological entity, if the pathological findings are absent, CPM is not present. Although cerebral demyelinating lesions may result from improper therapy of hyponatremia in laboratory animals,[61] a human analogue is very rare.[7] Extrapontine cerebral demyelinating lesions have sometimes been mistakenly diagnosed as CPM, but unless the patients have severe liver disease, the pons is rarely involved, thus negating the diagnosis. The lesions often described as CPM are characteristic of hypoxia,[62] and are frequently observed following carbon monoxide poisoning, drowning, and cardiac arrest. Respiratory insufficiency with hypoxia is a frequent complication of hyponatremic encephalopathy,[5] which often leads to diffuse cerebral demyelination.[7]

SUMMARY

Hyponatremia is the most common electrolyte abnormality among hospitalized patients. Death or brain damage associated with hyponatremia has been described since 1935, and it is now evident that hyponatremia can lead to death in otherwise healthy individuals. In the past, it had been assumed that the likelihood of brain damage from hyponatremia was directly related to either a rapid decline in plasma sodium or a particularly low level of plasma sodium. Recent studies have demonstrated that other factors may be more important. These factors include the age and gender of the individual, with children and menstruant women the most susceptible. Although many clinical settings are associated with hyponatremia, those most often associated with brain damage are postoperative, polydipsia, pharmacological agents, and heart failure. Morbidity and mortality associated with hyponatremia are primarily a result of brain edema, hypoxemia, and associated hormonal factors. Management of hyponatremia is largely determined by symptomatology. If the patients is asymptomatic, discontinuation of drugs plus water restriction is often sufficient. If the patient is symptomatic, active therapy to increase the plasma sodium with hypertonic NaCl is usually indicated. Although inappropriate therapy of hyponatremia can lead to brain damage, such an occurrence is rare. Thus, the risk of not treating a symptomatic patient far exceeds that of improper therapy.

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diabetes. Most patients have no means of assessing control apart from the presence or absence of symptoms. Home monitoring of blood glucose concentrations is economically impracticable for most patients, but easier access to urine dipsticks would probably increase patients' interest and motivation in improved control and would not add greatly to total direct costs.

The need for inpatient admission should also be considered carefully, especially for newly presenting patients. Wherever possible admission is best avoided if the patient and family are able to receive initial daily outpatient education and supervision.[15] Patients should be admitted only if they require nursing care or circumstances do not permit easy attendance at outpatient clinics. Admission rates for diabetic patients in Tanzania are six times higher than in the general population.[16] When patients are admitted careful consideration should be given to the need for investigations. Testing urine four times or more daily for example, may be unnecessary if blood glucose concentrations are also being measured. Consideration should also be given to the period of admission since patients are often kept in the wards until most urine results are glucose free.

The small proportion of direct costs due to nurses' and doctors' services reflects the low rates of pay of medical staff in most sub-Saharan countries. A lecturer in medicine, for example, is paid $60 monthly. The reasons for such low rate of remuneration are understood, but attention must also be paid to this problem since the motivation and interest of those caring for patients can have a significant impact on the quality of care.

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Hyponatraemia and death or permanent brain damage in healthy children

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Abstract

***Objective*—To determine if hyponatraemia causes permanent brain damage in healthy children and, if so, if the disorder is primarily limited to females, as occurs in adults.**

***Design*—Prospective clinical case study of 16 affected children and a review of 24 412 consecutive surgical admissions at one medical centre.**

***Patients*—16 children (nine male, seven female; age 7 (SD 5) years) with generally minor illness were electively hospitalised for primary care. Consultation was obtained for the combination of respiratory arrest with symptomatic hyponatraemia (serum sodium concentration ≤128 mmol/l).**

***Main outcome measures*—Presence, gender distribution, and classification of permanent brain damage in children with symptomatic hyponatraemia in both prospective and retrospective studies.**

***Results*—By retrospective evaluation the incidence of postoperative hyponatraemia among 24 412 patients was 0·34% (83 cases) and mortality of those afflicted was 8·4% (seven deaths). In the prospective population the serum sodium concentration on admission was 138 (SD 2) mmol/l. From three to 120 inpatient hours after hypotonic fluid administration patients developed progressive lethargy, headache, nausea, and emesis with an explosive onset of respiratory arrest. At the time serum sodium concentration was 115 (7) mmol/l and arterial oxygen tension 6 (1·5) kPa. The hyponatraemia was primarily caused by extrarenal loss of electrolytes with replacement by hypotonic fluids. All 16 patients had cerebral oedema detected at either radiological or postmortem examination. All 15 patients not treated for their hyponatraemia in a timely manner either died or were permanently incapacitated by brain damage. The only patient treated in a timely manner was alive but mentally retarded.**

***Conclusions*—Symptomatic hyponatraemia can result in a high morbidity in children of both genders, which is due in large part to inadequate brain adaptation and lack of timely treatment.**

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Introduction

In previous studies from our laboratories we have described the symptomatology, clinical course, effects of treatment, and pathological findings in more than 225 adults (aged over 16) with symptomatic hyponatraemia.[1-8] Although the actual incidence of hyponatraemia seems to be similar among men and women,[8,9] almost all adult patients suffering hyponatraemic brain damage are women. Although there are a number of reported paediatric cases of hyponatraemia,[10-12] there are few reported cases of death or permanent brain damage among children with this disorder,[13,14] and most such children had pre-existing neurological disorders.[15-17] Neither the gender distribution nor the incidence of brain damage among children with hyponatraemia is known.[10,12-17] Among children suffering brain damage from hyponatraemia neither the type nor the gender distribution is known. We describe both a prospective and a retrospective analysis of generally healthy children who were elect-

ively hospitalised. Sixteen children who developed severe symptomatic hyponatraemia either died or suffered permanent brain damage. Unlike the situation in adults, both males and females were adversely affected among these children.

Patients and methods

Prospective studies—Over a period of six years (1984-90) we were consulted about 16 previously healthy children (aged under 16) who had developed symptomatic hyponatraemia and either died or suffered permanent brain damage. These 16 patients were seen in consultation from five tertiary and nine community hospitals. The age of the children was 7 (SD 5) years (range 1·5 to 15 years), and the gender distribution was nine males and seven females. The mean weight was 23·8 (12·9) kg (range 10 to 52 kg). Symptomatic hyponatraemia developed within five days of admission to the hospital.

Epidemiological studies—We retrospectively studied all surgical admissions to a 456 bed tertiary paediatric university teaching hospital over three years (1989-91). The records of all paediatric (age under 16) surgical patients were evaluated for those who had postoperative hyponatraemia (serum sodium concentration 128 mmol/l or less) and the number who either died or suffered permanent brain damage as a result of the hyponatraemia. The epidemiological data were generated by computer search of the hospital records using the SAS database[18] to obtain information on all paediatric surgical patients who had a postoperative serum sodium concentration of 128 mmol/l or less. There were 24 412 consecutive inpatient operations over the three years ended 31 December 1991. In addition, we calculated an approximation of the incidence of hyponatraemic brain damage in children in the United States from our epidemiological data plus a statistical database from the medical literature.[19 20]

Results

STUDY PATIENTS

The table shows the clinical circumstances which resulted in hospitalisation of the 16 patients. All data are presented as means (SD). Symptoms were not known in three patients, who were either too young (less than 18 months) or intubated and thus unable to vocalise any complaints. Of the remaining 13 patients, 11 had progressive lethargy, weakness, nausea, and emesis and 12 had headache. All patients suffered respiratory arrest after a mean of 37 hours (range three to 120 hours) from the start of intravenous fluid administration.

CLINICAL COURSE

At admission the serum sodium concentration was 138 (2) mmol/l. As early as two hours after starting hypotonic fluid administration those patients able to communicate became progressively more lethargic and complained of headache and nausea, with subsequent emesis. All such symptoms were generally unresponsive to conventional agents (phenothiazines and narcotics). After a mean of 37 hours all 16 patients suffered respiratory arrest, at which time the serum sodium concentration was 115 (7) mmol/l and urine osmolality 676 (66) mmol/kg. This level of urine hypertonicity in the presence of hyponatraemia suggests that the plasma antidiuretic hormone concentration was raised.[21] The onset of respiratory arrest was often explosive in nature, and hyponatraemia was generally not considered as a possible cause.

Immediately after respiratory arrest but before oxygen administration or intubation the arterial oxygen tension was evaluated in 11 patients and was 6·0 (1·5) kPa. During the 37 hours between the time of admission and onset of respiratory arrest the patients had received a mean of 125 (83) ml hypotonic intravenous fluids per kg daily. Urine output was 34 (34) ml/kg per day and other fluid losses averaged 28 (25) ml/kg per day (nasogastric suction, n=2; emesis, n=10; cerebrospinal fluid drainage, n=1; not charted, n=3) with mean net output of 74 (82) ml/kg daily and net positive fluid balance of only 27 (14) ml/kg per day. Hyponatraemia in these children was thus largely due to extensive extrarenal loss of electrolyte containing fluids with replacement by hypotonic fluids. Most of the intravenous fluids were administered as 280 mmol glucose per litre either in water or in sodium chloride 38 mmol/l, but the plasma glucose concentration was

Clinical characteristics of 16 children with symptomatic hyponatraemia

Case No	Gender and age (years)	Weight (kg)	Serum sodium (mmol/l)		Duration of intravenous fluid treatment (hours)	Net fluid intake (ml/kg)	Net fluid output (ml/kg/*)	Clinical history	Hospital procedures	Respiratory arrest	Treatment after respiratory arrest	Clinical outcome
			Initial	Lowest								
1	M 3·5	2·27	139	114	46	246	222	Fever, dysphagia, pharyngitis, tonsilitis	Antibiotics+fluids	Yes	154 mM sodium chloride	Vegetative, quadriplegia
2	F 5	18·0	141	123	14	96	33	Tonsillitis	Tonsillectomy	Yes	None	Died
3	F 4	18·2	139	115	21	114	NA	Tonsillitis	Tonsillectomy	Yes	None	Died
4	M 15	44·6	134	101	74	164	73	Fever, dysphagia, pharyngitis, tonsilltis	Antibiotics+fluids	Yes	154 and 514 mM sodium chloride	Aspiration pneumonia, sepsis, died
5	M 3·5	15·0	138	121	9	61	5	Tonsillitis	Tonsillectomy	Yes	None	Died
6	F 12	31·8	137	120	33	57	11	Elbow fracture from car accident	Setting of fracture	Yes	514 mM sodium chloride; intubation	Ambulatory, mental retardation
7	M 4	16·4	139	118	27	109	88	Elbow fracture from fall	Setting of fracture	Yes	None	Died
8	M 3	10·0	137	113	8	300	NA	Stricture of urethra; tonsillits	Urethral dilatation; tonsillectomy	Yes	None	Died
9	F 1·5	10·6	137	114	120	283	253	Hydrocephalus	Ventriculoperitoneal shunting	Yes	None	Vegetative
10	M 9	27·0	137	120	32	79	NA	Fractures from car accident	Operative setting of fractures	Yes	None	Vegetative
11	F 15	52·0	138	102	94	87	57	Fractures from car accident	Operative setting of fractures	Yes	154 mM sodium chloride; intubation	Vegetative and blind
12	F 4	16·8	138	107	16	88	56	Tonsillitis	Tonsillectomy	Yes	None	Died
13	M 2	11·4	138	116	3	123	NA	Undescended testicle	Orchiopexy	Yes	None	Died
14	M 6	15·0	138	119	12	40	11	Severe epistaxis	Posterior packing	Yes	None	Died
15	M 12	42·0	137	123	19	34	9	Fever, appendicitis, ruptured appendix	Appendicectomy plus drainage	Yes	None	Died
16	F 12	28·5	134	116	66	113	72	Pneumonia	Antibiotics+fluids	Yes	None	Vegetative
Mean	7	23·8	138	115	37	125	74					
SD	5	12·9	2	7	34	83	82					
SE	1	3·2	1	2	9	21	24					

*Urine+emesis+gastric drainage+cerebrospinal fluid. NA=Not available.

only 7·0 (0·7) mmol/l at the time hyponatraemia was diagnosed. Four patients (two male, two female) subsequently developed the syndrome of central diabetes mellitus and central diabetes insipidus[5] with hypotonic polyuria. In these four patients the mean serum sodium concentration rose (without treatment) from 114 (6) mmol/l to 164 mmol/l and the glucose concentration to 31·1 mmol/l. None of these patients had been treated for their hyponatraemia.

OUTCOME

All 16 patients either died or suffered permanent brain damage (table): one was mentally retarded, 10 died, and five were in a persistent vegetative state which persisted for follow up intervals of at least two years. Twelve patients received no specific treatment for their hyponatraemia. Of these, nine died and three remained in a persistent vegetative state.[22] Four patients were eventually treated with intravenous sodium chloride 154 and 514 mmol/l (table) such that the serum sodium concentration was increased from 108 (9) to 138 (4) mmol/l in 44 hours. The average delay from respiratory arrest to start of treatment was eight hours, all four patients were comatose, apnoeic, and intubated at the time treatment was begun, and none awoke either during treatment or for three days thereafter. Only one patient (case 6), who survived mentally retarded, was treated within 10 minutes of respiratory arrest.

NECROPSY FINDINGS

Postmorten examination of the brain was performed in 10 patients (three girls, seven boys). In nine patients who had received no treatment and died in less than 48 hours there was cerebral oedema and herniation on gross examination of the brain. The brain weight (unfixed) in six patients (three male, three female) whose mean age was 3·8 years was 1354 (95) g. For comparison, the normal brain weight in men is 1450 g, in women 1250 g, in 4-5 year old boys 1300 g, and in 4-5 year old girls 1150 g.[23] Thus brain weight was increased by more than 10% above control values for children of the age range studied.[23] That transtentorial herniation was present in all nine patients subjected to postmortem evaluation correlates well with the observation that the human brain can expand by only about 5-7% of its normal volume[24] before herniation occurs. We have shown that men's brains can usually adapt to hyponatraemia within a few hours whereas women's brains may not adapt within several days.[8] In all 16 children presented here the brains were unable adequately to adapt to hyponatraemia.

EPIDEMIOLOGICAL FINDINGS

Among 24 412 paediatric surgical admissions to a 456 bed university paediatric hospital there were 83 (0·34%) patients who developed hyponatraemia. Among these, seven (8·4%) died of complications of the hyponatraemia. Among the seven deaths, four were in boys and three in girls. Hence the incidence was 340 cases of paediatric postoperative hyponatraemia and 29 hyponatraemic deaths per 100 000 inpatient operations on children. There are 2·02 million paediatric inpatient operations a year in the United States.[19 20 25] The estimated yearly incidence in the United States is 7448 cases of paediatric postoperative hyponatraemia, with 626 such hyponatraemic deaths in children. The most common inpatient operations on children in the United States[20] are to the nose, mouth, and pharynx (17%); digestive system (17%); musculoskeletal system (15%); and nervous system (13%), of which 43% are performed in girls. This was essentially the distribution in our series, in which 92% of operations were in these four groups and 44% of the patients were female (table).

Discussion

These cases show that generally healthy children with symptomatic hyponatraemia (101-123 mmol/l) can abruptly develop respiratory arrest and either die or develop permanent brain damage. The permanent brain damage can include pituitary infarction with resultant central diabetes insipidus and mellitus, a syndrome not previously described in children.[5] The incidence of postoperative hyponatraemia in children (0·34%) was less than in adults (1-4%).[8 21] However, among paediatric patients who developed symptomatic hyponatraemia the incidence of permanent brain damage was substantially higher than in adults.[8 21] Both the types of surgery and gender distribution among our 16 patients (table) were the same as the most common operations and gender distribution in the United States as a whole,[20] and thus our 16 patients were representative of the spectrum of elective paediatric surgical patients.

The hyponatraemia in these children seems to have been caused by extensive extrarenal loss of electrolyte containing fluids and intravenous replacement with hypotonic fluids (table) in the presence of antidiuretic hormone activity. Increased plasma concentrations of antidiuretic hormone are usually found in both children and adults with hyponatraemia,[9 12-14 16 26] and the hormone has multiple cerebral and vascular effects which can impair the ability of the brain to adapt to hyponatraemia.[27 28] However, the genesis of hyponatraemia in children is usually different from that in adults. In adults there has often been administration of very large quantities of intravenous fluid (net retention 63 ml/kg per day in adults *v* 28 ml/kg per day in children; $p<0·01$)[3 5] or diuretic induced loss of cations.[2 6 29] It is important to recognise that in children, when there is substantial extrarenal loss of electrolytes, a minimal positive balance of hypotonic fluid can lead to fatal hyponatraemia. Another major factor which may have contributed to the high morbidity among these children was the virtual absence of timely treatment in the presence of obvious symptoms.[10 11 16 17] Furthermore, the types of operations and the clinical conditions in this patient population were similar to those most common in the United States.[20] Thus the index of suspicion for electrolyte disorders in generally healthy children undergoing elective surgery may be quite low.

BRAIN ADAPTATION TO HYPONATRAEMIA IN CHILDREN

In adults oestrogens seem to impair the ability of the brain to adapt to hyponatraemia and androgens may augment such adaptation.[30-33] However, prepubescent children have only minimal to absent concentrations of either hormone, thus negating such effects. Most adults suffering permanent brain damage from hyponatraemia are female,[3 5 7 8] but in the current series a minority of affected patients (43%) in both the prospective and retrospective studies were female. Thus unlike the marked gender differential in adults, male and female children seem to be at similar risk of developing hyponatraemia encephalopathy (NS (χ^2 test)). Furthermore, neither the actual concentration of serum sodium nor the rapidity of development of hyponatraemia seemed to predict the ultimate outcome in these 16 children (table). Hyponatraemia developed over a mean of 37 hours and the range of serum sodium values was 101-123 mmol/l, values quite similar to those previously reported in children with symptomatic hyponatraemia who did not develop brain damage.[10 12 13 16]

EFFECTS OF PHYSICAL FACTORS

When hyponatraemia was present all 16 children had radiological evidence (computed tomography, magnetic resonance imaging) of cerebral oedema

whereas at necropsy nine of 10 evaluated had cerebral oedema with herniation. These findings show that adequate adaptation of the brain to hyponatraemia had not occurred. There are several unique characteristics of the paediatric central nervous system which may impair the ability to adapt to hyponatraemia. Such characteristics may include physical factors resulting from differences in the ratio of intracranial capacity to brain size, cerebrospinal fluid volume, and brain water and electrolyte content.

The early adaptation of brain to hyponatraemia involves a loss of blood and cerebrospinal fluid followed by extrusion of sodium from brain cells.[34 35] Later adaptation includes loss of potassium and possibly amino acids, which act further to decrease brain cell osmolality and limit the gain of water.[1 34] In humans and laboratory animals brain water content is more than 2·5 times higher in the young, decreasing progressively with age.[36-38] In children the ratio of brain to skull size is such that there is less room for expansion of the paediatric brain in the skull than there is in adults.[39] As adults age there is a progressive decline in the brain volume whereas skull size remains constant.[39] Hence anatomically there is decreased room for expansion of the brain within the skull in children as compared with adults.[23]

Adult brain size is reached at about age 6 whereas full skull size is not reached until age 16. Additionally, the intracerebral volume of cerebrospinal fluid is more than 10% greater in adults than in the young.[39] When brain swelling occurs the intracerebral loss of cerebrospinal fluid increases the available volume in which the brain can expand.[35 40] As the percentage of cerebrospinal fluid in the brain increases with age[38 39] adults of both genders have more room in the rigid skull for the brain to expand than do children.[39] Furthermore, the brain intracellular concentration of sodium is about 27% higher in children than in adults[37] and may reflect a relative decreased ability to pump sodium out of the brain.[1 31 34]

PREVENTION AND TREATMENT OF HYPONATRAEMIC ENCEPHALOPATHY

Symptomatic hyponatraemia can best be prevented by not infusing hypotonic fluids to hospitalised children unless there is a clear cut indication for their use. Headache, nausea, emesis, weakness, and lethargy are consistent symptoms of hyponatraemia in children. If the condition is allowed to go untreated there can follow an explosive onset of respiratory arrest, coma, and transtentorial cerebral herniation. At present there is no way to predict which children may suffer respiratory arrest. As found recently in adults neither the magnitude of hyponatraemia nor its duration is the major determinant of brain damage.[8] Recent studies show that recovery from symptomatic hyponatraemia in children, even after the onset of seizures and apnoea, may be possible if appropriate treatment is instituted in a timely manner.[11]

When a paediatric patient receiving hypotonic fluids begins to have headache, emesis, nausea, or lethargy the serum sodium concentration must be measured. Although these symptoms are somewhat non-specific, the diagnosis is easily established at minimal cost and with virtually no risk to the patient by evaluating plasma electrolyte values. When symptomatic hyponatraemia is diagnosed the patient should be moved to a location where constant monitoring can be provided, such as the intensive therapy unit. Hypertonic sodium chloride (514 mmol/l) should be infused as described,[4 11 41] such that the serum sodium concentration is increased to 125-130 mmol/l but by no more than 25 mmol in the initial 48 hours. In addition to hypertonic sodium chloride, treatment may include intubation and assisted mechanical ventilation when required.

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Addendum

After submission of this paper a report appeared describing 34 paediatric patients with water intoxication.[42] Two of the patients became hyponatraemic secondary to intravenous hypotonic fluid administration (serum sodium concentrations 112 and 114 mmol/l). Both suffered respiratory arrest and died, and at necropsy both had cerebral oedema. These two patients had a clinical course similar to the 16 in our series. The other 32 patients had oral water intoxication, and all survived because of timely and appropriate treatment.

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First use of heroin: changes in route of administration over time

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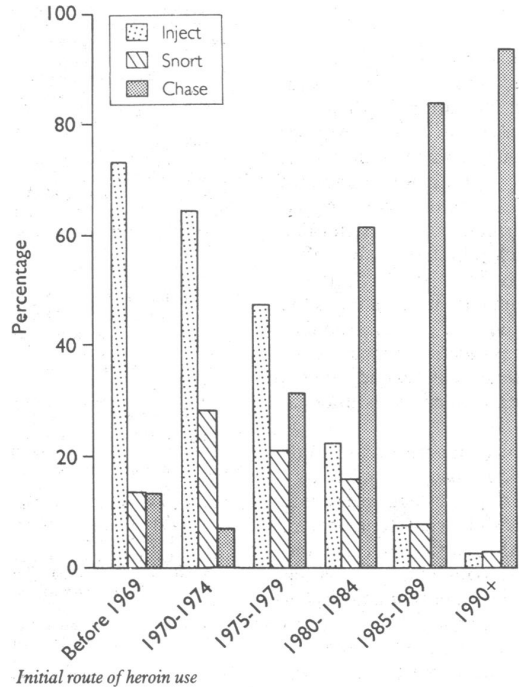
AIDS and drug misuse are linked mainly by the injection of many drugs. Major changes in the methods of heroin use, however, have fundamentally altered the importance of heroin use in the transmission of HIV. Recent reports describe the extent of "chasing the dragon" (inhaling sublimated heroin after heating it on tinfoil) as a new route of heroin use but give no information on the emergence of this pattern.[1,2] During the 1960s heroin use was by injecting.[3] What events occurred (and when) to account for this substantial change in the nature and the link with HIV of the heroin epidemic?

Subjects, methods, and results

Four hundred heroin users were contacted and interviewed by trained peer group interviewers through a structured and tape recorded interview. A total of 204 (51%) were currently out of contact with any treatment service, 100 (25%) were currently attending a drug clinic, and 124 (31%) were currently attending a needle exchange scheme. A total of 136 (34%) had never had contact with either treatment services or an exchange scheme. Their ages ranged from 17 to 53 (mean (SD) 27·6 (6·3) years); 248 (62%) were male; 96 (24%) were in current employment. There was wide variation in first year of use of heroin use (1954 to 1991): 16 (4%) started during the '60s, 28 (7%) during the early '70s, 76 (19%) during the late '70s, 124 (31%) during the early '80s, 120 (30%) during the late '80s, and 36 (9%) during the '90s.



Initial route of heroin use

Three different routes of initial drug use were identified: injecting, snorting, and "chasing the dragon." Analysis of these data by year revealed a major change in the annual proportion who were initiated by either injecting or chasing (figure).

"Chasing" was a route of initiation for a minority of users up to the late 1970s but has become an increasingly common route of initiation since 1975. By 1979 there were as many initiations by chasing as by injecting, and by 1981 more than half of the initiations into heroin use were by chasing (with the annual proportion remaining above half since 1981). By 1985 more than three quarters of initiations were by chasing, and since 1988, 87 out of 93 initiations (94%) were by chasing. During most years, a tenth to a quarter of users were initiated by snorting.

Comment

Heroin use today is not what it was yesterday. Initiation no longer occurs by injecting but by the new route of "chasing the dragon." The emergence of new non-injecting routes of heroin use may partly explain not only the major heroin epidemic in the United Kingdom during the 1980s but also its apparent continuation[4] despite the addition of AIDS as a potential consequence. Perhaps the protective societal taboo against injecting was circumvented and a less fettered epidemic has developed. In the 1990s virtually all initiations into heroin use in our London sample were by "chasing the dragon," even though heroin use in other countries (for example, the United States) and even in other British cities (for example, Edinburgh)[5] continues to be by injection. Should the change in London be regarded as an isolated development in a few "chasing" cities, or is it an indication of likely future changes on a wider scale? And what is the significance for tomorrow's prevention and treatment programmes?

Our level of ignorance about changing routes of drug administration is not only scientifically disturbing but also interferes with the development of prevention and treatment programmes. Effective primary prevention strategies depend greatly on the adequacy of knowledge about the gateways into drug use, and yet our understanding of the phenomenon is informed largely by

Fortnightly Review

Management of hyponatraemia

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Hyponatraemia occurs in many different systemic disease states and is the most frequent electrolyte abnormality seen in a general hospital population, with an incidence of about 1%.[1,2] Hyponatraemia is usually the result of dilution, although both total body water and extracellular volume may be high, low, or normal. Asymptomatic hyponatraemia is often benign, but when patients have central nervous system symptoms treatment is mandatory to prevent permanent brain damage. Almost all of the morbidity associated with hyponatraemia is due to brain damage, and recent studies show that the age and sex of the patient are major determinants of such brain damage. The incidence of symptomatic hyponatraemia is similar among men and women,[2] but most patients who develop permanent brain injury are children and menstruant women (tables I and II).[2,3] Earlier studies suggesting that severe hyponatraemia was often benign had generally evaluated only postmenopausal women and older men,[4] groups not generally susceptible to hyponatraemia induced brain injury.[2,3]

Summary points

- The morbidity associated with hyponatraemia is most closely related to the age or sex of the affected patient (highest in children and menstruant women) and is not related to either the magnitude or duration of the hyponatraemia
- When hyponatraemia is accompanied by central nervous system manifestations (hyponatraemic encephalopathy) there is substantial morbidity, whereas asymptomatic hyponatraemia is often benign
- A major cause of hyponatraemic encephalopathy and subsequent morbidity is hypotonic fluids given to postoperative patients
- Symptomatic hyponatraemia requires treatment, usually hypertonic sodium chloride infusion, limiting the magnitude of correction to about 25 mmol during the initial 24-48 hours; a loop diuretic or intubation is often indicated as adjunctive treatment
- The morbidity associated with hyponatraemic encephalopathy is primarily due to brain oedema, respiratory insufficiency, and hypoxaemia, with resultant hypoxic brain damage

Brain damage and hyponatraemia

When symptomatic hyponatraemia occurs there is usually brain oedema. If adaptation of the brain is not adequate pressure of the swollen brain on the skull can lead to a decrease in cerebral blood flow and pressure necrosis. Initial adaptation of the brain to hyponatraemia is by loss of blood and cerebrospinal fluid, followed by cellular extrusion of osmotically active cations (initially sodium, then potassium and possibly amino acids), which tends to lower the osmolality without substantial gain of water.[5] If symptomatic hyponatraemia is not corrected oedema may increase with possible tentorial herniation, often leading to respiratory arrest and cerebral hypoxia and ischaemia.[6,7]

The above sequence has been verified by computed tomography, magnetic resonance imaging, and postmortem studies in over 40 hyponatraemic patients.[2,6-8] Recent evidence suggests that contributory factors to hyponatraemic brain injury may also include (*a*) systemic hypoxaemia; (*b*) a direct vasoconstrictive effect of antidiuretic hormone on cerebral blood vessels; (*c*) female sex; (*d*) physical factors; and (*e*) preexisting liver disease, alcoholism, or structural lesions in the central nervous system.[2,3] Neither magnitude of fall nor rate of fall in serum sodium concentration is important in the genesis of brain damage (table III).[2]

TABLE I—*Distribution of cases of permanent brain damage among men and women who suffered postoperative hyponatraemia*

	All postoperative patients (n=76 678)	All hyponatraemic controls (n=674)	All hyponatraemic encephalopathy cases (n=65)	All cases with brain damage (n=34)
No (%) of men	37 626 (49)	307 (46)	25 (68)	1 (3)
No (%) of women	39 052 (51)	367 (54)	40 (62)	33 (97)

Data from Ayus *et al.*[2]
Statistical comment: Sex distribution was not significantly different among the hyponatraemic controls or the 65 cases. But of the 34 patients who died or suffered permanent brain damage, 33 were women ($p<0.001$). Relative risk of dying or developing permanent brain damage was 28 times greater in women than men (95% confidence interval 5 to 141).

TABLE II—*Menstruant states of women with brain damage resulting from asymptomatic postoperative hyponatraemia*

	All postoperative female patients (n=39 052)	All female hyponatraemic controls (n=367)	All female cases with brain damage (n=33)
No (%) of menstruant patients	21 088 (54)	39 (11)	25 (76)
No (%) of postmenopausal patients	17 964 (46)	328 (89)	8 (24)

Data from Ayus *et al.*[2]
Statistical comment: Among female controls distribution of menstruant and postmenopausal patients was significant ($p<0.001$). Distribution of menstruant and postmenopausal patients was also significant among patients with brain damage ($p<0.001$). Relative risk of dying or developing brain damage from postoperative hyponatraemia was 26 times as great among menstruant women than among postmenopausal women (95% confidence interval 11 to 62).

Causes of hyponatraemia

POSTOPERATIVE HYPONATRAEMIA

Postoperative hyponatraemia is a frequent and potentially dangerous complication among adults in

TABLE III—*Effects of rate of fall of plasma sodium concentration and magnitude of postoperative symptomatic hyponatraemia in men and women*

	Duration of hyponatraemia (hours)		Plasma sodium concentration (mmol/l)	
	<24	≥24	86-115	116-128
No (%) of men	14 (56)	11 (44)	15 (60)	10 (40)
No (%) of women	13 (42)	27 (68)	19 (48)	21 (52)

Data from Ayus *et al.*[2]
Statistical comment: Whatever the grouping, mortality was significantly greater in women than in men ($p<0.001$). Differences in mortality between women whose plasma sodium concentration was greater than on up to 115 mmol/l or whose duration of hyponatraemia was greater than or up to 24 hours were all not significant.

the United States and United Kingdom.[1,2] In the United States the incidence of postoperative hyponatraemia is about 1%, or about 250 000 cases among the roughly 25 million inpatient operations that are performed each year.[2] Raised plasma antidiuretic hormone concentrations with impaired excretion of free water occur in almost all patients in the first two to six days after operation[1] in response to multiple non-osmotic stimuli—for example, pain, fear, blood loss, anaesthesia, anxiety, vomiting, volume depletion, and narcotics or sedative-hypnotics.[9] During certain operations—for example, transurethral prostate resection and endometrial ablation—hypotonic solutions used to irrigate the operative site may be rapidly absorbed through opened veins, with an effect similar to intravenous administration.[10,11] Thus any patient in the postoperative period should be considered at risk of hyponatraemia and be given appropriate prophylaxis. Of critical importance is the choice of intravenous fluids.

INTRAVENOUS FLUIDS

The most common cause of in hospital hyponatraemia in the United States and United Kingdom is intravenous hypotonic fluids. Apparently based on anecdotal data and recommendations made before 1950, some physicians still infuse hypotonic solutions postoperatively, often glucose in water (280 mmol/l).[7] The rationale for using hypotonic fluids in the postoperative period is unclear, as few objective data support the practice. Before 1950 there were suggestions that postoperative infusion of isotonic sodium chloride might lead to complications,[12] including worsening of glomerulonephritis,[13] with vague references to postoperative "salt intolerance".[14] However, data published after the early 1950s all suggest that the practice is probably without scientific justification. Since the 1930s a profusion of studies have shown the propensity of intravenous hypotonic solutions to cause death or permanent brain damage in the postoperative period.[9,15] Since the 1960s most textbooks of surgery, gynaecology, medicine, and nursing have emphasised the dangers of postoperative hypotonic fluids.[9,16] Permanent brain damage from hyponatraemia is very often a direct consequence of improper fluid administration.[2,3,5-7,17]

AIDS

AIDS is a major cause of hyponatraemia.[18] The hyponatraemia in AIDS may be secondary to inappropriate secretion of antidiuretic hormone, often associated with pulmonary or intracranial lesions; to volume deficiency (due to vomiting or diarrhoea) and replacement by hypotonic fluids[18,19]; or to mineralocorticoid deficiency, often with intact glucocorticoid secretion.[18,20] In the presence of mineralocorticoid deficiency the result of the corticotrophin stimulation test may be normal, possibly because AIDS often affects the zona glomerulosa of the adrenal gland.[20] In such patients fludrocortisone acetate is indicated if renal salt wasting can be shown in the presence of hyponatraemia.

ROLE OF HORMONES

The plasma antidiuretic hormone concentration is often "inappropriately" raised in hyponatraemia.[6] Associated clinical conditions include volume depletion, secretion of antidiuretic hormone by certain malignant tumours, and certain brain and pulmonary lesions.[9] Symptomatic hyponatraemia may occur during labour and delivery or during treatment for gastrointestinal haemorrhage in patients receiving hypotonic fluid and either vasopressin or oxytocin. These agents should be given in isotonic sodium chloride. Desmopressin given with excess free water has been associated with symptomatic hyponatraemia.[8] Both adrenal insufficiency and hypothyroidism may contribute to hyponatraemia. Finally, oestrogen may impair and testosterone augment brain adaptation to hyponatraemia.[8]

PHARMACOLOGICAL AGENTS

Many pharmacological agents may interfere with the ability of kidney to excrete free water. They include sedatives, hypnotics, analgesics, oral hypoglycaemics, tranquillisers, narcotics, antineoplastic drugs, antipsychotic agents, and diuretics. In most instances there is retention of ingested free water. In the case of thiazide associated hyponatraemia there is often an idiosyncratic reaction to thiazides, with a combination of massive loss of sodium and potassium in the urine and associated polydipsia.[21] Often hyponatraemia which occurs as a side effect of a drug will respond to discontinuation of the offending agent. If such patients have symptoms hypertonic sodium chloride should be instituted in order to prevent respiratory insufficiency and permanent brain damage.[21,22]

PSYCHOGENIC POLYDIPSIA

Another common setting in which symptomatic hyponatraemia may occur is psychogenic polydipsia.[23] Maximal free water clearance in adults is around 700 ml/h (17 l/day) or more. Thus to develop hyponatraemia in the absence of raised plasma concentrations of antidiuretic hormone a 60 kg adult would need to drink over 20 l/day. Most patients who have psychogenic polydipsia and hyponatraemia associated with oral water intoxication have actually ingested less water than the maximal daily renal excretion. Instead, they have a smaller fluid intake but abnormal urinary dilution with excessive antidiuretic hormone secretion.[24] Beer potomania somewhat resembles psychogenic polydipsia, but the hyponatraemia is associated with massive ingestion of beer and carries a high mortality.[25]

Treatment

ASYMPTOMATIC HYPONATRAEMIA

Asymptomatic hyponatraemia generally does not require aggressive treatment with hypertonic sodium chloride, as pharmacological measures combined with water restriction are often sufficient, particularly if the plasma sodium concentration exceeds 120 mmol/l. In patients who are obviously volume depleted isotonic (154 mM) sodium chloride is usually the fluid of choice. When adrenal insufficiency or hypothyroidism has been identified appropriate hormone replacement is warranted. If the patient is receiving drugs which might contribute to hyponatraemia they should be discontinued if possible. Water restriction is theoretically important in patients without symptoms, but from practical considerations, particularly compliance, it is generally not useful. Fluid restriction of less than 1 l/day will result in a negative water balance but only a

slow increase in the serum sodium concentration, rarely exceeding 1·5 mmol/l/24 h.

Several medical regimens have been used for the long term management of patients with asymptomatic hyponatraemia. With chronic "inappropriate" increase in the antidiuretic hormone concentration lithium will often induce nephrogenic diabetes insipidus, but generally produces an erratic response. Lithium toxicity may affect kidneys, central nervous system, heart, haemopoietic system, and thyroid.[15] Demeclocycline, a tetracycline antibiotic, may be used to induce nephrogenic diabetes insipidus in doses above 600 mg/day. It has been used successfully to treat patients with raised antidiuretic hormone concentrations, but acute renal failure and renal tubular toxicity have been reported in hyponatraemic patients with heart failure or cirrhosis.[15] Other possible pharmacological agents for chronic hyponatraemia include urea and inhibitors of antidiuretic hormone. Finally, correction of the functional state of intravascular volume depletion that exists in heart failure and decompensated cirrhosis are often associated with improvement of hyponatraemia. In cirrhosis with ascites this can sometimes be achieved after placing a peritoneal-jugular shunt.

SYMPTOMATIC HYPONATRAEMIA

In patients with symptomatic hyponatraemia the most frequent presenting symptoms are headache, nausea, vomiting, and weakness, the presence of at least one of these defining encephalopathy.[7] Less frequent and more severe symptoms are shown in box 1. Respiratory arrest with hypoxia is a persistent feature in symptomatic hyponatraemic patients who suffer brain damage.[2,3] Thus the therapeutic objective in such patients is reduction of brain oedema by increasing the serum sodium concentration such that the patient becomes asymptomatic with adequate ventilation. In patients with symptomatic hyponatraemia the morbidity and mortality associated with treatment by water restriction are unacceptably high.[26-28] The most appropriate therapeutic regimen for such patients is hypertonic (usually 514 mM) sodium chloride,[26] often given in conjunction with a loop acting diuretic such as frusemide (box 2).[29] In some patients, particularly those with raised antidiuretic hormone concentrations, hyponatraemia, and volume expansion or circulatory insufficiency, simultaneous administration of frusemide may be necessary to prevent circulatory overload.[29] Isotonic (154 mM) sodium chloride is indicated only if the patient is volume and sodium chloride depleted. Such patients include those with volume depletion due to vomiting, sweating, or diarrhoea, who have ingested free water.

The most appropriate setting for correction of symptomatic hyponatraemia is the intensive care unit, where neurological, respiratory, and haemodynamic function can be monitored. Patients with arterial hypoxaemia or respiratory insufficiency should be intubated and mechanically ventilated. Total body water volume should be estimated (figure); the mean in hospitalised adults is about 50%.[9]

Hypertonic (514 mM) sodium chloride should be delivered by a constant infusion pump, with correction planned over 24 to 48 hours at a rate set to increase the serum sodium concentration by about 1 mmol/l/h (box 2). The end point is a plasma sodium concentration that is increased by 20-25 mmol/l or has reached 130 mmol/l, or a patient who has become asymptomatic

Box 1—Signs and symptoms of hyponatraemia

Early hyponatraemic encephalopathy

- Headache
- Nausea
- Vomiting
- Weakness

Advanced hyponatraemic encephalopathy

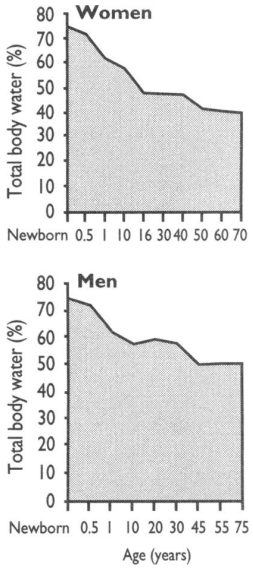
- Impaired response to verbal stimuli
- Impaired response to painful stimuli
- Bizarre (inappropriate) behaviour
- Visual hallucinations
- Auditory hallucinations
- Obtundation
- Urinary incontinence
- Faecal incontinence
- Hypoventilation

Very advanced hyponatraemic encephalopathy (manifestations secondary to increased intracranial pressure)

- Decorticate or decerebrate posturing, or both
- Unresponsiveness
- Bradycardia
- Hypertension
- Altered temperature regulation (hypothermia or hyperthermia)
- Dilated pupils
- Seizure activity (focal or grand mal or both)
- Respiratory insufficiency
- Respiratory arrest
- Coma
- Polyuria (secondary to central diabetes insipidus)

Box 2—Treatment of symptomatic hyponatraemia: basic outline

- Active treatment (infusion of hypertonic sodium chloride) is needed only if the hyponatraemia is symptomatic
- Target of treatment is a serum sodium concentration of about 130 mmol/l, but correction by no more than 25 mmol/48 h
- Determine patient's total body water volume (litres)
  as a percentage of body weight (kg)
- Subtract patient's serum sodium concentration (mmol/l) from 130 mmol/l. Difference is the needed correction of the serum sodium concentration (in mmol/l)
- Needed correction of the serum sodium concentration (in mmol/l) is the same as the number of hours over which the serum sodium concentration should be corrected
- Multiply the total body water volume (litres) by the needed correction of the serum sodium concentration (mmol/l). This gives the number of mmol of sodium needed to correct the patient's serum sodium concentration to 130 mmol/l
- Number of mmol of sodium needed for correction is then divided by 514 (the number of mmol of sodium in 1 litre of 514 mM sodium chloride). This number times 1000 gives the number of ml of 514 mM sodium chloride needed to correct the serum sodium value to 130 mmol/l
- Divide the number of ml of 514 mM sodium chloride to be given by the number of hours needed for correction of the serum sodium value. This gives the infusion rate of 514 mM sodium chloride in ml/h
- For patients with circulatory impairment, or hypervolaemia with raised plasma concentrations of antidiuretic hormone, give frusemide concomitantly with hypertonic sodium chloride such that there is a net free water diuresis without a net loss of sodium in the urine



Total body water volume as percentage of body weight in women and men throughout life

TABLE IV—*Change in plasma sodium concentration with rapid correction of severe symptomatic hyponatraemia in 167 paediatric and adult patients from three different countries and six different states in the United States*

	Initial plasma sodium (mmol/l)	Final plasma sodium (mmol/l)	Absolute change (after 24-48 hours) (mmol/l)	Rate of correction (mmol/l/h)
Mean (SD)	112 (8)	132 (5)	20 (5)	1·6 (0·8)

Data compiled from Arieff and Ayus,[10] Worthley and Thomas,[17] Ayus *et al*,[22] Cheng *et al*,[23] Ayus *et al*,[26] Hantman *et al*,[29] and Sarnaik *et al*.[30]

(table IV). The serum sodium concentration should not be corrected to normal values, nor should hypernatraemia be allowed to develop. The regimen may require modification in patients with severe hepatic, renal, or cardiac disease. The absolute increase in the serum sodium concentration must be limited to 25 mmol/l within the initial 48 hours of treatment,[26] but the rate of correction of hyponatraemia is not important in the outcome.[2 17 30] Initially the patient's total body water volume should be estimated (figure). Total body water volume varies with age, sex, and weight from about 72% in infants to 35% in elderly obese women.

COMPLICATIONS OF CORRECTING HYPONATRAEMIA

Circulatory congestion is a potential complication of correcting hyponatraemia with intravenous sodium chloride solutions. Such a complication is rare and may be forestalled by giving hypertonic sodium chloride and frusemide.[29] In the past there was controversy regarding the rate of correction of symptomatic hyponatraemia. It was suggested that development of a rare neurological syndrome, central pontine myelinolysis[31] (sometimes called "osmotic demyelination"), might be the result of "rapid" correction of "chronic" hyponatraemia.[4] It had been proposed that if the increase in serum sodium concentration did not exceed some arbitrary rate, often said to be 0·6 mmol/l/h, such complications could be prevented.[4 15] Virtually all hyponatraemic patients in whom cerebral lesions developed after active correction had suffered a hypoxic episode or had their serum sodium concentration corrected to either normonatraemic or hypernatraemic levels or increased by more than 25 mmol/l during the first 48 hours.[26] The vast majority of patients with central pontine myelinolysis have not had hyponatraemia but, rather, severe associated medical conditions, such as advanced liver disease, alcoholism, extensive burns, sepsis, or malignancies.[15 31]

The diagnosis of central pontine myelinolysis requires either histological confirmation or radiological studies with computed tomography or magnetic resonance imaging.[8] With such criteria central pontine myelinolysis is almost never observed in patients who have been hyponatraemic. Rather, the observed lesions are diffuse areas of cerebral infarction with secondary cerebral demyelinating lesions.[6 8] Multiple clinical conditions occur in the absence of hyponatraemia but which are associated with brain lesions which resemble central pontine myelinolysis—for example, subcortical arteriosclerotic encephalopathy, radiotherapy, multiple ischaemic lesions, and sequelae of head trauma.[15] Furthermore, cerebral lesions similar to those sometimes called "osmotic demyelination" are found in untreated hyponatraemic patients.[6] Thus use of terms such as "central pontine myelinolysis" or "osmotic demyelination syndrome" to describe patients with hyponatraemia and brain damage seems unwarranted. The rate of correction is not a factor in the genesis of hyponatraemic brain injury. There are worldwide prospective reports of over 160 patients who have undergone "rapid" correction (mean 1·6 mmol/l/h) of symptomatic hyponatraemia without morbidity,[10 17 22 23 26 29 30] clearly documenting both the safety and the efficacy of this approach (table IV).

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Correction

Guidelines for the management of spontaneous pneumothorax

An authors' error occurred in figure 1 of this article by A C Miller and J E Harvey on behalf of the standards of care committee of the British Thoracic Society (10 July, pp 114-6). In section 4 of figure 1, on simple aspiration, the cannula is described as being of French gauge 16 or larger; this should read standard wire gauge 16.

antiarrhythmic drugs are ineffective or not tolerated. Patients who have frequent atrial ectopic beats with a consistent P wave morphology indicating a single ectopic focus are most suited to focal ablation (fig 3). This procedure is new and has not yet been adopted by all regional electrophysiology centres.

For persistent and permanent atrial fibrillation, ablation of the His bundle and implantation of a pacemaker is a good option if satisfactory control of heart rate cannot be achieved with atrioventricular node blocking drugs, or if side effects occur. This procedure can also be used for paroxysmal atrial fibrillation in patients not suited to focal ablation. Although promising, linear ablation is still an experimental treatment and requires further evaluation before it can be recommended in clinical practice.

Competing interests: None declared.

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Lesson of the week

Acute hyponatraemia in children admitted to hospital: retrospective analysis of factors contributing to its development and resolution

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Do not infuse a hypotonic solution if the plasma sodium concentration is less than 138 mmol/l

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continued over

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Hyponatraemia (plasma sodium concentration less than 136 mmol/l) is acute if the decrease in natraemia occurs within 48 hours. The major dangers from this are brain cell swelling and herniation.[1 2] Two factors are required for hyponatraemia to develop: a source of electrolyte free water and vasopressin to prevent the excretion of that water.[3] Electrolyte free water is given routinely as maintenance fluids based on formulas developed in studies in healthy children more than 40 years ago.[4 5] There are many reasons to anticipate that vasopressin will be released in sick patients (box).[6] Patients with an acute illness may arrive in hospital with a low plasma sodium concentration because of previous water intake. Hence, to minimise the potential threat of brainstem herniation it is important to measure the plasma sodium concentration if intravenous solutions are to be given.

We describe symptomatic hyponatraemia developing over 48 hours in children. In each patient, hypotonic solutions were infused using current guidelines.[7] We related the volume of electrolyte free water given to the decrease in natraemia and assessed whether actions of vasopressin persisted to guide emergency corrective therapy.[8]

Causes of vasopressin release

- Hypernatraemia (most important stimulus, but not in these patients)
- Low "effective" circulating volume (greater than 7% decrease in extracellular fluid volume)
- Nausea, pain, anxiety
- Drugs (some act through inducing nausea)
- Afferent stimuli by way of the vagus nerve—for example, lung lesions
- Disturbances of the central nervous system (meningitis, encephalitis)
- Metabolic and endocrine disorders—for example, hypothyroidism, hypoadrenalism, porphyria

We reviewed all patient charts (306 charts) with a recorded diagnosis of hyponatraemia for the past 10 years. Patients were included if their decrease in natraemia was to less than 130 mmol/l and this occurred within 48 hours, if intravenous fluids were given, and if an underlying disease did not compromise renal handling of sodium or water. Thirty patients had acute hyponatraemia. Crucial information was missing for seven, leaving 23 patients in the study group. The median age was five years (range one month to 21 years), with males predominating (18 of 23); 13 developed hyponatraemia in the postoperative period. Fifteen patients were referred to the critical care unit after the development of symptomatic hyponatraemia while receiving intravenous fluids—11 were from the hospital wards and four were transferred from other institutions. Symptoms included seizures (18 patients) and vomiting,[17] a warning sign of an increased intracranial pressure. Treatment was withdrawn from five patients after brainstem coning. One patient sustained permanent, severe neurological damage.

Results

All the children received hypotonic fluids while their plasma sodium concentration was less than 140 mmol/l, because of the wide belief in paediatric practice that "maintenance fluids" should be hypotonic.[9] In fact the volume of maintenance fluid given was 50% greater than recommended values in 16 of the 23 patients. This infusion of hypotonic fluids increased the risk of acute hyponatraemia and brain swelling because vasopressin is typically present in this setting.[1 2 10 11] In quantitative terms, some of the electrolyte free water infused was retained in six of the patients because their urine sodium plus potassium concentration was less than 25 mmol/l (fig 1). In six patients more electrolyte free water was infused than needed to cause the observed decline in natraemia (points above line of identity in fig 2). The remainder of the patients had a decrease in natraemia that exceeded the decline if the entire volume of electrolyte free water infused was retained (points below broken line in fig 2). Therefore there was either another non-recorded input of water or the excretion of a large volume of hypertonic urine (a desalination of infused isotonic saline[12]).

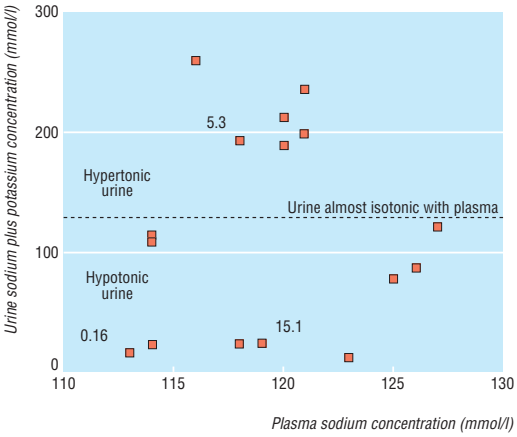

Fig 1 Concentration of sodium and potassium in urine at nadir observed for plasma sodium concentration in 17 patients (numbers represent rate of urine flow)

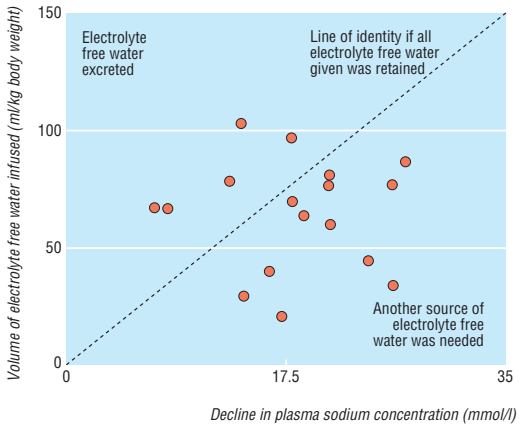

Fig 2 Comparison of decline in plasma sodium concentration with amount of electrolyte free water given in 17 patients. Difference in sodium concentration was between initial value and that at its nadir

Discussion

One objective of our study was to assess the renal actions of vasopressin. Because six patients had very hypotonic urine at their recorded nadirs of natraemia, their plasma sodium concentration might have been much lower before water diuresis began (fig 1). Had their plasma sodium concentration been measured after this large water diuresis, the erroneous conclusion might have been drawn that acute hyponatraemia had never been present. Hence its incidence may be much higher than shown by an analysis of hospital records. Therefore acute hyponatraemia could have been an occult cause of morbidity and mortality.

Another implication of cessation of the release of vasopressin concerns treatment. Treatment for acute, symptomatic hyponatraemia causes a prompt decline in the size of brain cells.[10] Hypertonic saline (3%) is the commonest treatment for shrinking brain cell volume, thereby lowering intracranial pressure. Treatment must be prompt because deterioration may be rapid and irreversible, even when symptoms are mild. Enough hypertonic saline (a total of 5 mmol of sodium chloride per litre of body water[13]) is needed acutely to lower intracranial pressure sufficiently to minimise this risk (the plasma sodium concentration should be increased by 5 mmol/l over several hours). Because an excessively rapid rate of correction of hyponatraemia might have deleterious effects,[6] hypertonic saline should not be given if there is a brisk water diuresis. For example, the plasma sodium concentration will also increase by 1.2 mmol/l/h if 6 ml of electrolyte free water are excreted per kilogram per hour (total body water is close to 600 ml/kg; 6 ml is a 1% change of 120 mmol/l). Whereas excretion of hypotonic urine indicates that electrolyte free water is being excreted (6 of 17 patients, fig 1), it is also important to consider the rate of urine flow. Little electrolyte free water was excreted in the index oliguric patient (flow 0.16 ml/kg/h). By contrast, the excretion of electrolyte free water was high enough to increase the plasma sodium

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concentration by close to 3 mmol/l/h in the polyuric index patient who recovered (15 ml/kg/h). Vasopressin continued to act in patients excreting isotonic or hypertonic urine, so hypotonic intake must be avoided in them. With these high urine tonicities a further decrease in natraemia would be anticipated if the urine output was high (index case designated with a urine output of 5.3 ml/kg body weight, fig 1).[12] Finally, vasopressin concentrations may decline abruptly, increasing the excretion of electrolyte free water.

Serious symptoms may become evident when hyponatraemia approaches 120 mmol/l, but there are cases where symptoms become evident with a higher plasma sodium concentration, whereas others tolerate this electrolyte disorder without developing seizures.[14] Apart from underlying conditions that might make a patient more susceptible to seizures, a possible important factor could be the extracellular fluid volume of the brain. If this volume was expanded by a large infusion of isotonic saline, a higher intracranial pressure might be present at a given degree of hyponatraemia. Moreover, because there is a relatively larger proportion of brain cell volume to extracellular fluid volume in young patients, they are more vulnerable to an increase in brain cell volume.

Study limitations

Because of a reporting and referral bias, the incidence of adverse outcomes from hyponaetremia cannot be deduced from these data. Our results highlight the dangers of the routine use of hypotonic solutions when vasopressin acts. The currently used guidelines for maintenance fluids in children admitted to hospital must be changed because they do not take into account the unpredictability of vasopressin secretion. We recommend that the concentration of plasma sodium should be measured when starting an intravenous infusion. If it is less than 140 mmol/l then isotonic and not hypotonic fluids should be given. The use of hypotonic solutions should be reserved for patients who have a plasma sodium concentration greater than 140 mmol/l. If a patient receives intravenous fluid that exceeds 5% of total body water (30 ml/kg) then their plasma sodium concentration should be measured. If an intravenous infusion is started to give drugs, a small volume should be used, and the solution should be isotonic if possible.

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When I use a word …

The last word

Sometimes short words are the most interesting. Like the definite and indefinite articles, "the" and "a(n)" (see also *BMJ* 1999;318:1758 and 2000;321:953). Not for nothing does the *Oxford English Dictionary* devote four pages to the different forms and meanings of "the."

When President Kennedy visited Berlin in June 1963 he made a famous speech in which he proclaimed that "All free men, wherever they may be, are citizens of Berlin, and, therefore, as a free man, I take pride in the words 'Ich bin ein Berliner.'" Now had he been in Hamburg and announced that he was a Hamburger, he would have immediately caused some amusement. But, at home at least, the fact that he had announced himself to be a doughnut (ein Berliner) went virtually unnoticed. And although his version was not an appalling solecism, "Ich bin Berliner" (without the definite article) would have been better.

Nowadays politicians take greater care over their definite articles. As I have previously pointed out (*BMJ* 2000;320:1480), "the" is used by modern spin doctors to give verisimilitude to non-existent entities. For instance, when Tony Blair talks about "the international community," he is trying to persuade us to believe that there is such a thing.

Politicians also sometimes talk about the psychological moment, meaning the time at which something is best done. When they do so they fail to realise that the phrase originally meant something completely different. It came from the German, das psychologische Moment, the psychological momentum. The psychological moment would have been der Moment, not das. French journalists were to blame. According to Fowler in *Modern English Usage* (1926) and Burchfield in *The New Fowler's Modern English Usage* (1996) they translated it during the German siege of Paris in 1870 as "le moment psychologique." Unfortunately, in French, as in English, moment means only moment and not also momentum.

Another journalist, Mary McCarthy, showed how much damage the definite article could wreak in a scathing comment about Lilian Hellman, for which Hellman sued for $2m (dying before judgment was passed). "Every word [Hellman] writes," said McCarthy, "is a lie, including 'and' and 'the.'"

But perhaps the (literally) last word should be left to James Joyce. He ended *Ulysses* with "the least forceful word I could possibly find … the word 'yes,' which is barely pronounced, which denotes acquiescence, self abandon, relaxation, the end of all resistance." For *Finnegans Wake* he searched harder: "This time, I have found the word which is the most slippery, the least accented, the weakest word in English, a word which is not even a word, which is scarcely sounded between the teeth, a breath, a nothing, the article *the*."

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ORIGINAL ARTICLE

Hypotonic versus isotonic saline in hospitalised children: a systematic review

K Choong, M E Kho, K Menon, D Bohn

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Background: The traditional recommendations which suggest that hypotonic intravenous (IV) maintenance fluids are the solutions of choice in paediatric patients have not been rigorously tested in clinical trials, and may not be appropriate for all children.
Aims: To systematically review the evidence from studies evaluating the safety of administering hypotonic versus isotonic IV maintenance fluids in hospitalised children.
Methods: Data sources: Medline (1966–2006), Embase (1980–2006), the Cochrane Library, abstract proceedings, personal files, and reference lists. Studies that compared hypotonic to isotonic maintenance solutions in children were selected. Case reports and studies in neonates or patients with a pre-existing history of hyponatraemia were excluded.
Results: Six studies met the selection criteria. A meta-analysis combining these studies showed that hypotonic solutions significantly increased the risk of developing acute hyponatraemia (OR 17.22; 95% CI 8.67 to 34.2), and resulted in greater patient morbidity.
Conclusions: The current practice of prescribing IV maintenance fluids in children is based on limited clinical experimental evidence from poorly and differently designed studies, where bias could possibly raise doubt about the results. They do not provide evidence for optimal fluid and electrolyte homoeostasis in hospitalised children. This systematic review indicates potential harm with hypotonic solutions in children, which can be anticipated and avoided with isotonic solutions. No single fluid rate or composition is ideal for all children. However, isotonic or near-isotonic solutions may be more physiological, and therefore a safer choice in the acute phase of illness and perioperative period.

Intravenous (IV) maintenance fluids are designed to provide free water and electrolyte requirements in a fasting patient. The prescription for IV maintenance fluids was originally described in 1957 by Holliday and Segar, who equated free water requirements from energy expenditure in healthy children.[1] They rationalised adding 3.0 and 2.0 mEq/100 kcal/24 h of sodium and potassium respectively, as it approximates the electrolyte requirements and urinary excretion in healthy infants.[2 3] This is the basis for the current recommendation that hypotonic IV maintenance solutions are ideal for children.[4 5] The Holliday–Segar system remains the most universally used to date, because of the simplicity of their formula. While these recommendations may be appropriate for the healthy child, they do not necessarily apply in acute illness, where energy expenditure and electrolyte requirements deviate significantly from this formula.[6]

The numbers of deaths and significant neurological sequelae from hospital acquired hyponatraemia in children receiving hypotonic maintenance solutions have increased in the past 10 years.[7–11] Several narrative reviews have suggested potential harm with these solutions and recommend that routine use in children be reconsidered.[12 13] Despite these concerns, standard texts and guidelines continue to recommend hypotonic maintenance solutions for all paediatric patients.[4 5] The objective of this systematic review was to evaluate the safety of hypotonic versus isotonic IV maintenance solutions in hospitalised children. Our secondary objective was to identify subgroups who are at greater risk of morbidity, in whom hypotonic solutions should be avoided.

METHODS

Search strategy

We searched Medline (1966–2006), Embase (1980–2006), and the Cochrane Library, using the terms: ''fluid therapy'', ''hypotonic solution'', ''isotonic solution'', and synonyms or related terms (Appendix 1; see http://www.archdischild.com/supplemental). We searched online (FirstSearch, Conference Proceedings) or published conference proceedings, and Current Controlled Trials (www.controlled-trials.com). Abstracts from the following 2002–05 scientific forums were hand searched: World Congress on Pediatric Intensive Care, Society for Pediatric Research, Critical Care Congress, and American Academy of Pediatrics. We reviewed the reference lists of all identified studies and reviews, and also personal files, and contacted experts and first authors to identify other published or unpublished studies.

Study selection

Citations considered potentially relevant by either of two reviewers (KC or MK) were retrieved using the following inclusion criteria:

- Controlled trials, cohort, and case-control studies. Cohort studies had to compare patients receiving hypotonic IV maintenance solutions with a control group or unexposed cohort who received isotonic solutions. Case-control studies had to compare cases, to a control group who did not have the outcomes of interest.
- Children (1 month to 17 years) hospitalised for any medical or surgical condition. We included a diverse paediatric population to capture all potential patients who currently receive ''standard IV maintenance therapy''.
- Intervention: currently used hypotonic and isotonic IV maintenance solutions. Solutions were classified as

Abbreviations: CI, confidence interval; ECF, extracellular fluid; IV, intravenous; PNa, plasma sodium; RCT, randomised controlled trial; WMD, weighted mean difference

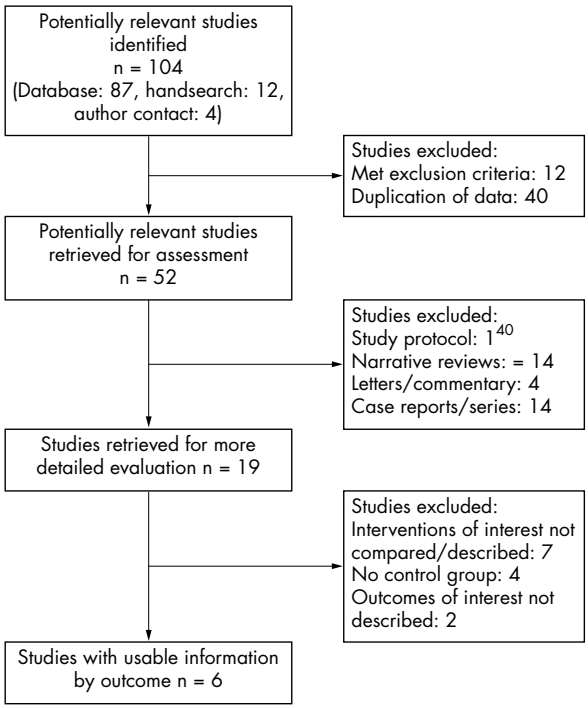

Figure 1 Flow diagram of the study selection process for this systematic review.[33]

''hypotonic'' if they contained <0.9% NaCl, or ''isotonic or near isotonic'' (i.e. 0.9% NaCl or Ringers Lactate). We excluded case reports and studies of fluid resuscitation and oral rehydration therapy. Studies enrolling neonates, patients with pre-existing hyponatraemia and co-morbidities which result in sodium derangements (e.g. renal disease, diabetes insipidus, diuretic therapy), were also excluded.

Study outcomes

Studies were included if any of the following outcomes related to the development of acute hospital acquired plasma sodium (PNa) derangements and/or their attributed morbidity were reported: fluid balance, clinical evidence of volume overload, hypertension, seizures, cerebral oedema, death, paediatric intensive care unit admission, and length of stay. We used PNa as a surrogate outcome, as it is a convenient reflection of tonicity balance, and represents the potential for fluid shifts between intracellular and extracellular fluid (ECF) compartments. This in turn may result in clinically relevant morbidity, such as the defined outcomes of interest. A priori, we defined hyponatraemia as PNa <136 mmol/l, and severe hyponatraemia as PNa <130 mmol/l, or any level of hyponatraemia associated with symptoms. We also examined hypernatraemia since the arguments against the use of isotonic solutions in children include renal solute loading and the risk of increasing PNa. We defined hypernatraemia as PNa >145 mmol/l.

Data abstraction and study quality

In duplicate and independently, we abstracted data to describe the methodological quality and clinical characteristics of these trials. We contacted authors where necessary for additional data on outcomes of interest. We extracted the following information: study population, sample size, intervention, duration, and type of exposure and outcomes. The methodological quality of included studies was assessed using predefined criteria (Appendices 2 and 3; see http://www.archdischild.com/supplemental).

Data analysis

Cohen's Kappa statistic was used to calculate agreement between raters. For categorical outcomes, treatment effects were expressed as odds ratios (OR) and 95% confidence intervals (CI). We described treatment effects of continuous outcomes using weighted mean differences (WMD) and 95% CI. We calculated summary risk differences and 95% CI using a random effects model (RevMan Version 4.2). Where statistical pooling was not possible, we described our findings qualitatively.

RESULTS

Study selection

We identified 52 potentially relevant articles from 104 citations (fig 1); 33 did not meet inclusion criteria. Of the 19 studies retrieved for detailed evaluation, seven did not describe or compare the interventions of interest, four did not describe a control group, and two did not report any of the outcomes of interest. Six studies satisfied all criteria (table 1). Cohen's Kappa for inclusion decisions was 0.81 (almost perfect agreement).

Study characteristics

We report the characteristics of the six included studies in table 1. There were two unmasked randomised controlled trials (RCT),[14 15] and one non-randomised controlled trial.[16] Three were observational studies.[17–19] Tables 3–5 outline the study quality and methodological characteristics—the overall quality of included studies was often limited; allocation concealment, blinding of patients, clinicians, outcomes assessors, and outcomes were inconsistently or not reported across studies.

Clinical outcomes

Plasma sodium

The standard deviations (SD) were not presented for PNa in one of the studies.[14] Thus, we calculated a pooled SD to compare the PNa across studies. Hypotonic maintenance solutions significantly increased the risk of developing hyponatraemia (OR 17.22; 95% CI 8.67 to 34.2) (fig 2). Mean PNa in patients following hypotonic solutions was significantly lower (−3.39 mmol/l; 95% CI −5.35 to −1.43), than those who received isotonic solutions (fig 3). The PNa also decreased significantly greater in patients who received hypotonic solutions (−5.37 mmol/l; 95% CI −8.79 to −1.94, fig 4). None of the studies reported the development of hypernatraemia. However, three studies reported a *decrease* in PNa despite the infusion of isotonic or near-isotonic IV maintenance fluids (table 1).[15 17]

Morbidity attributed to hyponatraemia

Adverse clinical outcomes were reported in three studies.[17–19] Wilkinson reported seizures in 2/26 patients receiving hypotonic fluids (OR 6.22; 95% CI 0.29 to 135.8).[19] Hoorn reported nausea and vomiting more commonly in patients with hospital acquired hyponatraemia (68%, $p = 0.008$)[18] than isonatraemic controls. The presence of increased pulmonary interstitial fluid on chest *x* ray was reported by Burrows in 15/20 of patients receiving hypotonic solutions and 2/4 in the near-isotonic group.[20] The clinical significance of this finding was not commented on by the authors. Other outcomes of interest as listed in our objectives were not reported.

Table 1 Characteristics of included studies

	Brazel (1996)[14]	Dagli (1997)[16]	Neville (2006)[15]	Hoorn (2004)[18]	Burrows (1983)[17]	Wilkinson (1992)[19]
Participants						
n	12	60	104	148	24	56
Age (years)	12.3–18.1	1–12	6 months–14 years	7±6	6–16	2 months–14 years
Inclusion criteria	Adolescent females undergoing idiopathic scoliosis repair	ASA 1 patients undergoing elective minor surgery	Gastroenteritis with dehydration	37 patients with hospital acquired hyponatraemia, 111 isonatraemic historical controls	Previously healthy patients with idiopathic scoliosis undergoing surgical correction	Craniofacial surgery
Methodology	RCT, unmasked	Controlled trial	RCT, unmasked	Case control	Cohort study	Retrospective chart review
Intervention (all solutions included appropriate dextrose content unless otherwise stated)	Near isotonic solution (LR), n=5; v hypotonic solutions: (0.3%–0.18% NaCl), n=7	Gp 1: LR Gp 2: 1% Dextrose in LR Gp 3: 3.3% Dextrose in 0.3% NaCl	Gp1: 0.45% NaCl Gp 2: 0.9% NaCl	Standard prescription for maintenance IV fluids	Postoperative maintenance fluids: Isotonic (LR), n=4 Hypotonic (0.25–0.5% NaCl), n=20	Isotonic (LR or NS), n=30 Hypotonic (0.16–0.5% NaCl), n=26
Outcomes						
PNa mmol/l	Greater and more sustained drop in PNa in hypotonic group ($p<0.01$)	Post-op PNa in Gp 3 significantly lower ($p<0.05$). No significant change in Gp 1 and 2	Mean PNa after 4 hours: Gp 1 134.3 mmol/l (2.1) Gp 2 136.3 mmol/l (3.3)	Cases: PNa dropped from 139±3 to 133±2 mmol/l in 19±10 hours Controls: PNa 140±2 mmol/l	Greater fall in PNa in hypotonic group: 6.2±2.9 mEq/l ($p\leqslant0.05$); 3.0±0.8 mEq/l in isotonic group	Median PNa: 130.5 (121–136) in hypotonic Gp; 139 in isotonic group
Hyponatraemia (PNa <136)	1 patient in LR group, 7 in hypotonic group	PNa in hypotonic group (Gp 3): 133.3±4.6 mEq/l ($p<0.05$)	21/31 in Gp 1, 2/21 in Gp 2	All cases by definition	Post-op PNa: 131±2.8 in hypotonic group; 135±1.9 mmol/l in isotonic group	20/26 patients in hypotonic group, 2/30 in isotonic group
Severe hyponatraemia (PNa <130)	4 in hypotonic group	Not described	5/22 in Gp 1 (PNa $\leqslant$130); 0/22 in Gp 2	Not described	5 patients in hypotonic group	11 in hypotonic group
Clinical sequelae related to hyponatraemia	Not mentioned	Not described	None described	More nausea and vomiting reported in hyponatraemic group	Increased interstitial pulmonary fluid in hypotonic group ($p<0.05$)	Seizures: 2/26 in hypotonic group
Hypernatraemia (PNa >145)	None	None	None	None	None	None

CVS, cardiovascular; LR, Lactated Ringers; NS, normal saline; PNa, plasma sodium; pre/post-op, pre- or postoperative; Gp, group; NaCl, sodium chloride; RCT, randomised controlled trial.

Table 2 Characteristics of excluded studies

Study	Methods	Participants	Interventions	Primary outcome of study	Reason for exclusion
Neville (2005)[15]	Cohort study	Children with gastroenteritis (n = 52)	Hypotonic IV fluids	PNa, osmolality, ADH, urine electrolytes and osmolality, cortisol, and thyroid hormone	No control group
Cupido (2000)[25]	Cohort study	Post-op craniofacial patients (n = 16)	Isotonic fluid	PNa	No control group
Halberthal (2001)[30]	Retrospective chart review	Hospital acquired severe hyponatraemia within 48 h admission (n = 23).	Hypotonic fluid	Factors contributing to hospital acquired hyponatraemia	No control group
Gerick (1996)[21]	Case-control study	103 cases, 31 age matched controls	IV/PO fluid therapy	ADH and plasma renin activity in cases *v* controls	Outcomes of interest not described
Levine (2001)[24]	Cohort study	Craniofacial patients (n = 10)	Isotonic IV fluid	Serum and urine electrolytes	No control group
Judd (1990)[34]	Case-control study	Tonsillectomy (n = 13)	Gp 1: perioperative NS IV fluid. GP 2: NPO, no IV fluids	Serum electrolytes, ADH, and plasma renin activity	Only one intervention of interest described
Duke (2002)[35]	RCT	Children with meningitis	Hypotonic IV fluids *v* moderate oral fluid restriction	Survival and neurological status	Only one intervention of interest described
Cowley (1988)[20]	Cohort study	8 healthy children undergoing scoliosis repair	Type of fluids not described individually	Serum and urine electrolytes, ADH and renin activity	Type of fluids not individually described
Arieff (1999)[36]	Retrospective chart review	Fatal cases of post-op hyponatraemia	Not described	Volume of fluid administered	Intervention not described, primarily adult study
Wattad (1992)[37]	Retrospective chart review	Patients admitted with hyponatraemia	Not described	Aetiology of hyponatraemia	Interventions of interest not described
Dunn (1997)[38]	Retrospective chart review	Patients with PNa>165 or Na<130	Not described	Aetiology of hospital acquired PNa derangements	Interventions of interest not described
McCormick (1999)[39]	Retrospective chart review	Elective paediatric general surgical cases	Hypotonic or isotonic fluids	Not described	Outcomes of interest not described
Powell (1990)[23]	RCT	Children with meningitis	Fluid restriction *v* maintenance plus deficit replacement	PNa, plasma AVP levels	Type of fluids not individually described

ADH, antidiuretic hormone; IV, intravenous; PO, oral.

Table 3 Quality assessment; controlled trials

	Subjects			Intervention		Outcomes		Follow up		Analysis	
Author	Description of subjects	Allocation concealment	Method of randomisation described	Well defined/ objective interventions	Care taker/pt blinding	Definition	Blinding	Sufficient (≥90%)	I TT	Adjustment for confounders	Data provided to confirm results
Brazel	Yes	No	No	Yes	No	Yes	No	Yes	No	No	Yes
Dagli	Yes	No	No	Yes	No	Yes	No	Yes	No	No	Yes
Neville	Yes	Unclear	Yes	Yes	No	No	No	Yes	No	No	Yes

Table 4 Quality assessment; observational studies—cohort studies

	Selection				Comparability	Outcome		
Author	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study		Assessment	Follow up: outcomes	Follow up: cohorts
Burrows		*		*			*	*
Wilkinson		*	*			*	*	*

Table 5 Quality assessment; observational studies—case-control studies

	Selection				Comparability	Exposure		
Author	Case definition	Representativeness	Selection of controls	Definition of Controls		Ascertainment	Method of ascertainment	Non-response rate
Hoorn	*	*		*	*	*	*	*

Volume of IV fluid administration

Hoorn reported that patients with hospital acquired hyponatraemia did not receive significantly greater total fluid volume than isonatraemic patients, however the calculated electrolyte-free water intake was three times greater compared to the isonatraemic controls ($p < 0.001$). The total sodium intake in mmol/kg/h was not significantly different between the two groups.[18] The volume of IV fluid infused was not a determinant of the change in PNa at four hours in Neville's study of patients with gastroenteritis.[15] Fluid balance and volumes of fluid infused were not specifically presented in the other studies, but described as ''same in both groups''.

Subgroups

Four of the included studies were in surgical patients,[14 16 17 19] and one study enrolled patients with gastroenteritis.[15] Hoorn identified more surgical patients in the hospital acquired hyponatraemia group (16%), than in the isonatraemic controls (5%, $p = 0.04$).[18] All studies examined associations using univariate analyses; none used multivariate analyses to adjust for confounding factors.

Heterogeneity

Given the small number of studies, we chose to include and analyse results from both controlled trials and observational studies. Visual inspection of the Forrest plots indicated study heterogeneity; however formal statistical tests in this instance are underpowered to detect and adjust for clinically important heterogeneity, given the small number of outcomes, patients, and studies. We thus chose to describe the sources of clinical heterogeneity. (1) *Patients* included in this systematic review were heterogeneous, however the majority of studies were in the surgical population. (2) The degree of *exposure to the interventions* varied between studies—the timing of PNa measurements occurred after variable degrees and duration of exposure to intervention. (3) The majority of studies were limited in their *quality* (tables 3–5). Despite apparent heterogeneity in study design, participants, and quality among these studies, the treatment effect nevertheless appears to be remarkably consistent across the studies.

DISCUSSION

Intravenous fluids are used in children to either expand a contracted ECF space or as ''maintenance'' to replace urine

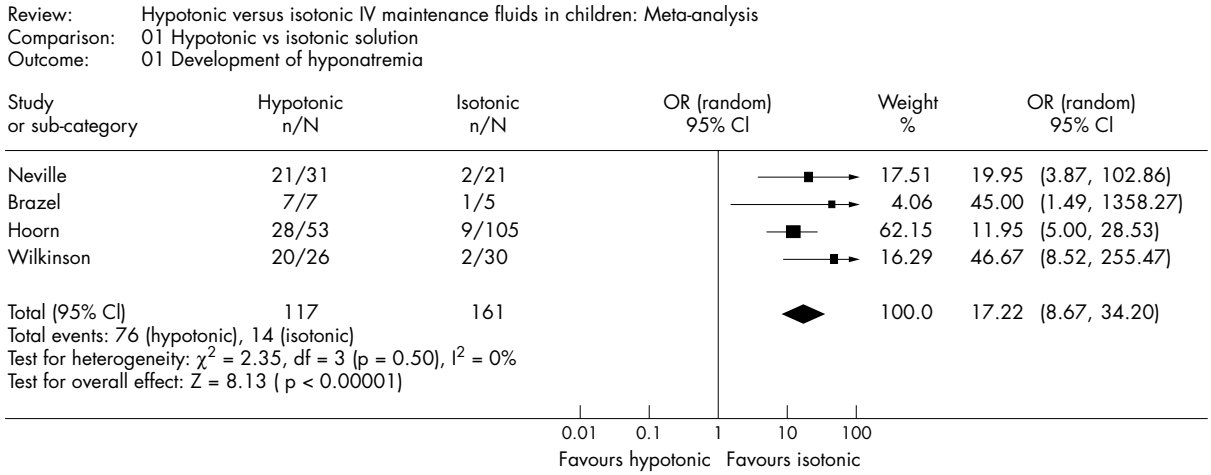

Figure 2 Forrest plot summarising the odds ratios and associated 95% confidence intervals for developing hyponatraemia in children receiving hypotonic compared to isotonic IV maintenance fluids.

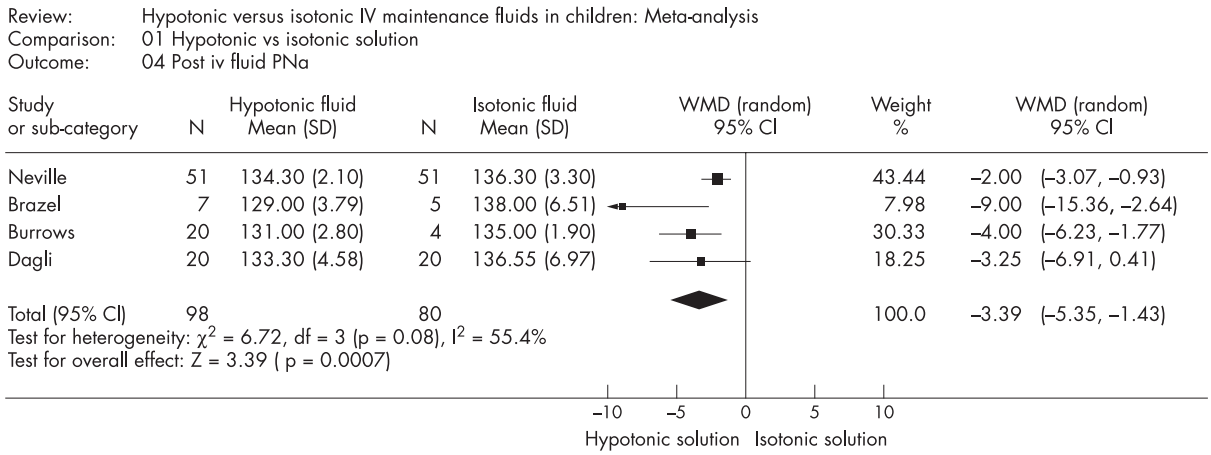

Figure 3 Comparison of PNa levels following hypotonic versus isotonic or near-isotonic IV maintenance fluids.

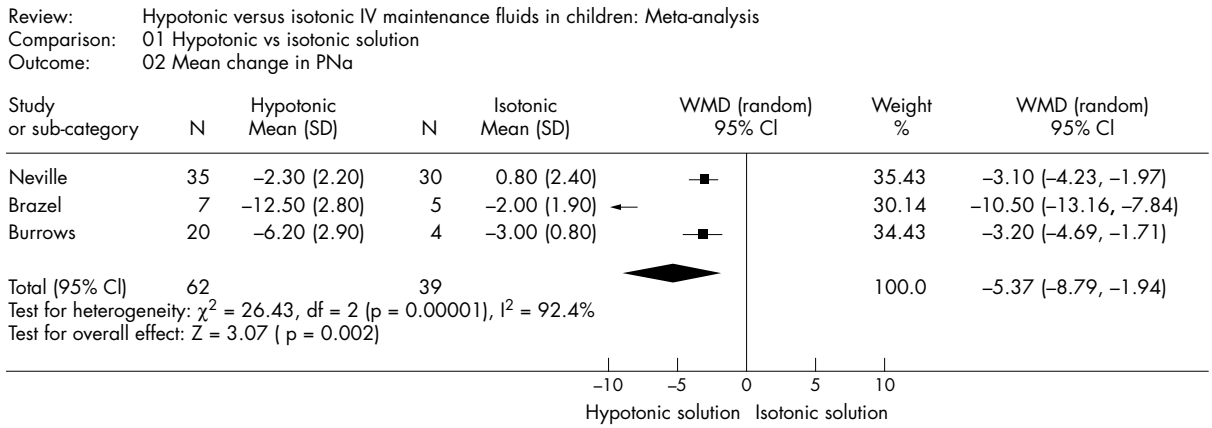

Figure 4 Mean change in PNa following hypotonic versus isotonic IV maintenance fluids.

output and insensible losses. In the former instance isotonic or near-isotonic saline is recommended on the basis that it is the physiologically appropriate solution. In the latter case hypotonic saline solutions are the accepted standard of care. This systematic review reveals that the evidence for the safety of this ubiquitous practice is limited, with only six published studies (only two of which were RCTs) reporting data on a total of 404 patients. The current level of evidence suggests that hypotonic maintenance solutions in children are not benign, but in fact potentially dangerous. The overall treatment effect is remarkable with the odds of developing hyponatraemia following hypotonic solutions being *17.2 times greater* than with isotonic fluids. Hence, there are potential risks associated with the use of hypotonic solutions in children, such as cerebral oedema precipitated by an acute fall in serum osmolality.

Hyponatraemia occurs due to a positive balance of electrolyte free water, combined with an impaired ability to excrete hypotonic urine secondary to ADH secretion. A significant correlation between free water intake and decrease in PNa has been demonstrated.[20] The primary source of electrolyte free water is the exogenous administration of hypotonic fluid. In contrast to healthy individuals, hospitalised patients have multiple non-osmotic stimuli for ADH secretion, which prevents them from producing water diuresis even in the presence of a PNa that is lower than 136 mmol/l.[12 15 21] In such patients, there will be very little if any excretion of electrolyte free water, because ADH makes the later parts of the distal nephron permeable to water.[22] The risk of hyponatraemia in these patients is under-recognised,[14 17 21] and is thus compounded by the administration of hypotonic solutions. However, the administration of isotonic maintenance solutions at least in children with meningitis, has been shown to result in a more rapid return of ADH to normal concentrations, when compared to hypotonic fluids.[23] Neville demonstrated that patients admitted with gastroenteritis have obligate urinary sodium losses irrespective of initial PNa.[15] The urinary tonicity at presentation of these patients approximates that of normal saline. Therefore infusion of a hypotonic solution which is lower in tonicity than that of urine passed is predictive of a decrease in subsequent PNa.

The concern that isotonic maintenance fluids may cause hypernatraemia is not supported in the studies we reviewed, nor is it reported in adults where the use of isotonic solutions is routine. On the contrary, the risks of hyponatraemia may also extend to patients who receive isotonic fluid.[14–16 21 24] This can be explained at least in part by the excretion of relatively hypertonic urine as demonstrated by Neville and others.[15 24 25] Steele observed that the expansion of the ECF with Ringers Lactate in the perioperative period results in the production of a hypertonic urine resulting in ''desalination''.[26] However,

What is already known on this topic

- The current standard of prescribing maintenance IV fluids is based on historical evidence
- The safety of this practice is yet to be tested in well conducted clinical trials

What this study adds

- This is the first systematic review which examines the evidence for standard IV maintenance solutions in children
- This review provides evidence that, at least in some paediatric patients, hypotonic solutions exacerbate the risks of hyponatraemia, while isotonic solutions may be protective

hypernatraemia can occur during the administration of isotonic saline if a hypotonic urine is produced, leading to a positive sodium balance.

The traditional guidelines for fluids in children, published 50 years ago, and more recently reiterated,[27 28] were derived from estimates of insensible water losses, and electrolyte requirements for normal growth.[1] These calculations have since been criticised, and may lead to an overestimation of hypotonic fluid requirement in sick children.[6 29] It has been demonstrated that it is not simply Na^+ intake, but moreover its ratio to electrolyte free water intake that influences PNa.[18] These findings challenge the previous recommendations made by Holliday and Segar, and argue for a maintenance solution and volume which maintains tonicity balance during acute illness, rather than one which merely provides a daily sodium or caloric requirement. We used PNa as a surrogate measure of morbidity related to fluid shifts between intra- and extracellular compartments. PNa is a convenient marker as it reflects the ratio between effective osmoles and total body water. As Na^+ is the principal extracellular cation and therefore the main determinant of ECF volume, it regulates water movement across cell membranes and explains the development of intracellular oedema that occurs in the presence of hyponatraemia. The expansion of intracellular fluid volume is of major importance in the central nervous system as the brain is confined in a rigid bony cage and has only limited ability to expand. Thus brain cell swelling is very likely to increase intracranial pressure and predispose to brain herniation. Children are at greater risk of this sequela because their brains have a larger intracellular fluid volume per total skull volume.[30] Certainly among children who develop symptomatic hyponatraemia, the incidence of permanent brain damage is substantially higher than in adults.[31]

The results of this systematic review validate the growing concerns expressed in reports which question the safety of our current practice.[13 32] The strengths of this report include a comprehensive search strategy, explicit selection criteria for relevant primary studies, reliability assessment of study screening and study quality, validity assessment of primary studies, statistical pooling of effect sizes, focus on adverse events, and reporting according to QUOROM guidelines.[33] The weaknesses are that most studies reviewed were heterogeneous in design, small, and of variable quality, did not allow for confounding factors, and focused on a limited paediatric population. Therefore we cannot state with certainty that the principles are applicable to all children prescribed IV maintenance fluids. On the other hand, we can state that, based on published case reports of deaths and neurological injury from acute hyponatraemia that the administration of hypotonic solutions to children with a PNa $<$138 mmol/l is potentially hazardous, given the fact that ADH is likely to be acting.

Conclusions

The current practice of prescribing IV maintenance fluids in children is not based on clinical experimental evidence using patient-important outcomes, and does not provide optimal fluid and electrolyte homoeostasis in hospitalised children. There is evidence that, at least in some paediatric patients, hypotonic solutions exacerbate the risks of hyponatraemia, while isotonic solutions may be protective. Our current responsibility however, is to refrain from adopting a ''new standard of care'', until rigorous clinical trials comparing the safety and effectiveness of different IV fluid regimens in children have been completed.

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Fluid therapy for acute bacterial meningitis (Review)

Maconochie IK, Baumer JH

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[Intervention Review]

Fluid therapy for acute bacterial meningitis

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ABSTRACT

Background

Acute bacterial meningitis remains a disease with high mortality and morbidity rates. However, with prompt and adequate antimicrobial and supportive treatment, the chances for survival have improved, especially among infants and children. Careful management of fluid and electrolyte balance is an important supportive therapy. Both over- and under-hydration are associated with adverse outcomes.

Objectives

To evaluate differing volumes of fluid given in the initial management of bacterial meningitis.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 3), which includes the Cochrane Acute Respiratory Infections Group's Specialised Register; MEDLINE (1966 to Week 4, July 2010); EMBASE (1980 to August 2010); and CINAHL (1982 to August 2010).

Selection criteria

Randomised controlled trials (RCTs) of differing volumes of fluid given in the initial management of bacterial meningitis were eligible for inclusion.

Data collection and analysis

The initial search identified six trials; on careful inspection three of these met the inclusion criteria. Data were extracted and trials were assessed for quality by all four of the original review authors (one author, ROW, has died since the original review, see acknowledgements). We combined data for meta-analysis using risk ratios (RR) for dichotomous data or mean difference (MD) for continuous data. We used a fixed-effect statistical model.

Main results

The largest of the three trials was conducted in settings with high mortality rates. The meta-analysis found no significant difference between the maintenance-fluid and restricted-fluid groups in number of deaths (risk ratio (RR) 0.82, 95% confidence interval (CI) 0.53 to 1.27); acute severe neurological sequelae (RR 0.67, 95% CI 0.41 to 1.08); or in mild to moderate sequelae (RR 1.24, 95% CI 0.58 to 2.65). However, when neurological sequelae were defined further, there was a statistically significant difference in favour of the maintenance-fluid group in regard to spasticity (RR 0.50, 95% CI 0.27 to 0.93); seizures at both 72 hours (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 three months follow-up (RR 0.42, 95% CI 0.20 to 0.89).

Authors' conclusions

Some evidence supports maintaining intravenous fluids rather than restricting them in the first 48 hours in settings with high mortality rates and where patients present late. However, where children present early and mortality rates are lower, there is insufficient evidence to guide practice.

PLAIN LANGUAGE SUMMARY

Fluids for people with acute bacterial meningitis

Bacterial meningitis is an infection of the fluid in the spinal cord and surrounding the brain. Antibiotics are prescribed as treatment. Supportive care includes other drugs and the regulation of fluid intake. Despite treatment, there is a risk of death or long-term complications from the infection, especially in the youngest and oldest patients.

There has been disagreement as to whether fluids should be restricted (hormones secreted by very ill patients reduce normal fluid output by the body). There are potential risks from giving too much fluid (especially brain swelling) as well as too little fluid (especially shock). Three trials involving over 400 children (over 350 of which were in a single trial) were included. All trials were set in countries where death rates are high and where patients seek help late.

Analysis of available trials found no significant differences in death rates or overall effects on brain function, either immediately or later. However, one study found a significantly lower rate of seizures and spasticity (abnormal body tone) in children receiving normal amounts of fluid compared to those receiving restricted fluids.

An adverse effect in children with restricted fluid intake was that they were less likely to have low levels of sodium in their blood and therefore, they would experience greater reductions in body fluids.

An adverse effect of unrestricted fluid administration was reported in one study as short-term fluid swelling of the face and low sodium levels in the blood one to two days after fluids were started, although the largest study found no difference in sodium levels in the blood.

The review found limited evidence from these trials in support of not restricting fluids in settings with high death rates. As there were no trials in other settings, there is no evidence to guide clinicians where children present early and mortality rates are lower.

BACKGROUND

Description of the condition

Acute bacterial meningitis remains a disease with high mortality and morbidity rates. The outcome in individual patients with bacterial meningitis is correlated with many factors, including age of patient, time and clinical stability before effective antibiotic treatment is begun, type of microorganism, number of bacteria or quantity of active bacterial products in the cerebrospinal fluid (CSF) at the time of diagnosis, intensity of the host's inflammatory response and time elapsed to sterilise cerebral spinal fluid cultures (Feldman 1977; Mustafa 1990; Saez-Llorens 1990; Waage 1987).

Description of the intervention

The highest rates of mortality and morbidity occur in the neonatal period and in the elderly. Nearly one in four adults with the illness will die, and many survivors sustain neurological deficits (Bohr 1983; Pfister 1993). Morbidity and mortality are high in neonates, infants and children. In fact, bacterial meningitis causes more than 100,000 deaths worldwide each year in infants and young children (Duke 1998). A 1993 meta-analysis examined the overall and organism-specific frequencies of death and persistent neurologic sequelae in children two months to 19 years of age (Baraff 1993). A total of 4920 children with acute bacterial meningitis were included in 45 reports that met the inclusion criteria. Children described in the 19 reports of prospectively-enrolled cohorts

from high-income countries had lower mortality than the children included in trials from low-income countries (4.8% versus 8.1%) and were more likely to have no sequelae (82.5% versus 73.9%). A further study that examined the long-term consequences of having meningitis during the first year of life found that 1.8% of children died within five years (Bedford 2001). Not only did almost a fifth of children with meningitis have a subsequent permanent, severe or moderately severe disability but subtle deficits were also more prevalent.

How the intervention might work

The chances for survival are improved with prompt and adequate antimicrobial and supportive treatment, especially in infants and children for whom case fatality rates have been reduced to less than 10% for bacterial meningitis and less than 5% for meningococcal meningitis (Saez-Llorens 2003). Two Cochrane reviews have now been completed that examine the effectiveness and safety of steroids and different antibiotic regimens, respectively, which are used in the treatment of acute bacterial meningitis (Brouwer 2010; Prasad 2007).

Careful management of fluid and electrolyte balance is also important in the treatment of meningitis. Over- or under-hydration are associated with adverse outcomes. Fluid restriction in the initial management of meningitis in children has been widely advocated (Conner 1980; Feigin 1992). However, this has also been challenged (Conner 1980; Powell 1990; Singhi 1995). The practice of fluid restriction is based on reports of hyponatraemia (lower than normal concentration of sodium in the extracellular fluid/blood) that is attributed to increased concentrations of circulating antidiuretic hormone (ADH) (a hormone that prevents excretion of water from the body). Over 50% of children have hyponatraemia at the time of admission (Kaplan 1983). There are associations between the degree of hyponatraemia and the presence of seizures and severity of acute disease, and adverse neurodevelopmental outcomes (Feigin 1977). These findings have subsequently been linked with a high incidence of cerebral oedema (swelling of the brain) in patients who die from acute bacterial meningitis (Conner 1980; Dodge 1965; Williams 1964), and it has been suggested that inappropriately increased concentrations of ADH lead to water retention, which in turn exacerbates cerebral swelling. Some researchers have concluded that fluid restriction will avoid exacerbating cerebral oedema and may improve neurological outcome (Brown 1994).

However, clinical dehydration has also been found in children with acute bacterial meningitis without any accompanying significant risk of mortality (Duke 1998). It has also been found that in children who received maintenance fluid plus replacement of volume deficits the high ADH concentrations normalised over 24 hours; in those who were restricted to two-thirds maintenance fluids ADH concentrations remained high (Powell 1990). The conclusion from this was that ADH concentrations are increased in children with meningitis because of hypovolaemia (a decrease in the volume of circulating blood) and only become normal when sufficient sodium and fluid are given.

Why it is important to do this review

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 at the time of presentation. If dehydration, rather than inappropriately increased antidiuresis, is the major factor in the pathogenesis of hyponatraemia in meningitis then the rationale for fluid restriction is open to question.

OBJECTIVES

The objective of this review was to evaluate treatment of acute bacterial meningitis with differing volumes of initial (up to 72 hours after first presentation) fluid administration on death and neurological sequelae.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) examining the effectiveness of different volumes of initial fluid administration in the treatment of acute bacterial meningitis were eligible for inclusion. We planned to consider trials of fluids administered to treat shock at presentation but no such trials eventuated.

Types of participants

All age groups with a diagnosis of acute bacterial meningitis made either by clinical diagnosis or culture of cerebrospinal fluid (obtained at lumbar puncture) were eligible for inclusion.

Types of interventions

1. Fluid administered in the initial treatment of acute bacterial meningitis; irrespective of route of administration, type or volume of fluid.
2. Comparisons of the initial volume of fluid administered in the treatment of acute bacterial meningitis; irrespective of route of administration, or type of fluid or duration of fluid restriction.

Types of outcome measures

Primary outcomes

1. Death
2. Short-term (within the first four weeks of illness) and long-term (persisting after the first four weeks of illness) neurological sequelae

Secondary outcomes

1. Oedema (including cerebral)
2. Total body water
3. Extracellular water
4. Serum and urinary sodium
5. Plasma and urinary osmolality
6. Duration of hospital stay
7. Raised intracranial pressure
8. Seizures
9. Status epilepticus

Search methods for identification of studies

Electronic searches

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 3), which includes the Cochrane Acute Respiratory Infections Group's Specialised Register; MEDLINE (1966 to Week 4, July 2010); EMBASE (1980 to August 2010); and CINAHL (1982 to August 2010).

For the previous update in 2007 we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 1) which includes the Cochrane Acute Respiratory Infections Group's Specialised Register; MEDLINE (1966 to March 2007); EMBASE (1980 to March 2007); and CINAHL (1982 to February 2007). MEDLINE, EMBASE and CINAHL were searched using OVID software. The MEDLINE search strategy is in Appendix 1.

The following search strategy was used to search MEDLINE and CENTRAL. The MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2009). The search strategy was adapted to search Embase.com (see Appendix 2) and CINAHL (see Appendix 3).

MEDLINE (Ovid)

1 exp Meningitis/
2 meningit*.tw.
3 or/1-2
4 exp Fluid Therapy/
5 fluid*.tw,nm.
6 Sodium Chloride/
7 saline*.tw,nm.
8 Rehydration Solutions/
9 (rehydrat* or hydrat* or dehydrat*).tw.
10 exp Water-Electrolyte Balance/
11 electrolyt*.tw,nm.
12 (hyponatr* adj2 solution*).tw.
13 exp Albumins/
14 exp Plasma/
15 exp Plasma Substitutes/
16 albumin*.tw.
17 plasma*.tw.
18 (starch* or dextran* or gelofus* or haemacc* or hemacc*).tw.
19 or/4-18
20 3 and 19

Searching other resources

We searched references from relevant articles and contacted trial authors where necessary. In addition, we contacted experts in the field for unpublished works. We searched the following trial registers: National Health and Medical Research Council (NHMRC) Clinical Trials Register, and Meta-Register. We attempted to contact authors of all open and/or unpublished trials identified. We sought publications in the literature that described, or may have described, the use of fluid therapy for the treatment of acute bacterial meningitis. We applied no language or publication restrictions. We searched the citation lists of relevant publications, review articles, abstracts of scientific meetings and included studies for both published and unpublished studies.

Data collection and analysis

Selection of studies

Two review authors (HB, IM) undertook study selection after running the search strategy outlined above. Both review authors independently assessed whether the studies met the inclusion criteria; any discrepancies were to be resolved by a third author (ROW, see acknowledgements), but this proved unnecessary. We sought further information from the trial authors where papers contained insufficient information to make a decision about eligibility.

Data extraction and management

We collected information regarding location of the study, methods of the study (as per quality assessment checklist), participant characteristics (age range, eligibility criteria), types of interventions and outcomes for each included trial. Where possible, we sought missing data from the trial authors. Four review authors

(IM, HB, MS (see acknowledgements), ROW) independently performed data extraction. Any discrepancies were to be resolved by discussion but this proved unnecessary.

Assessment of risk of bias in included studies

All four reviewers (HB, IM, MS, ROW) independently assessed the quality of all studies which were deemed eligible for the review; discrepancies were to be resolved by discussion but this proved unnecessary. The quality of allocation concealment was graded as either: adequate (A), unclear (B), or inadequate (C).
Assessment of methodological quality was graded as follows:
clearly yes - rate A;
not sure - rate B (seek details from authors);
clearly no - rate C.
Section (i): internal validity.
Was the assigned treatment adequately concealed prior to allocation?
Were the outcomes of patients who withdrew or were excluded after allocation described and included in an 'intention-to-treat' analysis?
Were the outcome assessors blind to assignment status?
Were the treatment and control groups comparable at entry?
Were the participants blind to assignment status following allocation?
Were the care programmes, other than the trial options, identical?
Were the withdrawals less than 10% of the study population?
Section (ii): external validity.
Were the inclusion and exclusion criteria for entry clearly defined?
Were the outcome measures used clearly defined?
Were the accuracy, precision, and observer variation of the outcome measures adequate?
Was the timing of the outcome measures appropriate?
Were the outcome measures clearly reported?

Measures of treatment effect

We analysed each dichotomous outcome for effect in terms of risk ratio (RR) with 95% confidence intervals (CIs) and combined the outcomes for meta-analysis using Review Manager software (RevMan 2008). Where data were sufficient, we calculated a summary statistic for each outcome using a fixed-effect model. Continuous outcomes were shown as mean differences (MD) between groups and 95% CIs. We used a fixed-effect approach in the meta-analysis as there was no significant heterogeneity.

Unit of analysis issues

We did not include any studies with non-standard designs. The comparisons under consideration would not lend themselves to cluster randomised or other similar designs.

Dealing with missing data

Where there were missing participants due to drop-out, we searched for the use of an intention-to-treat (ITT) analysis by the trial authors and reported this in the review. Where there were missing statistics (such as standard deviations or correlation coefficients) that made analysis impossible, we approached the trial authors, and where there remained missing data, we reported this in the review.

Assessment of reporting biases

We intended to investigate for publication bias and other reporting biases initially by the use of funnel plots. However, as there were only three included studies, we were unable to do so.

Subgroup analysis and investigation of heterogeneity

We had planned that if there was a sufficient number of trials of adequate size, with the required information recorded in the trial publication, we would conduct subgroup analyses on the following:

- age;
- volume of fluid administered;
- organism causing the meningitis;
- hypoperfusion status at enrolment; and
- clinical diagnosis versus laboratory-confirmed diagnosis.

Unfortunately, there were insufficient data to complete any of these subgroups with the exception of hypoperfusion at entry. One study (Singhi 1995) subgrouped each intervention group into those with hyponatraemia and those without hyponatraemia at enrolment.
We assessed clinical heterogeneity by establishing the overall mortality rates and duration of symptoms where possible. We used this to distinguish between participants studied in different health settings. We did not deem meta-analysis appropriate where it was evident that studies were undertaken in different health contexts. We determined statistical heterogeneity by a combination of visual inspection of graphs of risk ratios (RRs) as well as using the I^2 statistic, and the Chi^2 test.

Sensitivity analysis

We had planned to perform an a priori sensitivity analysis on results to look at the possible contribution of differences in methodological quality, but we were unable to do this due to the paucity of trials.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Six abstracts identified in the search initially appeared to fit the inclusion criteria for the review. After obtaining the full papers, we excluded three of these, leaving three papers eligible for inclusion (415 children). In this 2010 update, we retrieved 105 records during the searches. We did not find any new included or excluded trials for this update.

Included studies

1. Trial design characteristics

a) Volume and constitution of fluid

The first trial (Duke 2002) compared milk-based fluids delivered at 60% of that required for maintenance fluids with 100% of normal maintenance fluids. Maintenance fluids were defined as "100 ml/kg/day for the first 10 kg of body weight, 50 ml/kg for the second 10 kg, and 20 ml/kg for over 20 kg". The milk-based fluids comprised expressed breast milk or other milk feed given via a nasogastric tube for at least 48 hours, or longer with reduced conscious state, convulsions, impaired upper airway reflexes or persistent respiratory distress. Normal maintenance fluids (defined as above) of a solution containing 0.45% sodium chloride and 5% dextrose plus 10 mmol/L of potassium chloride per litre were delivered intravenously for at least the first 48 hours.

The second trial (Powell 1990) compared two-thirds of required maintenance fluids (maintenance fluids were similarly defined as "100 ml/kg for the first 10 kg of body weight, plus 50 ml/kg for the next 10 kg (10 kg to 20 kg), plus 20 ml/kg for each kilogram in excess of 20 kg") with full maintenance fluids, plus replacement fluids for any estimated deficit over 24 hours. Rehydration was begun by administering 10 or 15 ml/kg by rapid intravenous infusion. Fluids were given intravenously with the composition determined by the attending consultant.

The third trial (Singhi 1995) compared restricted fluids at 65% of the calculated maintenance fluid requirement with maintenance fluid requirements (110 ml/kg for first 10 kg, 50 ml/kg for next 10 kg and 25 ml/kg for subsequent weight), both given intravenously. The restricted fluids comprised one-fifth normal saline in 5% dextrose for 24 hours, followed by "a gradual liberalisation at a rate of 10 ml/kg over eight hours, if, after 24 hours of hospital stay, the serum sodium and plasma osmolality had returned to normal and there were no clinical signs of dehydration".

b) Duration of fluid therapy

One study administered fluids for 48 hours (Duke 2002); one study administered fluids for 24 hours (Powell 1990); and the third study administered fluid for 24 hours with a gradual increase thereafter until children in both arms received the full normal maintenance requirement after 48 hours (Singhi 1995).

2. Baseline characteristics of participants

a) Age

All studies included only children. One study included children between one month and 12 years of age (Duke 2002), the second included children between three months and 16 years (Powell 1990) and the third included children between two months and seven years of age (Singhi 1995).

b) Health status

The children in the study carried out in Papua New Guinea (Duke 2002) were from a population in which 25% were undernourished at the time of their presentation. In regard to the meningitis symptoms, the mean duration of symptoms was six days, with two-thirds of children having convulsions, before presentation; and 20% of children were hypoglycaemic.

The second study (Powell 1990) gave no specific details but said that they only enrolled "previously healthy children". Malnourished children were excluded in the Singhi 1995 study and children had a duration of symptoms ranging from one to 10 days on presentation.

c) Diagnostic techniques used to establish a diagnosis of bacterial meningitis

The first study (Duke 2002) made a diagnosis according to clinical signs of meningitis and a cloudy or turbid cerebrospinal fluid (CSF) with a moderate or large number of leucocytes and amount of protein, determined by dipstick testing (Multistix-10-SG, Bayer Australia Ltd, Sydney, Australia). The second study (Powell 1990) diagnosed meningitis on the basis of clinical examination, CSF cytology and chemical studies. The final study (Singhi 1995) made a diagnosis on a suggestive history, physical examination and CSF findings of hypoglycorrhachia, increased protein concentration and polymorphonuclear leucocytosis.

3. Studied outcomes

a) Death

Two studies reported death as an outcome (Duke 2002; Singhi 1995). Personal communication with the lead author of the third study (Powell 1990) reported no fatalities.

b) Short-term (within the first four weeks of illness) and long-term (persisting after the first four weeks of illness) neurological sequelae

Two studies reported acute neurological sequelae (Duke 2002; Singhi 1995). One of these studies also reported individual neurological components at 14 days (spasticity, hemiparesis/hemiplegia, visual impairment and no response to sound) and neurological sequelae at three months (Duke 2002).

c) Oedema (including cerebral)

One study reported facial oedema, pulmonary oedema and hydrocephalus (Duke 2002).

d) Status epilepticus

No study reported on incidence of status epilepticus.

e) Seizures

One study reported the incidence of seizures at both 72 hours and 14 days (Duke 2002).

f) Total body water

One study reported total body water as an outcome (Singhi 1995).

g) Extracellular water

One study reported extracellular water as an outcome (Singhi 1995).

h) Serum and urinary sodium

Two studies (Powell 1990; Singhi 1995) reported comparisons of mean serum-sodium concentrations. The third (Duke 2002) reported the proportion of children with serum-sodium concentrations below 130 mmol/litre at 72 hours. One study reported urinary sodium as an outcome (Singhi 1995).

i) Plasma and urinary osmolality

One study reported plasma and urinary osmolality as an outcome (Singhi 1995).

j) Duration of hospital stay

No study reported duration of hospital stay as an outcome.

k) Raised intracranial pressure

No study reported on raised intracranial pressure.

Excluded studies

We excluded three studies as they were not RCTs (Brown 1994; Duke 1998; Floret 1999).

Risk of bias in included studies

A graphical representation of the risk of bias for the included studies is shown in Figure 1. A summary of methodological quality of the included trials is given in Figure 2.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

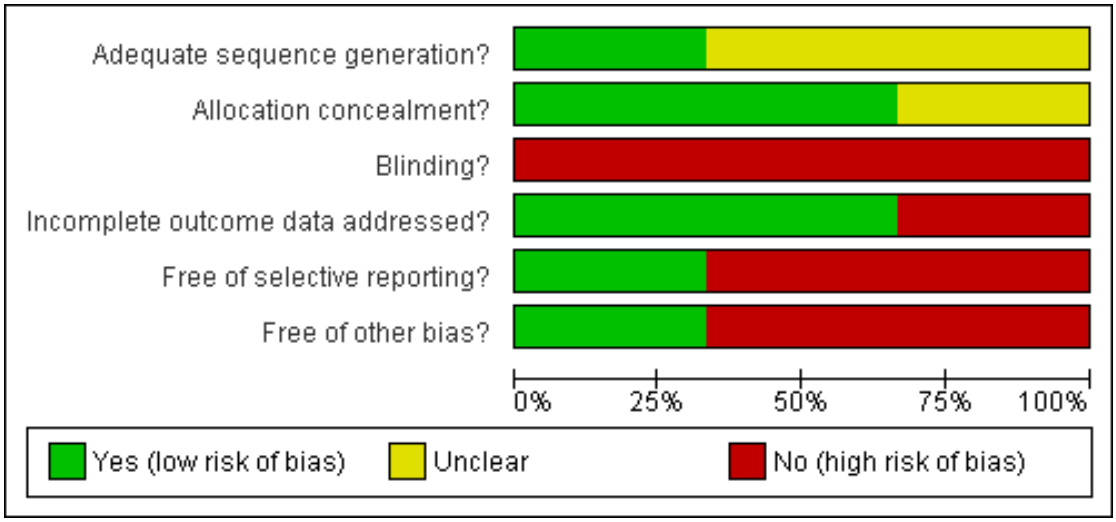
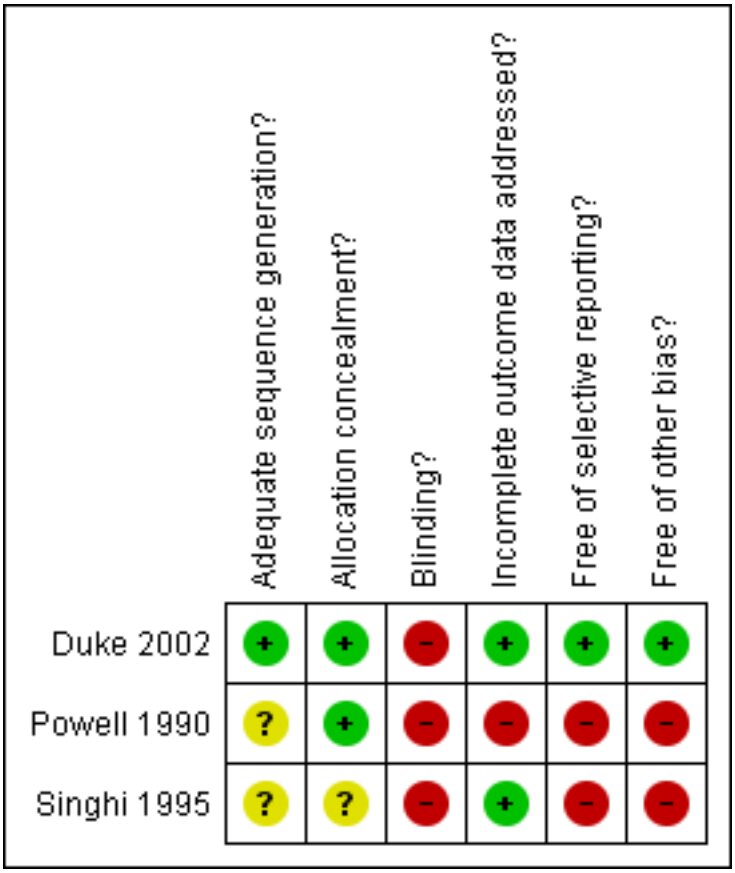


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Two studies used opaque, sealed, sequentially numbered envelopes (Duke 2002; Powell 1990). The remaining study used a random numbers table (Singhi 1995). Two trials displayed adequate allocation concealment (Duke 2002; Powell 1990). The quality of allocation concealment in the third study was unclear (Singhi 1995).

Blinding

Two studies had no blinding (Duke 2002; Powell 1990). It was unclear whether or not there was blinding in the remaining study (Singhi 1995).

Power calculations

Two studies documented power calculations (Duke 2002; Singhi 1995). One calculated a required participation of 354 to detect a one-third reduction in adverse outcomes (Duke 2002). The study randomised 357 and analysed results for 346 children immediately at completion of treatment. The second study calculated that 31 children in each group were needed to detect a 25% change in intact survival rate from 50%, with a significance of 0.05 (Singhi 1995). This study was terminated early but enrolled 25 in each group.

Number of centres

One study had three participating centres (Duke 2002). The remaining two were single-centre studies (Powell 1990; Singhi 1995).

ITT analysis

No study reported an ITT analysis.

Incomplete outcome data

The largest study had relatively small numbers of drop-outs (11 of 357 enrolled patients) by the end of treatment, when most of the outcomes were measured (Duke 2002). By three months from diagnosis there were over 10% drop-outs.
The second study had five exclusions from 24 patients enrolled, and this would have introduced the possibility of significant bias (Powell 1990). The third study (Singhi 1995) had no drop-outs.

Selective reporting

There was no evidence of selective reporting of data in one study (Duke 2002). Both short-term and longer-term morbidities were reported. Powell 1990 only reported short-term sodium levels. Singhi 1995 only reported total numbers with short-term neurological impairment and did not attempt to break these down by type of impairment.

Other potential sources of bias

The main concern was the marked discrepancy in size between the largest study and the two other, very small RCTs

Effects of interventions

(a) Death

All participants, regardless of serum sodium at enrolment

The meta-analysis of the three studies (Duke 2002; Powell 1990; Singhi 1995) (415 children) for deaths, where one study reported no fatality amongst their participants (Powell 1990), found no significant difference between deaths in the maintenance-fluid and restricted-fluid groups (RR 0.82, 95% CI 0.53 to 1.27) (Analysis 1.1.1).

Patients with or without hyponatraemia

The study (Singhi 1995) that subdivided maintenance-fluid and restricted-fluid groups into children with or without hyponatraemia at presentation found no significant difference in death rates in either those presenting with hyponatraemia (26 children) or those without hyponatraemia (24 children). With hyponatraemia, the RR for children given the two different fluid intakes was RR 0.15 (95% CI 0.01 to 2.50) (Analysis 1.1.3); without hyponatraemia, the RR was 0.79 (95% CI 0.16 to 3.90) (Analysis 1.1.2).

(b) Short-term (within the first four weeks of illness) and long-term (persisting after the first four weeks of illness) neurological sequelae

Short-term neurological sequelae

The meta-analysis of acute severe neurological sequelae (two studies, 407 children) found no significant difference between the maintenance-fluids and restricted-fluids groups (RR 0.67, 95% CI 0.41 to 1.08) (Analysis 1.2.1).
Data on mild to moderate sequelae at fourteen days (one study, 357 children) also showed no significant difference between maintenance-fluid and restricted-fluid groups (RR 1.24, 95% CI 0.58 to 2.65).
However, when neurological sequelae were categorised further, the available data produced the following results.

- Hemiparesis/hemiplegia (one study, 357 children): no significant difference between groups (RR 0.97, 95% CI 0.52 to 1.81).
- Spasticity (one study, 357 children): there was a statistically significant difference in favour of the maintenance fluid group (RR 0.50, 95% CI 0.27 to 0.93).
- Seizures (one study, 357 children): there was a statistically significant difference in seizure activity at both 72 hours (RR 0.59, 95% CI 0.42 to 0.83) and 14 days (RR 0.19, 95% CI 0.04 to 0.88) in favour of the maintenance fluid group.
- Visual impairment and response to sound (one study, 357 children): there was no statistically significant difference in either group. On visual impairment the RR was 0.77 (95% CI 0.44 to 1.35) and on response to sound, RR 0.60 (95% CI 0.25 to 1.41).

Patients with or without hyponatraemia

Analyses of data from participants with and without hyponatraemia at presentation showed no significant difference in acute neurological sequelae for either subgroup. Without hyponatraemia, the RR for children given maintenance fluids or restricted fluids was RR 0.59 (95% CI 0.13 to 2.64); with hyponatraemia, RR 0.91 (95% CI 0.34 to 2.47).

Long-term neurological sequelae

The data relating to chronic severe neurological sequelae (one study, 351 children) showed a statistically significant difference at three-month follow-up in favour of those in the maintenance fluid groups (RR 0.42, 95% CI 0.20 to 0.89).

(c) Oedema (including cerebral)

The data on facial oedema (one study, 357 children) showed a statistically significant difference in favour of the restricted-fluids group (RR 5.47, 95% CI 2.65 to 11.27). There was no statistically

significant difference in either pulmonary oedema (RR 8.75, 95% CI 0.47 to 161.38) or hydrocephalus (RR 0.28, 95% CI 0.06 to 1.32).

(d) Total body water

The data on change in total body water at 48 hours after admission (one study; 24 children without hyponatraemia, 26 children with hyponatraemia) showed a statistically significant greater reduction in the restricted-fluids group in both non-hyponatraemic and hyponatraemic children: MD (meq/litre) 24.50 (95% CI 9.91 to 39.09) and MD (meq/litre) 36.00 (95% CI 19.83 to 52.17), respectively.

(e) Extracellular water

The data on reduction in extracellular water at 48 hours after admission (one study; 24 children without hyponatraemia, 26 children with hyponatraemia) showed a greater reduction in the restricted-fluid groups: non-significant for non-hyponatraemic children: MD (meq/litre) 22.90 (95% CI -1.11 to 46.91) and a statistically significant change in hyponatraemic children: MD (meq/litre) 35.00 (95% CI 16.86 to 53.14).

(f) Serum and urinary sodium

One study (Duke 2002) reported the proportion of children with serum sodium concentrations below 130 mmol/litre at 72 hours and found no statistically significant difference between the restricted-fluid and maintenance-fluid groups (RR 0.72, 95% CI 0.34 to 1.55).

A meta-analysis of the two studies comparing mean sodium concentrations was not attempted as one (Powell 1990) measured serum sodium at 24 hours and the other (Singhi 1995) at 48 hours. The Powell study (13 children with bacterial meningitis) reported all children together and found no statistically significant difference in mean serum sodium at 24 hours: MD (meq/litre) 3.00 (95% CI -0.94 to 6.94). The Singhi study (one study; 24 children without hyponatraemia, 26 children with hyponatraemia) subgrouped children by hyponatraemia status at study entry. The study found a statistically significant difference in favour of the restricted-fluid group in children with hyponatraemia (MD (meq/litre) -4.20, 95% CI -6.20 to -2.2) and a near statistically significant difference in children without hyponatraemia (MD (meq/litre) -3.50, 95% CI -7.58 to 0.58, P = 0.09), although this was reported as statistically significant in the original paper. This study also found a significant difference in the change in serum sodium from baseline, in favour of the restricted-fluid group, in both children with and without hyponatraemia. Without hyponatraemia, the WMD (meq/litre) was -5.8 (95% CI -11.59 to -0.01); with hyponatraemia, MD (meq/litre) -4.40 (95% CI -6.97 to -1.83).

The one study (24 children without hyponatraemia at admission, 26 children with hyponatraemia) that reported urinary sodium found no significant difference at 48 hours in mean urinary sodium in children without hyponatraemia (MD (meq/litre) -14.0, 95% CI -31.60 to 3.6) but a statistically significant difference in children with hyponatraemia at admission (MD (meq/litre) -21.00, 95% CI -34.14 to -7.86). There was no significant change from baseline at 48 hours either in children without hyponatraemia (MD (meq/litre) 1.00, 95% CI -12.22 to 14.22) or with hyponatraemia (MD (meq/litre) 0.0, 95% CI -8.94 to 8.94).

(g) Plasma osmolality

There was a statistically significant difference in the change in plasma osmolality after 48 hours with a greater increase in the restricted-fluid group, in both the children presenting without hyponatraemia (one study, 24 children): MD (meq/litre) -5.00 (95% CI -9.82 to -0.18); and children presenting with hyponatraemia (one study, 26 children): MD (meq/litre) -6.00 (95% CI -11.36 to -0.64).

DISCUSSION

Summary of main results

The small number of studies identified by this review did not show any statistically significant difference in mortality from restricting fluids. Two studies reported high mortality rates overall, well above 10% (Duke 2002; Singhi 1995). The third study included very small numbers and reported no deaths. Meta-analysis of the two studies reporting neurological sequelae demonstrated statistically significant reductions in the rates of early spasticity and seizures, and later overall neurological sequelae, in children receiving maintenance fluids. There were no statistically significant differences in overall short-term neurological sequelae or in risk of hemiparesis, visual or hearing impairment.

Two of the studies (Powell 1990; Singhi 1995) involved very small numbers of children from single centres. The mortality and morbidity results, therefore, are dominated by the Duke 2002 study. The long delays before presentation and a high rate of malnutrition in the children in this study may have been associated with a high rate of dehydration at presentation. The finding of a higher rate of neurological sequelae in the restricted-fluid group in this study could result from inadequate initial treatment of dehydration. This might not be relevant in settings where patients present earlier.

Overall completeness and applicability of evidence

The largest of the three studies (Duke 2002) included multiple outcomes relevant to the review question. Its shortcoming was that it could only address the question in settings with high mortality and morbidity rates and long delays before presentation.
The other two studies were too small to allow any conclusions to be drawn. None of the studies included adults.
The results of short-term fluid and electrolyte balance do not in themselves provide adequate evidence on which to change practice. The reporting of sodium levels was different so that it was not possible to undertake a meta-analysis.

Quality of the evidence

The evidence identified in this review does not allow a robust conclusion regarding the most appropriate approach to fluid management in children with acute bacterial meningitis despite the existence of one large study (Duke 2002). In view of some important shortcomings such as a lack of blinding and a lack of ITT analysis, the somewhat equivocal findings in regard to neurological sequelae should be interpreted with great caution.

Potential biases in the review process

The nature of the intervention under review meant that electronic literature searches had to use a number of search terms in order to ensure that all relevant randomised controlled trials were identified. The methods used should otherwise have been able to avoid missing relevant studies.

Agreements and disagreements with other studies or reviews

The other available evidence from non-RCTs does not provide strong grounds for restricting fluid intake despite the common practice of initial fluid restriction. These other studies were not systematically reviewed.

AUTHORS' CONCLUSIONS

Implications for practice

There is some evidence to support the use of intravenous maintenance fluids, in preference to restricted fluid intake, in the first 48 hours in settings with high mortality rates and where patients present late. However, where children present early and mortality rates are lower, there is insufficient evidence to guide practice.

Implications for research

Large, good quality trials conducted in both countries with high and low mortality from acute bacterial meningitis are needed to assess the effectiveness of either restricting or giving maintenance fluids in populations where patients present early and where mortality rates are low.

ACKNOWLEDGEMENTS

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Morwenna Stewart (MS) was an author on the original review and the 2008 update. Morwenna performed independent data extraction and quality assessment of the included trials, and commented on all drafts of the review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Duke 2002

Methods	Unit of randomisation: child Method of randomisation: sequentially numbered, opaque, sealed envelopes Timing of randomisation: on determination of the child meeting all entry requirements and parental consent Blinding: no Power calculation: yes 354 to detect a 1/3 reduction in adverse events Number of centres: 3 357 randomised 11 exclusions during treatment with a further 39 lost at three month follow up 346 analysed at the end of treatment, 307 analysed at three months Source of funding: Roche, World Health Organization, and Royal Australasian College of Physicians
Participants	Children with clinical signs of meningitis, cloudy or turbid CFS with moderate or large amounts of leucocytes and protein on dipstick testing (Multistix 10SG, Bayer Australia Ltd, Sydney, Australia) were eligible for inclusion. Children with renal failure, congenital heart disease, who had received parenteral antibiotics for 48 hours or more in the week prior to presentation or who were septic or in hypovolaemic shock were excluded from enrolment Age: > 1 month to < 12 years Location: Papua New Guinea Timing and duration: September 1997 to October 2000
Interventions	Nasogastric tube fluids at 60% of maintenance fluids, (maintenance fluids defined by "100 ml/kg/day for the first 10 kg of body weight, 50 ml/kg for the second 10 kg, and 20 ml/kg for over 20 kg") as expressed breast milk or other milk feed, divided into feeds given every 3 hours versus 100% of normal maintenance fluids (defined as above) administered intravenously (given nasogastrically in 7 children because an intravenous cannula could not be inserted) given as a solution containing 0.45% sodium chloride and 5% dextrose plus 10 mmol/L of potassium chloride per litre Duration: 48 hours
Outcomes	Death Neurological sequelae Oedema (including cerebral) Serum and urinary sodium Seizures
Notes	260 of the 357 children had confirmed bacterial meningitis. The paper states that although no bacteria were isolated in the other children the diagnosis was "definitely meningitis". Numbers of children without isolated bacteria was similar between groups Severe sequelae were considered to be present if 14 days after commencing treatment

	there was a severe motor deficit (marked spasticity, hemiplegia, severe hypotonia) and at least one of the following: a major sensory deficit (inability to fix and follow in an age-appropriate way or no response to sound), persistent convulsions or coma All children received phenobarbitone, and received oxygen for the first 48 hours. The 1st 150 children received chloramphenicol, the rest ceftriaxone. Mechanical ventilation was not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Adequate, with comparable treatment and control groups at entry
Allocation concealment?	Low risk	Adequate, using sealed envelopes
Blinding? All outcomes	High risk	Clearly not
Incomplete outcome data addressed? All outcomes	Low risk	Adequate overall with 11 of 357 excluded post randomisation as found not to have meningitis. However, over 10% of participants lost to follow up at 3 months
Free of selective reporting?	Low risk	Adequate, with a good range of appropriate outcomes reported. 14 days is somewhat early to judge whether severe sequelae were present
Free of other bias?	Low risk	A large and well described study

Powell 1990

Methods	Unit of randomisation: child Method of randomisation: sealed envelopes prepared with a computer generated random number table Timing of randomisation: at diagnosis Blinding: no Power calculation: no Number of centres: 1 24 randomised (all pathogens) 5 exclusions (all pathogens) 19 analysed (13 bacterial, 6 aseptic). Source of funding: Hoffmann-La Roche, Praxis Biologies, National Institute of Health
Participants	Previously healthy children with a clinical diagnosis of meningitis, and confirmed by CFS cytology and by chemical studies were eligible for inclusion. Children with central nervous system disease, renal disease, who were prematurely delivered (at less than 36

Powell 1990 (*Continued*)

	weeks gestation), who have congestive heart failure, chronic pulmonary disease, malignancy, immunodeficiency, hepatic disease, on were on morphine/ phenobarbatone/ phenytoin/ dexamethazone or lithium were excluded from enrolment Age: 3 months to 16 years Location: USA Timing and duration: July 1985 to June 1988
Interventions	2/3 maintenance fluids (maintenance defined as 100 ml/kg for the first 10 kg of body weight, plus 50 ml/kg for the next 10 kg (10 to 20 kg), plus 20 ml/kg for each kilogram in excess of 20 kg) versus Full maintenance fluids (as defined above), plus replacement fluids for any estimated deficit over 24 hours. Rehydration was begun by administering 10 or 15 ml/kg by rapid intravenous infusion Duration: 24 hours
Outcomes	Serum osmolality Serum sodium
Notes	13 children with bacterial meningitis and 6 with aseptic meningitis were enrolled. Results were reported separately. However, the initially pathology of the 6 exclusions were not documented

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Not described
Allocation concealment?	Low risk	Adequate, using sealed envelopes
Blinding? All outcomes	High risk	Clearly not
Incomplete outcome data addressed? All outcomes	High risk	Clearly not, with 5 of 24 participants not included in final analysis
Free of selective reporting?	High risk	Clearly not. No reporting of important outcomes of death, intact survival
Free of other bias?	High risk	Most eligible patients not randomised. Poor reporting of details of study

Singhi 1995

Methods	Unit of randomisation: child Method of randomisation: sealed opaque sequential envelopes with numbers generated by a computer generated random number table Timing of randomisation: unclear Blinding: no Power calculation: yes (31 children in each group to detect a 25% change in intact survival rate from 50% for a significance of 0.05) Number of centres: 1 50 randomised 0 exclusions 50 analysed Source of funding: not stated
Participants	Children with a diagnosis of bacterial meningitis were eligible for inclusion. Children with heart disease, respiratory illness, gastrointestinal disease, renal disease, central nervous system disease, malnutrition (less than 60% of weight expected for age), endocrinopathy, malignancy, immunodeficiency, or who had received previous anticonvulsant therapy were excluded Age: 2 months to 7 years Location: India Timing and duration: not stated
Interventions	65% calculated maintenance fluid requirement, given as intravenous 1/5th normal saline in 5% dextrose for 24 hours, followed by "a gradual liberalisation at a rate of 10 ml/kg/8 hours after 24 hours of hospital stay if serum sodium and plasma osmolality had returned to normal and if there were no clinical signs of dehydration versus maintenance fluid requirements (110 ml/kg for first 10 kg, 50 ml/kg for next 10 kg and 25 ml/kg for subsequent weight) given as intravenously and comprising of a 1/5th normal saline in 5% dextrose "as long as they required intravenous fluids"
Outcomes	Intact survival with sequelae Death Total body water Extracellular water Serum sodium plasma osmolality Urine sodium Urine osmolality
Notes	Trial was stopped prematurely "when a trend toward poor outcome in the restricted-fluid group became obvious"

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Use of a list or table. Treatment and control groups were comparable at study entry
Allocation concealment?	Unclear risk	Unclear, with the use of a list or table

Singhi 1995 (*Continued*)

Blinding? All outcomes	High risk	Clearly neither outcome assessors, participants nor treatment providers blinded
Incomplete outcome data addressed? All outcomes	Low risk	Appeared to account for all subjects
Free of selective reporting?	High risk	Mixed neurological outcomes and complications, so some important outcomes unavailable
Free of other bias?	High risk	Study was stopped prematurely, with no a priori stopping rules, with a "trend towards poor outcome" in one group

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Brown 1994	Not a RCT
Duke 1998	Not a RCT
Floret 1999	Not a RCT

DATA AND ANALYSES

Comparison 1. Maintenance fluids versus restricted fluids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 All patients	2	407	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.53, 1.27]
1.2 Patients without hyponatraemia	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.16, 3.90]
1.3 Patients with hyponatraemia	1	26	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 2.50]
2 Severe neurological sequelae	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Acute (within the first 4 weeks)	2	407	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.41, 1.08]
2.2 Chronic (after the first 4 weeks)	1	351	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.20, 0.89]
2.3 Patients with hyponatraemia	1	26	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.34, 2.47]
2.4 Patients without hyponatraemia	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.13, 2.64]
3 Mild to moderate neurological sequelae	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 At 14 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 Hemiparesis/hemiplegia	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 At 14 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Spasticity	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 At 14 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Seizures	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Within the first 72 hours	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2 At 14 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Visual impairment	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 At 14 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8 No response to sound	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 At 14 days	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 Oedema	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 Acute facial oedema	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.2 Acute pulmonary oedema	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.3 Acute hydrocephalus	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Total body water - fall after 48 hours	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 Patients without hyponatraemia	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
10.2 Patients with hyponatraemia	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
11 Extracellular water - fall after 48 hours	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11.1 Patients without hyponatraemia	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable

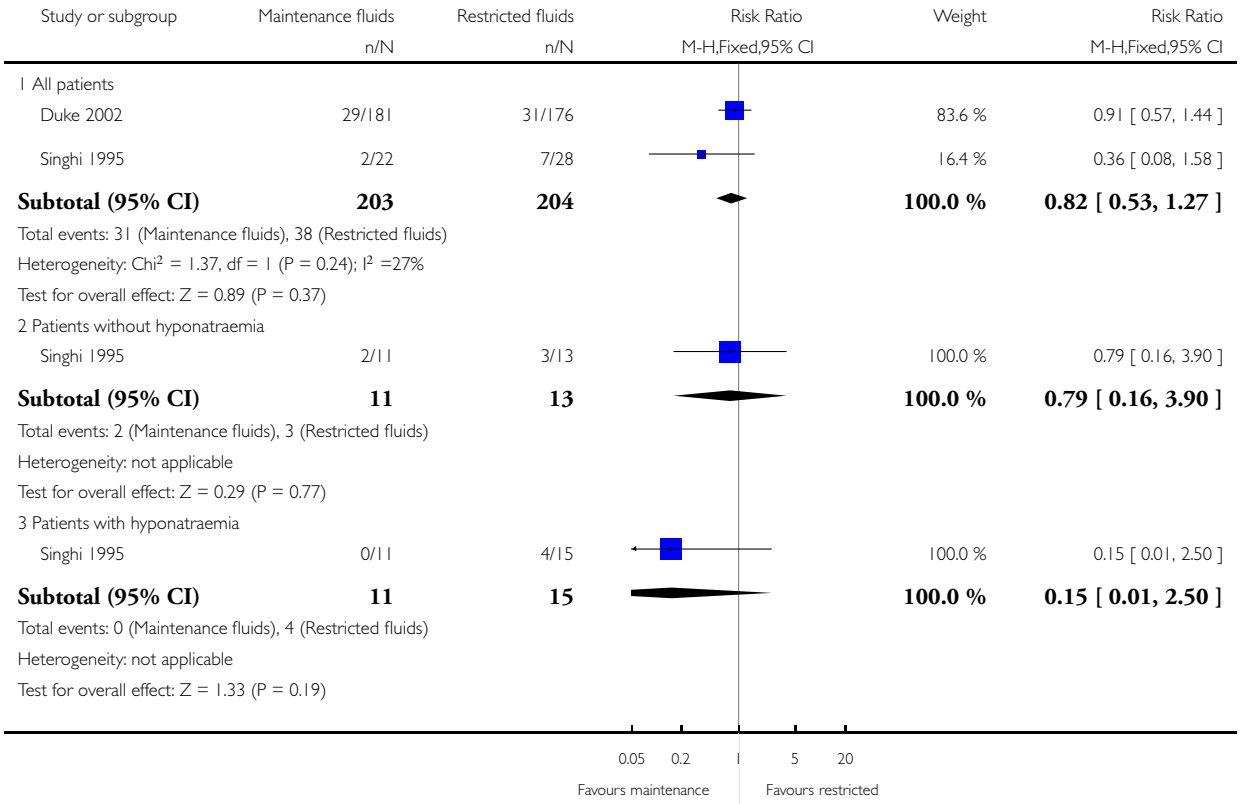
11.2 Patients with hyponatraemia	1	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12 Serum sodium	2	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 All patients (24 hours)	1	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.2 Patients without hyponatraemia (48 hours)	1	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.3 Patients with hyponatraemia (48 hours)	1	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.4 Change from baseline at 48 hours - without hyponatraemia	1	Mean Difference (IV, Fixed, 95% CI)	Not estimable
12.5 Change from baseline at 48 hours - with hyponatraemia	1	Mean Difference (IV, Fixed, 95% CI)	Not estimable
13 Plasma osmolality - change after 48 hours	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1 Patients without hyponatraemia	1	Mean Difference (IV, Fixed, 95% CI)	Not estimable
13.2 Patients with hyponatraemia	1	Mean Difference (IV, Fixed, 95% CI)	Not estimable
14 Urinary sodium	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14.1 Patients without hyponatraemia (48 hours)	1	Mean Difference (IV, Fixed, 95% CI)	Not estimable
14.2 Patients with hyponatraemia (48 hours)	1	Mean Difference (IV, Fixed, 95% CI)	Not estimable
14.3 Change from baseline at 48 hours - without hyponatraemia	1	Mean Difference (IV, Fixed, 95% CI)	Not estimable
14.4 Change from baseline at 48 hours - with hyponatraemia	1	Mean Difference (IV, Fixed, 95% CI)	Not estimable

Analysis 1.1. Comparison 1 Maintenance fluids versus restricted fluids, Outcome 1 Death.

Review: Fluid therapy for acute bacterial meningitis

Comparison: 1 Maintenance fluids versus restricted fluids

Outcome: 1 Death

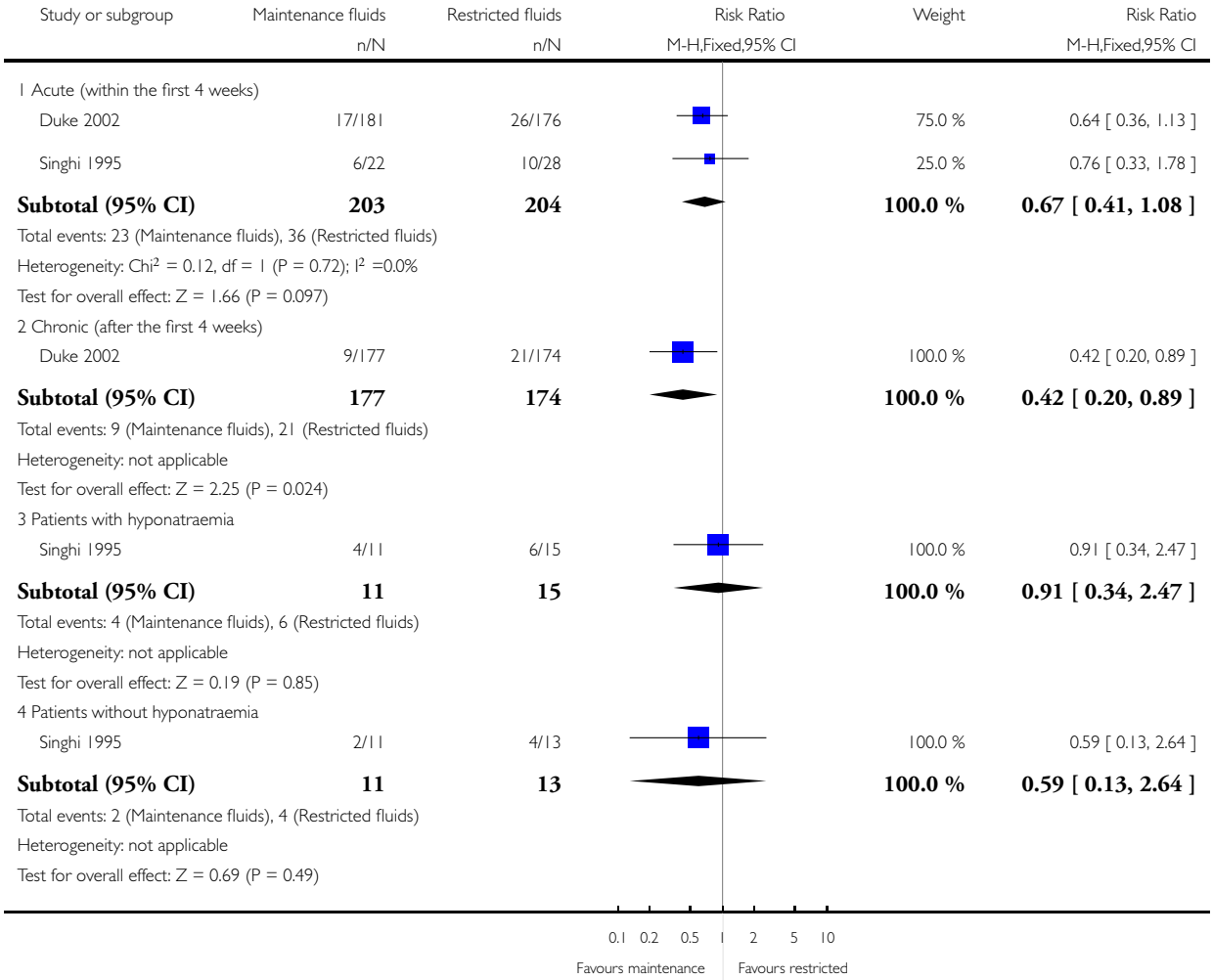


Analysis 1.2. Comparison 1 Maintenance fluids versus restricted fluids, Outcome 2 Severe neurological sequelae.

Review: Fluid therapy for acute bacterial meningitis

Comparison: 1 Maintenance fluids versus restricted fluids

Outcome: 2 Severe neurological sequelae

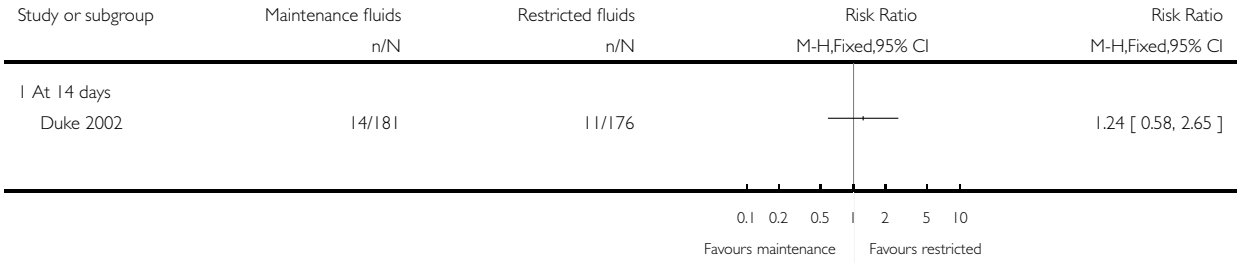


Analysis 1.3. Comparison 1 Maintenance fluids versus restricted fluids, Outcome 3 Mild to moderate neurological sequelae.

Review: Fluid therapy for acute bacterial meningitis

Comparison: 1 Maintenance fluids versus restricted fluids

Outcome: 3 Mild to moderate neurological sequelae

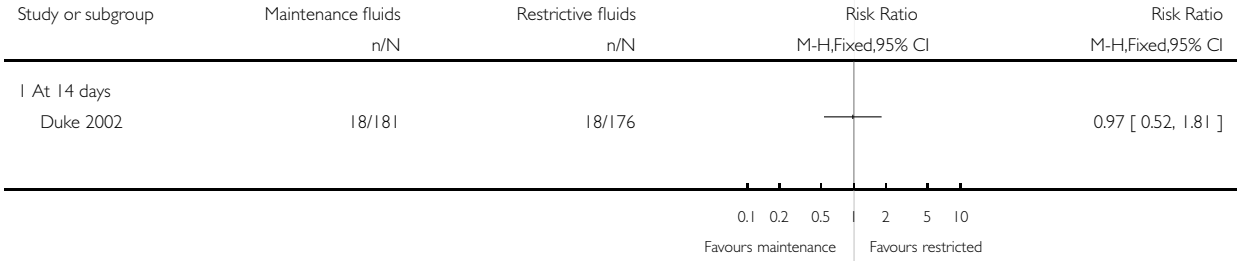


Analysis 1.4. Comparison 1 Maintenance fluids versus restricted fluids, Outcome 4 Hemiparesis/hemiplegia.

Review: Fluid therapy for acute bacterial meningitis

Comparison: 1 Maintenance fluids versus restricted fluids

Outcome: 4 Hemiparesis/hemiplegia



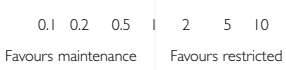
Analysis 1.5. Comparison 1 Maintenance fluids versus restricted fluids, Outcome 5 Spasticity.

Review: Fluid therapy for acute bacterial meningitis

Comparison: 1 Maintenance fluids versus restricted fluids

Outcome: 5 Spasticity

Study or subgroup	Maintenance fluids n/N	Restricted fluids n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 At 14 days				
Duke 2002	14/181	27/176		0.50 [0.27, 0.93]



Analysis 1.6. Comparison 1 Maintenance fluids versus restricted fluids, Outcome 6 Seizures.

Review: Fluid therapy for acute bacterial meningitis

Comparison: 1 Maintenance fluids versus restricted fluids

Outcome: 6 Seizures

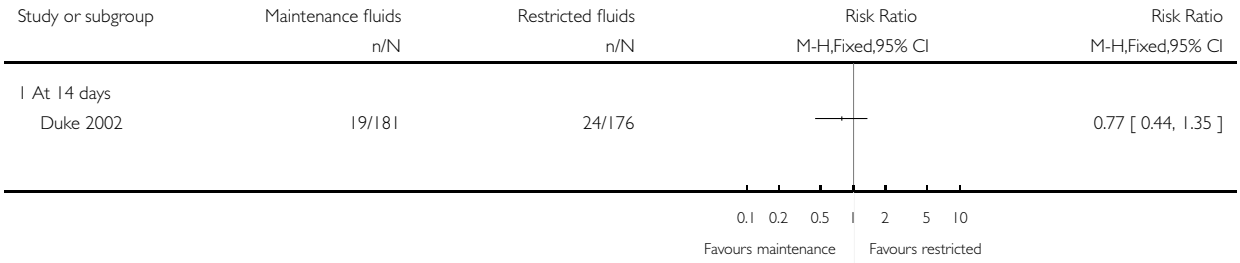
Study or subgroup	Maintenance fluids n/N	Restricted fluids n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Within the first 72 hours				
Duke 2002	38/181	63/176		0.59 [0.42, 0.83]
2 At 14 days				
Duke 2002	2/181	10/176		0.19 [0.04, 0.88]

Analysis 1.7. Comparison 1 Maintenance fluids versus restricted fluids, Outcome 7 Visual impairment.

Review: Fluid therapy for acute bacterial meningitis

Comparison: 1 Maintenance fluids versus restricted fluids

Outcome: 7 Visual impairment

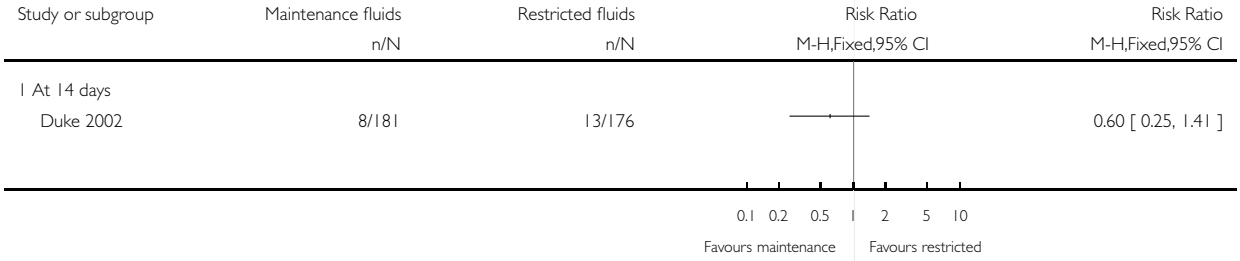


Analysis 1.8. Comparison 1 Maintenance fluids versus restricted fluids, Outcome 8 No response to sound.

Review: Fluid therapy for acute bacterial meningitis

Comparison: 1 Maintenance fluids versus restricted fluids

Outcome: 8 No response to sound

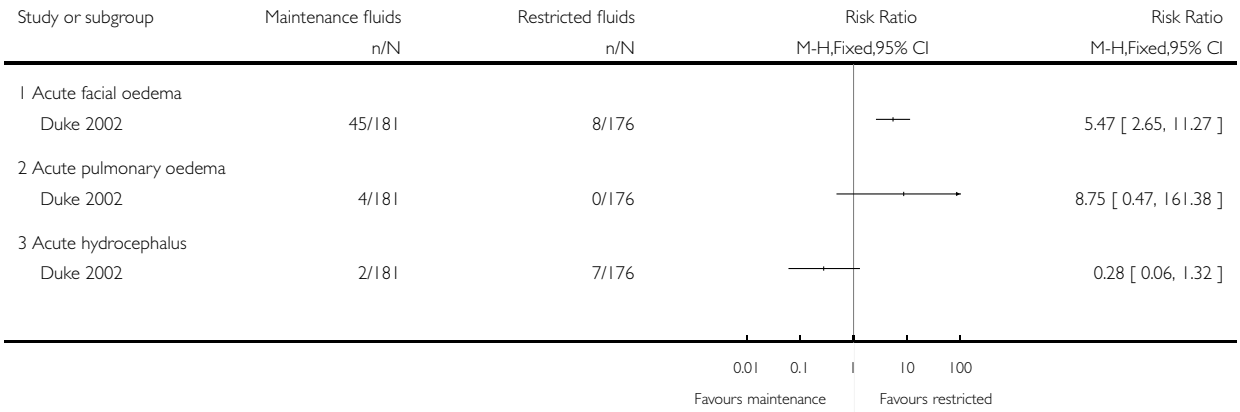


Analysis 1.9. Comparison 1 Maintenance fluids versus restricted fluids, Outcome 9 Oedema.

Review: Fluid therapy for acute bacterial meningitis

Comparison: 1 Maintenance fluids versus restricted fluids

Outcome: 9 Oedema

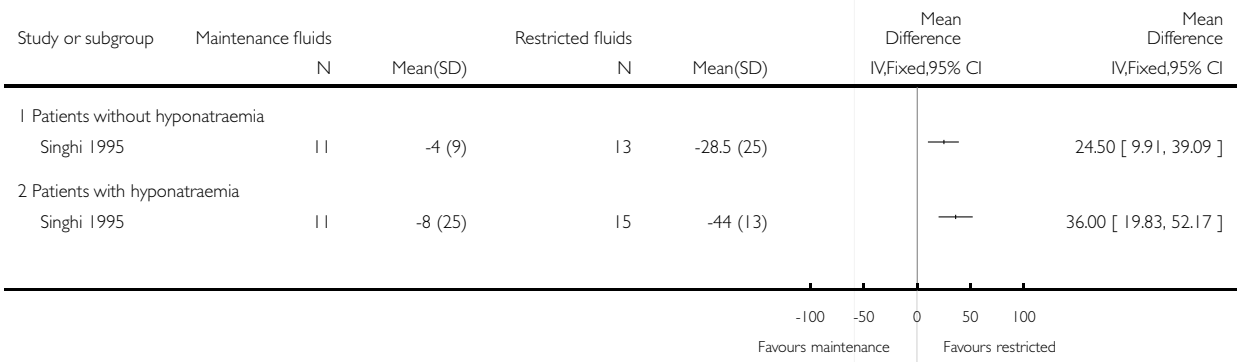


Analysis 1.10. Comparison 1 Maintenance fluids versus restricted fluids, Outcome 10 Total body water - fall after 48 hours.

Review: Fluid therapy for acute bacterial meningitis

Comparison: 1 Maintenance fluids versus restricted fluids

Outcome: 10 Total body water - fall after 48 hours



Analysis 1.11. Comparison 1 Maintenance fluids versus restricted fluids, Outcome 11 Extracellular water - fall after 48 hours.

Review: Fluid therapy for acute bacterial meningitis

Comparison: 1 Maintenance fluids versus restricted fluids

Outcome: 11 Extracellular water - fall after 48 hours

Study or subgroup	Maintenance fluids N	Mean(SD)	Restricted fluids N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Patients without hyponatraemia						
Singhi 1995	11	0.9 (28)	13	-22 (32)		22.90 [-1.11, 46.91]
2 Patients with hyponatraemia						
Singhi 1995	11	-7 (22)	15	-42 (25)		35.00 [16.86, 53.14]

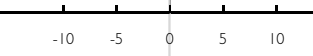
Analysis 1.12. Comparison 1 Maintenance fluids versus restricted fluids, Outcome 12 Serum sodium.

Review: Fluid therapy for acute bacterial meningitis

Comparison: 1 Maintenance fluids versus restricted fluids

Outcome: 12 Serum sodium

Study or subgroup	Maintenance fluids N	Mean(SD)	Restricted fluids N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 All patients (24 hours)						
Powell 1990	7	139 (3.61)	6	136 (3.61)		3.00 [-0.94, 6.94]
2 Patients without hyponatraemia (48 hours)						
Singhi 1995	11	133 (5.6)	13	136.5 (4.4)		-3.50 [-7.58, 0.58]
3 Patients with hyponatraemia (48 hours)						
Singhi 1995	11	130.7 (2.4)	15	134.9 (2.8)		-4.20 [-6.20, -2.20]
4 Change from baseline at 48 hours - without hyponatraemia						
Singhi 1995	11	-4 (9)	13	1.8 (4.2)		-5.80 [-11.59, -0.01]
5 Change from baseline at 48 hours - with hyponatraemia						
Singhi 1995	11	5 (2)	15	9.4 (4.5)		-4.40 [-6.97, -1.83]



Analysis 1.13. Comparison 1 Maintenance fluids versus restricted fluids, Outcome 13 Plasma osmolality - change after 48 hours.

Review: Fluid therapy for acute bacterial meningitis

Comparison: 1 Maintenance fluids versus restricted fluids

Outcome: 13 Plasma osmolality - change after 48 hours

Study or subgroup	Maintenance fluids N	Mean(SD)	Restricted fluids N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Patients without hyponatraemia						
Singhi 1995	11	-1 (5)	13	4 (7)		-5.00 [-9.82, -0.18]
2 Patients with hyponatraemia						
Singhi 1995	11	6 (3)	15	12 (10)		-6.00 [-11.36, -0.64]

Analysis 1.14. Comparison 1 Maintenance fluids versus restricted fluids, Outcome 14 Urinary sodium.

Review: Fluid therapy for acute bacterial meningitis

Comparison: 1 Maintenance fluids versus restricted fluids

Outcome: 14 Urinary sodium

Study or subgroup	Maintenance fluids N	Mean(SD)	Restricted fluids N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Patients without hyponatraemia (48 hours)						
Singhi 1995	11	24 (20)	13	38 (24)		-14.00 [-31.60, 3.60]
2 Patients with hyponatraemia (48 hours)						
Singhi 1995	11	22 (6)	15	43 (25)		-21.00 [-34.14, -7.86]
3 Change from baseline at 48 hours - without hyponatraemia						
Singhi 1995	11	-7 (16)	13	-8 (17)		1.00 [-12.22, 14.22]
4 Change from baseline at 48 hours - with hyponatraemia						
Singhi 1995	11	-24 (8)	15	-24 (15)		0.0 [-8.94, 8.94]

APPENDICES

Appendix 1. Previous MEDLINE search strategy

The following search strategy was used to search MEDLINE and CENTRAL and adapted for EMBASE and CINAHL.

MEDLINE (OVID)

1 exp MENINGITIS/
2 meningit$.mp
3 or/1-2
4 exp Fluid Therapy/
5 fluid resuscitation.mp.
6 fluid restriction.mp.
7 fluid maintenance.mp.
8 fluid management.mp.
9 intravenous fluid$.mp.
10 IV fluid$.mp.
11 hyponatr?emic solution$.mp.
12 exp Sodium Chloride/
13 saline.mp.
14 exp ALBUMINS/
15 exp PLASMA/
16 exp Plasma Substitutes/
17 (volume adj replac$).mp.
18 (human adj albumin$).mp.
19 ((frozen adj plasma) or (fresh adj plasma)).mp.
20 (plasma adj protein$).mp.
21 (hypoalbumin$ or (low adj albumin)).mp.
22 (starch or dextran$ or gelofus$ or haemacc$ or hemacc$).mp.
23 or/4-22
24 2 and 23

Appendix 2. Embase.com search strategy

1. 'meningitis'/exp
2. meningit*:ti,ab
3. #1 OR #2
4. 'fluid therapy'/exp
5. fluid*:ti,ab
6. 'sodium chloride'/exp
7. saline*:ti,ab
8. 'oral rehydration solution'/exp
9. rehydrat*:ti,ab OR hydrat*:ti,ab OR dehydrat*:ti,ab
10. 'electrolyte balance'/exp
11. electrolyte*:ti,ab
12. 'hypernatraemic solution':ti,ab OR 'hypernatremic solution':ti,ab OR 'hypernatraemic solutions':ti,ab OR 'hypernatremic solutions':ti,ab
13. 'albuminoid'/exp
14. 'plasma'/exp
15. 'plasma substitute'/exp
16. albumin*:ti,ab OR plasma*:ti,ab OR starch*:ti,ab OR dextran*:ti,ab OR gelofus*:ti,ab AND haemacc*:ti,ab OR hemacc*:ti,ab
17. #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
18. #3 AND #17
19. 'randomized controlled trial'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR

'crossover procedure'/exp
20. random*:ti,ab OR factorial*:ti,ab OR crossover*:ti,ab OR 'cross over':ti,ab OR placebo*:ti,ab OR 'double blind':ti,ab OR 'single blind':ti,ab OR assign*:ti,ab OR allocat*:ti,ab OR volunteer*:ti,ab
21. #19 OR #20
22. #18 AND #21

Appendix 3. CINAHL search strategy

S26	S18 and S24	Limiters - Publication Year from: 2007-2009 Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S25	S18 and S24	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S24	S19 or S20 or S21 or S22 or S23	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S23	TI (random* or placebo*) or AB (random* or placebo*)	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S22	TI (single blind* or double blind*) or AB (single blind* or double blind*)	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S21	TI clinical trial* or AB clinical trial*	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S20	PT clinical trial	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S19	(MH "Clinical Trials+")	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S18	S3 and S17	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S17	S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL

(*Continued*)

S16	TI (albumin* or plasma* or starch* or dextran* or gelofus* or haemacc* or hemacc*) or AB (albumin* or plasma* or starch* or dextran* or gelofus* or haemacc* or hemacc*)	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S15	(MH "Plasma Substitutes+")	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S14	(MH "Plasma")	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S13	(MH "Albumins+")	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S12	TI hyponatr* N2 solution* or AB hyponatr* N2 solution*	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S11	TI electrolyte* or AB electrolyte*	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S10	(MH "Fluid-Electrolyte Balance+")	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S9	TI (rehydrat* or hydrat* or dehydrat*) or AB (rehydrat* or hydrat* or dehydrat*)	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S8	(MH "Rehydration Solutions+")	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S7	AB saline* or AU saline*	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S6	(MH "Sodium Chloride+")	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S5	TI fluid* or AB fluid*	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL

(*Continued*)

S4	(MH "Fluid Therapy+")	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S3	S1 or S2	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S2	TI meningit* or AB meningit*	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL
S1	(MH "Meningitis+")	Expanders - Apply related words Search modes - Boolean/Phrase	Interface - EBSCOhost Search Screen - Advanced Search Database - CINAHL

WHAT'S NEW

Last assessed as up-to-date: 8 August 2010.

Date	Event	Description
9 August 2010	New search has been performed	Searches conducted. No new trials were included or excluded in this update

HISTORY

Protocol first published: Issue 2, 2004

Review first published: Issue 3, 2005

Date	Event	Description
19 May 2008	Amended	Converted to new review format.
1 March 2007	New search has been performed	Searches conducted.
17 March 2005	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

Ian Maconochie (IM) jointly (with Richmal Oates-Whitehead (ROW)) conceptualised the review; commented on drafts of the protocol and was involved in selecting trials for inclusion in the review; performed independent data extraction and quality assessment of the included trials; and commented on all drafts of the review.

Harry Baumer (HB) commented on drafts of the protocol and was involved in selecting trials for inclusion in the review; performed independent data extraction and quality assessment of the included trials; and commented on all drafts of the review. HB also led the update.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Royal College of Paediatrics and Child Health, UK.

External sources

- No sources of support supplied

NOTES

There were no new trials found in this updated review. The conclusions remain unchanged.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Developing Countries; Fluid Therapy [adverse effects; *standards]; Hyponatremia [etiology]; Meningitis, Bacterial [complications; *therapy]; Randomized Controlled Trials as Topic

MeSH check words

Child; Humans; Infant

REVIEW

Fluid therapy for children: facts, fashions and questions

Malcolm A Holliday, Patricio E Ray, Aaron L Friedman

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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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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Table 14.14 Reasons why epilepsy may be erroneously thought to be intractable

Incorrect diagnosis
Inappropriate treatment
Non-compliance
Inadequate trial of anticonvulsant
Drug induced seizures
Progressive disease
Psychosocial factors

seizures, social and emotional adjustment, educational attainment and employment prospects.

One of the most important prognostic indicators will be the type of epilepsy; a widely different prognosis may be expected, for example, between petit mal epilepsy and the Lennox Gastaut syndrome.

Studies which have looked at large populations have not separated different epileptic syndromes and have included both adults and children. Some generalizations however are possible. Overall the likelihood of remission of seizures is between 50% and 70% (Annegers et al 1979, Sillanpaa 1983). There are a number of reasons why epilepsy may be thought to be intractable (Table 14.14). Most relapses will occur during withdrawal of therapy or in the first 1–2 years after stopping treatment.

Individual factors that indicate a high chance of remission are absence of neurological abnormalities or brain lesion, normal intelligence, onset of seizure after the age of 3–4 years, low seizure frequency, brief duration of epilepsy prior to control, generalized tonic clonic seizures, typical absence seizures or simple partial seizures, no episodes of status, normal EEG background and normalization of EEG after onset of therapy (Aicardi 1986).

Prognosis for cognitive function in epilepsy

In general the same factors that indicate a good prognosis for seizure control will indicate a good prognosis for educational and social outcome. Patients with epilepsy will tend to score slightly lower on IQ tests when compared with normal siblings; 50–70% of patients will have normal IQ.

Overall, IQ scores are misleading in that a much larger proportion of children with epilepsy have learning difficulties. A recent study demonstrated significant difficulties in reading, spelling and arithmetic in up to 30% of epileptic children with normal or low normal IQ (Seidenberg 1989). Some authors have suggested that the problems relate to abnormal activity in the dominant hemisphere and correlate with left sided spikes seen on the EEG. However, this has not been confirmed by others. The learning problem may be due to the same brain damage that causes the epilepsy but not a result of the seizures. Antiepileptic drugs themselves may affect learning, particularly chronic treatment with phenytoin, primidone or phenobarbitone.

Some patients appear to show decreasing IQ as their epilepsy continues. This has particularly been noted in the Lennox Gastaut syndrome but has been described in other children with epilepsy. The role of non-convulsive status epilepticus in the dementia that occurs in the Lennox Gastaut syndrome has been extensively discussed. An effect of chronic toxic levels of anticonvulsants has been suggested particularly with phenobarbitone (Bourgeois et al 1983).

Social and behavioural outcome

Around 20–30% of children with epilepsy will experience behavioural or psychiatric problems. The causes of this are many but important factors are the degree of seizure control, type of epilepsy, the use of polytherapy and the family response. This illustrates that the behavioural outcome is the complex interaction between biological and psychosocial factors (Hermann et al 1989).

The overall prognosis may be good for populations of children with epilepsy. A poor outcome is often associated with a constellation of several problems, i.e. low intelligence, poor control of seizures and behavioural abnormalities. For optimal management of chronic epilepsy therefore three main areas need to be evaluated each time the child is seen:

1. The medical aspects of the disease
2. The educational and social development of the child
3. The response and adjustment of the family to the child with epilepsy.

Collaboration therefore with many other professionals is essential, including psychologists, psychiatrists, social workers and teachers.

ACUTE ENCEPHALOPATHIES

DEFINITION AND CLASSIFICATION

Acute encephalopathy denotes a non-specific brain insult in a patient manifested by a combination of coma, seizures, decerebration and, less commonly, ataxia, hemiplegia or cardiorespiratory arrest. Coma and seizures may be seen as neurological complications of many children's diseases, for example scalds and burns (Emery & Reid 1962), cardiac bypass surgery (Seshia et al 1979), leukaemia (Hanefeld & Riehm 1980), hepatic failure in fibrocystic disease (Conomy & Swash 1968), diabetic ketoacidosis (Frier et al 1980), and coeliac and nephritic crises.

Acute encephalopathies may be classified as:

1. Anoxic ischaemic
2. Infectious and parainfectious
3. Haemorrhagic
4. Traumatic (accidental and non-accidental)
5. Toxic
   a. Exogenous
   b. Endogenous
6. Epileptic.

AETIOLOGY

Infection accounts for approximately one-third of cases presenting with acute encephalopathy and coma. The causes are seen in Table 14.15. Most organisms are capable of invading the nervous system (with the direct effects of cerebral oedema, cerebritis, encephalitis, cerebral congestion, hydrocephalus, subdural effusion and empyemas, ventriculitis, thrombophlebitis, and abscess), but encephalopathy may also result from the effects of extracranial infection by inappropriate ADH, inflammatory brain oedema, thrombophlebitis, status epilepticus, severe endotoxaemic shock and circulatory failure and DIC.

As an example, tuberculous meningitis may present as an acute hemiplegia resulting from vasculitis, or as an acute encephalopathy with raised intracranial pressure from acute ventricular dilatation or multiple tuberculomata.

Table 14.15 Causes of infectious encephalopathies

Bacterial or fungal meningitis/encephalitis
Cortical thrombophlebitis
Cerebral abscess (including immunocompromised patients)
Meningitis with septicaemia (*Meningococcus*/B haemolytic *Streptococcus*)
Viral encephalitis (e.g. herpes simplex encephalitis)
Parainfectious demyelinization
Subacute sclerosing panencephalitis (acute presentation)
Meningoencephalitis (protozoal, helminthic and rickettsial), e.g. *Toxoplasma*
Cerebral malaria
Acute disseminated encephalomyelitis

On some occasions multiple factors may contribute to the encephalopathy. An example is viral gastroenteritis which may cause a direct invasive encephalitis following viraemia (enteroviruses) or meningitis from systemic *Salmonella* infections. *Shigella* and *Campylobacter* may both secrete a neurotoxin which causes fits and coma and is therefore a true toxic encephalopathy. There may be accompanying dehydration and hyperviscosity with venous sludging and cerebral venous thrombosis adding to the problems of gastroenteritis. Additionally osmotic imbalance or biochemical disorders (e.g. hypocalcaemia) may also result in seizures. The haemolytic uraemic syndrome may have an associated encephalopathy as a result of disseminated intravascular coagulation affecting intracranial vessels.

Viruses may result in an acute encephalopathy by virtue of their neurotropic nature or they may attack specific parts of the central nervous or peripheral system, e.g. polio and the anterior horn cells, chicken-pox and the cerebellum or mumps and the aqueduct of Sylvius. Viruses may also produce an acute encephalitis or perivascular demyelination as a result of myelinoclastic antibodies produced by the leucocytes involved in perivascular cuffing.

A reversible encephalopathy from virus invasion of neurones may result in the the 'pyrexial convulsion syndrome'. Virus infection may also result in a catabolic stress and precipitation of inborn errors of metabolism such as maple syrup urine disease or Leigh's syndrome (from pyruvate decarboxylase deficiency), biotinidase deficiency, cytochrome oxidase deficiency, or other complex mitochondrial cytopathies.

Hypoxic ischaemia

This is a common and frequently irremediable cause of acute encephalophathy. The pathogenesis of hypoxic ischaemic injury begins with hypoxia followed by a build up of $PaCO_2$, lactic acid, and a decreased pH. There follows a two-pronged insult:

1. To the brain cell membrane with inhibition of membrane ion pumps, resulting in accumulation of extracellular K^+ and intracellular Na^+ and Ca^{2+} and in depletion of ATP and phosphocreatine. The result is a cytotoxic oedema which contributes to the raised intracranial pressure and infarction.
2. To the cardiac muscle (as well as lung, liver, kidneys and gut) with a resultant systemic pressure failure below the limits of cerebrovascular autoregulation. This results in failure of cerebral perfusion and infarction. The low systemic pressure additionally adds a degree of vasogenic brain oedema.

Table 14.16 Hypoxic–ischaemic causes of acute encephalopathy

Perinatal asphyxia
Pulmonary disease (upper airways obstruction, laryngeal TB, epiglottitis)
Alveolar hypoventilation
CO poisoning
Methaemoglobinaemia
Anaemia
Status epilepticus
Near miss SIDS
Post cardiac arrest (any cause)
Cardiac bypass surgery
Near drowning
Cardiac dysrhythmia
Congestive cardiac failure
Hypotension
Disseminated intravascular coagulation
Hypoglycaemia
Vitamin or cofactor deficiency (B_{12}, B_6, folate etc.)
Anaesthetic accidents

The brain is able to withstand hypoxia without ischaemia (for example cyanotic congenital heart disease) but is especially sensitive to ischaemia. In hypoxia alone there is reversion to anaerobic metabolism with glucose converted to lactate and pyruvate. If the circulation is intact these metabolites are removed and later converted back to glucose in the liver when oxygen becomes available. With ischaemia (for example from raised intracranial pressure and reduced cerebral perfusion pressure), especially if there is plentiful glucose, glycolysis continues with an accumulation of lactate which is not cleared and causes intracellular acidosis. This prevents enzyme action and causes the lysosomes to rupture. Although status epilepticus is considered a separate cause of encephalopathies, the end result of uncontrolled and decompensated status epilepticus is cerebral oedema and hypoxic ischaemic injury with depleted ATP and PCr and increased lactate, and diminished cerebral blood flow. The hypoxic ischaemic causes of encephalopathy and coma are seen in Table 14.16.

Toxic and metabolic disorders

These may result in an exogenous or endogenous encephalopathy. The exogenous causes are seen in Table 14.17. Occasionally these may be non-accidentally delivered as part of the Munchausen's syndrome by proxy (Meadow 1977). Endogenous sources of toxins include liver and renal failure, carbon dioxide narcosis, and other causes seen in Table, 14.18.

Non-traumatic intracranial haemorrhage

This may be responsible for an acute encephalopathy, for example haemorrhage into a benign astrocytic cyst. Other causes are listed in Table 14.19.

Table 14.17 Causes of toxic encephalopathy (exogenous)

Antihistamines
Anticholinergics
Anticonvulsants
Antidepressants (tricyclics and phenothiazines)
Antimetabolites (vincristine, cyclophosphamide, methotrexate, asparaginase, vinblastine, cranial irradiation, cytosine arabinoside)
Hypnotics and analgesics (barbiturates, paracetamol, benzodiazepines and salicylates)
Antibiotics (penicillin, nalidixic acid)
Anti-inflammatory agents (steroids, cimetadine)
Abused drugs (alcohol, solvents, amphetamines etc.)
Environmental toxins (H_2S, CO, phosphates, DDT, iron, lead, hexachlorophane, aflatoxin, venoms, insecticides/pesticides, plants and minerals, heavy metals, hypothermia and heat stroke)

Table 14.18 Endogenous causes of acute encephalopathy

1. Fluid balance	—	Water intoxication Hypo- or hypernatraemia Hypo- or hypermagnesaemia Hypo- or hypercalcaemia Hypo- or hyperphosphataemia Acidosis/alkalosis Trace metal deficiency Scalds
2. Endocrine	—	Diabetes mellitus/hypoglycaemia Hypo- or hyperthyroidism Hypo- or hyperparathyroidism Hypopituitarism Hyperbilirubinaemia
3. Organ failure	—	Liver Kidneys Pancreas Intestinal/volvulus Hypertensive encephalopathy
4. Inborn errors of metabolism	—	Aminoacidopathies — branched chain ketoacidosis Organic acidaemia — propyl, malonyl, isovaleric and betaketothiolase Galactosaemia Urea cycle defects Carnitine deficiency Porphyria Medium chain acyl dehydrogenase deficiency

Table 14.19 Intracranial haemorrhage

Arteriovenous malformation
Ruptured aneurysm
Arteriovenous occlusion — thrombotic or traumatic a. Infection (focal or widespread) b. Cardiac c. Haemotological (sickle cell, polycythaemia or idiopathic thrombocytopenic purpura) d. Collagen (lupus erythematosus) e. Metabolic (diabetes mellitus) f. Moya moya
Intracranial venous thrombosis which may be sterile or secondary to thrombophlebitis

Trauma

Trauma may be accidental or non-accidental. Accidental head injury is discussed elsewhere (pp. 905–910). The young child who presents with an acute encephalopathy with retinal haemorrhages but little evidence of external trauma should be suspected of having had a 'whiplash shaking injury' (disciplinary injury). The shaking, with rotation of the head, results in subdural and petechial brain haemorrhages, cerebral oedema and retinal haemorrhages.

INVESTIGATION OF COMA

After the initial resuscitation of the cardiovascular and respiratory system and treatment of seizures, after a history has been obtained of the events leading to the coma, and after an examination of the child, the clinician's approach to investigating the comatose child is twofold. First, investigations are aimed at making a diagnosis (Table 14.20) and second, supportive investigations are necessary regardless of the aetiology (Table 14.21). The coma state will require monitoring itself. Initially one of the coma scales is used, such as the original Glasgow coma scale (Table 14.22) (Teasdale & Jennett 1974), or the modified Glasgow coma scale (Table 14.22) (Jennett et al 1977). Alternatives are the Adelaide scale (Simpson & Reilly 1982), the 0–IV scale (Huttenlocher 1972, Seshia et al 1977) (Table 14.22), the 'Jacobi scale' (Gordon et al 1983), the children's coma scale (Raimondi & Hirschauser 1984), and the children's orthopaedic hospital and medical centre scale (Morray et al 1984). We favour the Adelaide scale and the 0–IV scale, but once the patient is paralysed and ventilated, all scales are insufficient for following the progress of coma, and the coma state then needs monitoring by means of:

1. Occular examination (pupils, eye movements, etc.)
2. Bulbar reflexes
3. Temperature, pulse rate, respiratory rate and blood pressure.

MANAGEMENT

Whatever the cause of the encephalopathy, there are common factors responsible for the mortality and morbidity. These have led

Table 14.20 Strategy for coma management: diagnostic investigations

Obvious causes	Non-obvious causes
Hypoxic ischaemic	CT–ultrasound
Diabetic ketoacidosis	LP (incl. immunofluorescence etc.)
Poisoning	EEG
Infections	Toxicology (barbituates, toluene, benzodiazepines, salicylates, iron, lead, anticonvulsants, antidepressants)
Drowning	
Burns/scalds	Metabolic (NH_3, LFTs, porphyrins, amino acids, dicarboxylic acids, urine sugars, lactate/pyruvate/acidosis, urea/creatinine, calcium, T_4/TSH)
CVA	Tuberculin test
	Virology
	Technetium scan
	X-rays (skull, skeletal)
	Brain biopsy

Table 14.21 Strategy for coma management: supportive investigations (independent of cause of coma)

* Gases (4 hourly)
* Pulse oximeter (O_2 sat.)
CVP −/+ Wedge
* Dextrostix (4 hourly)
* Osmolality (8 hourly)
* Calcium and phosphate (bd)
EEG (continuous)
ICP/CPP (continuous) (mean pressure, pulse pressure, periodic waves)
* BP arterial (continuous)
Coagulation (once then prn)
* Temperature
* Fluid balance (vs output, weight, labstix)
* Blood count and haemoglobin
* CXR (portable)
Weight
Anticonvulsant levels
* ECG (continuous)
* Urea and electrolytes (twice daily)
* Infection screen
Visual evoked potentials
Brain stem evoked potentials
Liver function tests (once/day)
Arteriovenous oxygen difference or jugular venous oxygen saturation
Cerebral blood flow (initial + change) (autoregulation, CO_2 respiration and perfusion)
Cerebral blood flow velocity (continuous, intermittent daily)
Monitoring neurology and coma state
1. Glasgow coma scale
2. Ocular (pupils, external ocular movements, etc.)
3. Bulbar reflexes
4. Temperature, pulse rate, respiratory rate and blood pressure

* All coma regardless of cause.

to a philosophy of management of 'treating the treatable' which includes:

1. Treatment of infection
2. Control of seizures
3. Detection and treatment of raised intracranial pressure (maintenance of cerebral metabolism and blood flow)
4. Maintenance of homeostasis
5. Removal of circulating toxins.

Treatment of infection

The treatment of bacterial meningitis, cerebritis, encephalitis and thrombophlebitis is appropriate high dose intravenous antibiotic therapy or, in the case of herpes simplex encephalitis, acyclovir.

The cytological technique of cyctocentrifugation and millipore filter collection of cells has improved the identification of cell types in the CSF. The technique is useful in CNS leukaemia, as well as in acute and chronic spinal meningitis (Kontopolous et al 1986). It is particularly useful in cases of mild CSF pleocytosis. There is a significant discordance between lymphocytes and macrophages in the CSF and the ability to recognize the recovery phase of pyogenic CSF infection, by an increased macrophage count, is useful while treating meningitis or ventriculitis.

Antibiotics vary in their ability to penetrate the CSF. Antituberculous drugs penetrate well but the aminoglycosides as a group show very poor CSF penetration and need to be given intrathecally. Intrathecal therapy may also be necessary in cases of pneumococcal infection and cases of pyogenic meningitis with loculation of CSF. If intrathecal therapy is used then it is important to monitor the CSF levels of antibiotic as well as the cell count. Antibiotic serum levels should also be routinely monitored. Low 'peak levels' of antibiotic indicate that the frequency of administration needs to be increased while low trough levels indicate that the dose should be increased. It is important to ensure the antibiotic is instilled at the appropriate locus to be effective, as antibiotics injected into the lumbar CSF may not reach the basal cisterns if there is loculation, and very little will reflux back into the ventricles. In such situations a ventriculostomy reservoir may usefully be inserted for administration of the antibiotics.

In the case of tuberculous meningitis with coma the ideal management is first to obtain a CT scan, and since tuberculous meningitis is frequently accompanied by an acute hydrocephalus in children, this is followed by the insertion of a ventriculostomy reservoir into the frontal horn of the right lateral ventricle. The intracranial pressure is then measured and relief of the supratentorial pressure obtained by removal of CSF. With the intracranial pressure normal, a lumbar puncture is performed for lumbar CSF collection. The spinal meningitis is not necessarily accompanied by an increased cell count in the ventricular CSF. Persistent raised intracranial pressure needs to be treated by tapping the reservoir or by external drainage from the reservoir while at the same time sterilizing the CSF with the appropriate antituberculous medication.

Control of seizures

It is important to control seizures to prevent secondary hypoxic ischaemic damage and routine EEG monitoring (preferably continuous display) should be carried out. A single fit during an acute encephalopathy requires only short-term prophylactic anticonvulsants. Phenytoin is the anticonvulsant of choice. For epileptic encephalopathy, intravenous diazepam and intravenous mannitol with or without paraldehyde may be required.

Paraldehyde can be given in modern 'plasti-pak' syringes. It is usually given intramuscularly in a dose of 0.05 ml/kg or 1 ml/year of age. The half-life is approximately 6 h (range 6–9 h). It can in an urgent situation be given intravenously, but is not routinely recommended. The dose should be reduced in the presence of hepatic or pulmonary disease. Much care is needed with intravenous injections because of serious hepatic necrosis or pulmonary haemorrhage which may result. The rectal route is a satisfactory alternative, if given in a 10% solution with normal saline or mixed with equal quantities of oil. The dose of the 10% solution is 0.5 ml/kg. Estimation of blood levels of paraldehyde can be performed in some laboratories and the therapeutic range is 300–400 mg/ml (Curless et al 1983).

Intravenous phenytoin may be given as a 'slow epinutinization' or 'rapid epinutinization' regimen. For encephalopathies the rapid

Table 14.22 Coma scales for use in children

0–IV Scale (Seshia et al 1977, Huttenlocher 1972)		Children <5 years (Simpson & Reilly 1982)	
0	Arouses spontaneously and to stimuli	Eye opening	— 4 (same)
I	Stuperose. Spontaneous arousal rare. Roused readily but briefly by stimuli. Cough/gag present		— 3 — 2 — 1
II	Spontaneous arousal absent. Semipurposive/avoidance motor response to stimuli. Cough/gag depressed	Verbal response	— 5 oriented — 4 words — 3 vocal sounds — 2 cries — 1 nil
III	Arousal in form of motor response only to intense, sustained, painful stimuli. Cough/gag absent	Motor response	— 5 (same) — 4 — 3 — 2 — 1
IV	Not aroused even by intense/sustained painful stimuli. Cough/gag absent	(Normal developmental milestones taken into account)	
		0–6 months	9 points
		>6–12 months	11 points
		>1–2 years	12 points
		>2–5 years	13 points
		>5 years	14 points

regime is required — 10 mg/kg intravenously slowly at a rate of 10 mg/min, followed 1 h later by 5 mg/kg with a further 10 mg/kg in divided doses over the next 24 h. The blood level must be measured daily and maintained in a therapeutic range. In the newborn there is a large dose range (between 2 and 25 mg/kg) and blood level should be regularly checked. The dose required may change acutely in the second week of life. At high doses phenytoin may become epileptogenic and produce seizures which are resistant to benzodiazepines and paraldehyde. Prolonged thiopentone or chlormethiazole may result in enzyme induction and low phenytoin levels. The commonest reason for failure to control seizures in acute encephalopathy is failure to achieve adequate plasma concentrations of the drug.

Diazepam is useful to control seizures in the acute presentation of encephalopathies although some children may be diazepam resistant and have an exacerbation of seizure activity. With continuous EEG monitoring the benzodiazepine sensitivity can be readily assessed. There is a slight cerebral vasoconstrictor effect and therefore intracranial pressure is lowered. Following the first dose, if the fits have not ceased and provided the pupils have not dilated and blood pressure has not dropped, and the child is not benzodiazepine resistant, it may be repeated. The intravenous preparation should not be diluted for injection or a white precipitate may form in the mixture, which is irritant. It should not be mixed with other drugs and should be injected at a rate of 1 mg/min. Fast injection may cause apnoea or laryngeal spasm and hypotension. Other benzediazapines, such as clonazepam, are more likely to produce hypotension and bronchorrhoea. Peak brain levels of diazepam occur 1 min after injection but the drug leaves the brain rapidly and fits may recur after 20 min. The dose is 0.25–0.4 mg/kg (age in years plus 1). An intravenous infusion is possible for those cases responsive to diazepam.

Lignocaine, thiopentone and chlormethiazole are other alternative anticonvulsants for use with encephalopathies. With thiopentone the aim is to stop seizures and not to produce anaesthesia. One gram is dissolved in 500 ml of normal saline and the infusion is commenced at 5 ml/kg i.v. infused to keep the patient awake but seizure free.

The concentrations in the bottle may be reduced and the patient is weaned off 24 h after the last fit. Apnoea, hypotension and laryngospasm may all occur from fast infusion.

Detection of raised intracranial pressure

The methods and sites for monitoring the intracranial pressure are seen in Table 14.23 (Minns 1990). In children with encephalopathies, the preferred method of monitoring the intracranial pressure will depend on whether ventricular dilatation

Table 14.23 Sites for ICP monitoring

Ventricle	Catheter (percutaneous through the anterior fontanelle) Catheter (via burr hole) Reservoir Transducer (camino) Telemetry (± inline with shunt)
Subarachnoid (and subdural)	Bolt (Beeds, Richmond, Newell, Philly, Bolt) Catheter (cordis via burr hole) Catheter (Teflon via anterior fontanelle) Transducer (catheter tipped-gaeltec ICTb) Transducer (miniaturized, fitment to burr hole) Lumbar space (at LP or cannula)
Extradural	Catheter tip transducers Transducer (similar to subdural) Sensors (Ladd)
Brain parenchyma	Fibreoptic transducer (brain tissue pressure)
Fontanelle	Fontanometers (aplanation especially pneumatic)
Tympanic membrane	Impedance test of tympanic membrane tension

is present or whether the ventricles are small and shifted as a result of the brain swelling.

For the infant with a patent anterior fontanelle, and with ventricular dilatation, the ventricles can be punctured percutaneously. If ICP monitoring is needed continuously for long periods, then a ventriculostomy reservoir is neurosurgically inserted or a ventricular transducer placed in situ. For the infant with cerebral oedema it is possible to continuously monitor the intracranial pressure by the use of a subdural or subarachnoid Teflon catheter placed percutaneously through the anterior fontanelle. A ventricular transducer may be inserted which will record either the ventricular pressure or if not in the ventricle the brain parenchymal pressure. For the older child with acute ventricular dilatation it is Edinburgh practice to insert a ventriculostomy reservoir or, in the oedematous brain, to monitor the intracranial pressure from the brain surface by means of a 'Cordis fluid filled catheter' coupled to a pressure transducer.

Intracranial pressure

A common factor in children with encephalopathies and cerebral oedema is the secondary brain shifts which cause ischaemic brain damage. These are responsible for the mortality and the morbidity. They come about by a critical reduction in the vascular perfusion pressure to the brain produced usually by an increase in intracranial pressure.

Because of the need to compare the intracranial pressure with arterial blood pressure the same units of measurement are usually used. These are mm of mercury (1 mmHg = 1.36 cm of water) or if SI units are used ICP is expressed as kilopascals (1 kPa = 7.5 mmHg). The normal ICP in adults is 0–15 mmHg (0–2 kPa). In children the upper limit of normal ICP is lower and for the newborn levels should not be in excess of 3.5 mmHg, for the older infant 5.5 mmHg, and for the toddler 6.5 mmHg (Minns et al 1989).

Brief rises in the intracranial pressure may occur during coughing, straining, and crying, as well as other physiological activities that increase the central venous pressure. Sustained elevations or intermittent rises in pressure in the form of pressure waves may also occur (Fig. 14.28). Several wave forms have been described including the 'A' waves or plateau waves which show a rapid rise in ICP to 50 mmHg or more which last from 5 to 20 min. The second common type is the 'B' wave which consists of a series of sharply peaked waves lasting 30 s to 2 min. Both are thought to result from cerebral vasodilatation. In the 'A' waves this occurs against a background of reduced craniospinal compliance in which small increments of volume result in large increases in pressure. 'B' waves, on the other hand, may result from fluctuations in the cerebral vascular dimensions corresponding to alterations in arterial CO_2 tension. The third type of abnormal ICP wave form is the 'C' wave which consists of rapid sinusoidal fluctuations of about 6 per min corresponding to the Traube–Hering–Mayer fluctuations in the systemic arterial tree.

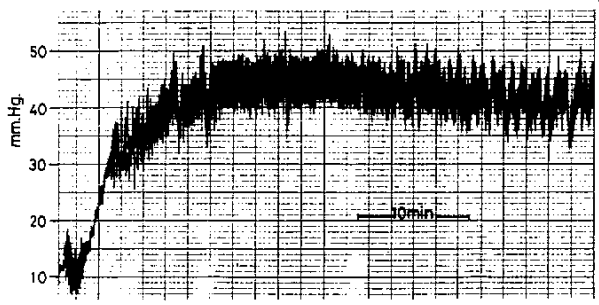

Fig. 14.28 Plateau or A-wave indicating reduced cerebral compliance in the presence of intact cerebrovascular autoregulation (mmHg = ventricular CSF pressure).

Table 14.24 Clinical features of brain herniations

Tentorial
Sunsetting
Dilated pupils
VI nerve palsy
Cortical blindness
Hemiplegia
Extensor motor pattern (decerebrate)
Coma
Respiratory irregularity
Systemic hypertension
Tonic seizures
Cingulate gyrus herniation
Diplegia or hemiplegia
Visual symptoms
Foramen magnum cone
Cardiorespiratory arrest
Bulbar palsy
Neck stiffness
Hypotonia
Stridor
Spinal flexion
Hypotension
Hyperthermia

An increase in the intracranial pressure may come about as a result of increasing either the brain, blood or CSF contents of the skull. The actual increases in ICP that result from a given increment in volume will depend on the intracranial pressure–volume status. Miller & Leech (1975) described the pressure–volume response (PVR) as an increase in ICP in mmHg/ml of CSF volume added or withdrawn in 1 s. Normal values were 0–2 mmHg/ml; values of 3 mmHg or more at baseline ICP levels indicated reduced craniospinal compliance (or increased elastance). Marmarov et al (1975) defined a pressure–volume index (PVI) as a volume which if added to the CSF would produce a 10-fold increase in the intracranial pressure. The normal range of PVI in an adult is 25–30 ml. In a child it is from 12 to 25 ml.

As a result of the increased intracranial pressure in encephalopathies with cerebral oedema, and because the brain is virtually incompressible, there is a resultant brain shift. The cingulate gyrus herniates under the lower margin of the falx as the midline is shifted. The medial part of the temporal lobe also herniates through the tentorial hiatus between the free edge of the tentorium and the mid-brain. At the same time the brain stem is shifted downward to the foramen magnum which tends to cut off the blood supply to the stem from the perforating branches of the basilar artery and this results in ischaemia. The signs of a cingulate gyrus herniation, tentorial herniation and foramen magnum cone are seen in Table 14.24.

Cerebral perfusion pressure

With increasing ICP there is an increase in the cerebral venous

pressure. This remains about 3 mmHg below the ICP so that cerebral circulation continues. The cerebral perfusion pressure is defined as the difference between the mean systemic arterial pressure (SAP) and intracranial pressure (ICP), i.e. CPP = mean SAP — ICP.

The relationship between intracranial pressure and cerebral perfusion pressure is complex. Raised intracranial pressure may be caused by an increase in cerebral blood flow or it may be the limiting factor producing a reduction in cerebral blood flow. In encephalopathies the brain is frequently pale and devoid of blood flow as a result of the raised intracranial pressure producing ischaemia. A cerebral perfusion pressure of 60–70 mmHg is normal and there is a progressive fall in perfusion to the brain with decreasing cerebral perfusion pressures down to 40 mmHg. Below this there is an absolute fall in the brain perfusion and levels of less than 18–20 ml/100 g of brain per min will result in ischaemic infarction.

Cerebral blood flow

The earliest measurements of blood flow involved the Fick principle with a method which involved inhalation of a metabolically inert gas that diffused freely in and out of brain tissue. The normal value in man is 50 ml/100 g per min. The normal cerebral arteriovenous oxygen content difference is 6 ml/100 ml of blood and therefore the normal cerebral oxygen uptake rate is 3 ml oxygen/100 g per min. Methods of measuring the cerebral blood flow are listed in Table 14.25. There is ordinarily coupling between cerebral blood flow and brain metabolism but in coma the cerebral metabolic rate consuming oxygen falls as well as the cerebral blood flow.

The determinant of cerebral blood flow is the arterial $PaCO_2$ level. Increases in the arterial $PaCO_2$ increase the cerebral blood flow and a fall in arterial $PaCO_2$ reduces the cerebral blood flow due to cerebral vasoconstriction. Changes in cerebral blood flow cause changes in the cerebral blood volume and this influences the ICP. Inducing hypocapnia by hyperventilation the ICP can be reduced (if the raised ICP had been due to cerebral vasodilatation). If, however, the cerebral blood flow is already low from cerebral oedema then hyperventilation will result in worsening ischaemia. CO_2 responsiveness may be lost globally or regionally.

The cerebral blood flow remains constant over an arterial pressure level of 60–140 mmHg in normal adults. With low systemic arterial pressures, below the limits of cerebrovascular autoregulation there is a fall in cerebral blood flow and with blood pressure rises above 140 mmHg there is a breakthrough of autoregulation (break point) with progressive cerebral oedema. Autoregulation, therefore, can be defined as a maintenance of the cerebral blood flow by alteration of the cerebral blood volume in response to large changes (increases or decreases) in the systemic perfusion pressure. Autoregulation can also be lost globally or regionally.

Table 14.25 Methods of measuring blood flow, velocity or perfusion

1. Flow meter
2. Electrical impedance
3. Doppler ultrasound
4. Magnetic resonance imaging
5. Single photon emission computerized tomography
6. Positron emission tomography
7. First pass (MTT)

Treatment of raised intracranial pressure

Removal of CSF is possible if a ventricular cannula is in situ but this is not always possible with small shifted ventricles and cerebral oedema. Despite this, for some conditions such as tuberculous meningitis this may be the optimal method of managing the raised intracranial pressure.

Steroids have a number of important actions on the brain — an immunosuppressant effect, an anti-inflammatory effect, and the reduction in CSF formation. The main actions are to tighten the endothelial junctions of the blood–brain barrier, stabilization of lysosomal activity, and restoration of the microcirculation. Other actions include inhibition of the release of free radicals, fatty acids, prostaglandins, and the products of catecholamine metabolism. Steroids also cause glial uptake and transcapillary efflux of water with resolution of oedema. Steroids cross the blood–brain barrier to reach neuronal receptor sites. There is an additional direct effect on cerebral metabolism with increased neuronal function and stimulation of glucose consumption.

Steroids are of little use in controlling the raised intracranial pressure in Reye's syndrome. They are most useful in reducing the perifocal oedema surrounding mass lesions. They may be positively harmful in hypoxic ischaemic brain damage and their use in herpes simplex encephalitis is debatable. Mannitol in combination with dexamethazone will prevent the unwanted escape of mannitol across the blood–brain barrier. Mannitol reduces brain water by controlled hyperosmolar dehydration, it reduces blood viscosity, and increases cerebral vasoconstriction (the cerebral blood flow remains normal while the cerebral blood volume is decreased). Mannitol also scavenges free radicals. If mannitol and frusemide are used together, the circulating volume is decreased and, depending on the central venous pressure, volume expansion may be necessary. Mannitol is given in a dose of 7 ml/kg of a 20% solution or 0.21 g/kg per dose.

Hyperventilation should not be used prophylactically in encephalopathies to control raised intracranial pressure. Its use should be restricted to episodic increases in intracranial pressure because the cerebral vasoconstriction, changes in pH, bicarbonate, and CO_2 reactivity are not maintained if hyperventilation is continued for longer than 24 h. Prolonged hyperventilation can lead to ischaemia. During episodes of raised intracranial pressure the $PaCO_2$ level should be reduced no lower than 3–3.5 kPa.

Barbiturates produce a concomitant reduction in the cerebral metabolic rate and cerebral blood flow. Their use is restricted to those patients unresponsive to mannitol, hyperventilation and steroids. It is important to carefully monitor the systemic blood pressure during their use for fear of reducing the cerebral perfusion pressure.

Other measures, such as decompression craniotomy or hypothermia, have some support in some units but, as with barbiturates, their use where first line methods have failed is less likely to be successful.

CEREBROVASCULAR DISEASE AND MIGRAINE

Intracranial and intracerebral haemorrhage is a common problem at the extremes of life in the neonatal period and in old age. In the postneonatal period the commonest cause of intracranial

haemorrhage is head trauma and this is considered on page 905. Cerebrovascular disease presenting as either stroke or an acute intracerebral haemorrhage is relatively rare and affects only about two per 100 000 of the childhood population. Intracranial haemorrhage is usually either subarachnoid or intracerebral with subdural bleeding being extremely rare other than from trauma. Infarction of the brain may result from many causes and may be due to vascular thrombosis, cerebral embolism, watershed zone lesion infarction, vascular compression or vascular injury.

The presentation is usually that of acute hemiplegia with a stroke, or sudden onset headache and vomiting with meningism or coma.

In 27 cases of intracerebral haemorrhage presenting after the neonatal period arteriovenous malformations were responsible for haemorrhage in 37% and aneurysm in 11%. Haemophilia and coagulopathies result in individual cases. Hypertension is a rare cause of primary intracerebral haemorrhage in children but haemorrhage into a tumour, particularly cerebellar astrocytomas, is responsible for 20% of cases. This may be the presenting feature so that haemorrhage into a benign astrocytic cyst may mask the underlying neoplasm.

INTRACRANIAL HAEMORRHAGE

Subarachnoid haemorrhage

Subarachnoid haemorrhage is most commonly due to a bleed from an arteriovenous malformation or an aneurysm. It presents classically in the older child with sudden onset of headache, vomiting, loss of consciousness with bilateral sixth nerve palsy, and possibly hyloid haemorrhages in the fundus.

Although diagnosis rests on finding blood stained CSF on lumbar puncture it should be stressed that lumbar puncture should never be performed on a child presenting with decreased conscious level without a prior CT scan. Since computerized tomograms are the most useful way now of diagnosing subarachnoid haemorrhage in most cases one can demonstrate the bleed on the scan without the need for a lumbar puncture. Only very small leaks may not show enough change in the density pattern of the CSF to be picked up on a CT scan and lumbar puncture is then necessary.

The CSF is found to be blood stained and after 6 h xanthochromia appears, the red cells are crenated and if there is any doubt as to whether one is dealing with a true subarachnoid haemorrhage or a traumatic puncture then spectrophotometry of the fluid is indicated. This will show a bilirubin peak together with haemoglobin in a true subarachnoid haemorrhage whilst the oxyhaemoglobin peak will predominate in a traumatic tap. There are still cases of subarachnoid haemorrhage in children missed with label of traumatic lumbar puncture who then have a fatal second bleed before the diagnosis is established.

In addition to arteriovenous malformations and aneurysm one can have the presentation of subarachnoid haemorrhage or a primary intraventricular haemorrhage such as haemorrhagic disease of the newborn, thrombocytopenia and rarely haemophilia secondary to bleeding from a coagulation disorder. Subarachnoid bleeding may also be prominent in non-accidental shaking injury.

Cerebral aneurysms

These are usually of the berry or saccular type but fusiform aneurysms can occur when there is a uniform dilatation of the blood vessel with a mycotic basis.

Aneurysms may occasionally be familial. Mycotic aneurysms secondary to bacterial endocarditis should be borne in mind, and a complete examination inclusive of the cardiovascular system is always mandatory. Aneurysms are associated with coarctation of the aorta, associated with Ehlers Danlos syndrome, polycystic disease of the kidneys and occasionally with abnormalities of the cerebral vessels themselves, such as a common trunk anterior cerebral artery with aneurysm of the pericallosal vessels. Vasculopathies occur in pseudoxanthoma elasticum. Although Kawasaki disease is associated with a vasculopathy and secondary aneurysm formation in the heart it is a very rare cause of cerebral aneurysms.

Between 1% and 3% of all aneurysms occur in children. They tend to occur under 2 years or over 10 years of age. In 23 aneurysms described by Heiskenen (1989), 10 were at the carotid bifurcation and 8 on the anterior communicating artery. Those on the middle cerebral artery are often on the distal part of the vessel.

Diagnosis is nearly always because of presentation with a subarachnoid haemorrhage. Occasionally calcification in an aneurysm is seen on a plain skull film. Local pressure on the third nerve presenting as an isolated third nerve palsy or on the hypothalamus with diabetes insipidus can occur but is unusual. The bleeding may occasionally be intracerebral as well as subarachnoid.

Bleeding into the subarachnoid space results in intense vasospasm which can itself result in secondary cerebral infarction. Occasionally posterior fossa aneurysms of the basilar artery or posterior inferior cerebellar artery occur in children and are more common in children than adults. Multiple aneurysms are rare, but in very young children under 2 years of age the aneurysms may reach quite a large size.

Arteriovenous malformation

These are of several types.

The capillary or telangiectasia type of capillary haemangioma. Characteristic of the Sturge Weber syndrome. Although this lesion may be extensive it rarely bleeds. Rarely as a result of status epilepticus it may thrombose and so cause infarction of the hemisphere with onset of a hemiplegia. This type of lesion has no large feeding vessels and may not show at all on angiography, but is shown well on isotope scan or MRI imaging.

Cavernous haemangiomas. These occur particularly in the neonatal period and may be part of a syndrome of multiple haemangiomas. They have small feeding vessels but large blood filled sinusoids reaching 1 mm in diameter which form a honeycomb (Herter et al 1988). There may be a familial occurrence of haemangiomas or blood vessel abnormalities elsewhere such as the eye, skin or viscera. These lesions have no capsule but have well-defined limits. They are not invasive and do not metastasize. They behave as hamartomas and may grow with the child so that presentation may be of a space occupying lesion with headache, focal signs and raised intracranial pressure with papilloedema as well as with the classical features of haemorrhage, which may be intracerebral, subarachnoid or intraventricular. Fits are often a symptom before a bleed occurs. Seventy-five per cent are supratentorial and 25% infratentorial, and they are most common in the territory of the middle cerebral artery.

When removed at surgery nearly all show evidence of repeated

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Acute Hyponatremia Related to Intravenous Fluid Administration in Hospitalized Children: An Observational Study

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Acute Hyponatremia Related to Intravenous Fluid Administration in Hospitalized Children: An Observational Study

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ABSTRACT. *Objective.* **To develop hyponatremia (plasma sodium concentration [P_{Na}] <136 mmol/L), one needs a source of water input and antidiuretic hormone secretion release to diminish its excretion. The administration of hypotonic maintenance fluids is common practice in hospitalized children. The objective of this study was to identify risk factors for the development of hospital-acquired, acute hyponatremia in a tertiary care hospital using a retrospective analysis.**

Methods. **All children who presented to the emergency department in a 3-month period and had at least 1 P_{Na} measured (n = 1586) were evaluated. Those who were admitted were followed for the next 48 hours to identify patients with hospital-acquired hyponatremia. An age- and gender-matched case-control (1:3) analysis was performed with patients who did not become hyponatremic.**

Results. **Hyponatremia (P_{Na} <136 mmol/L) was documented in 131 of 1586 patients with ≥1 P_{Na} measurements. Although 96 patients were hyponatremic on presentation, our study group consisted of 40 patients who developed hyponatremia in hospital. The case-control study showed that the patients in the hospital-acquired hyponatremia group received significantly more EFW and had a higher positive water balance. With respect to outcomes, 2 patients had major neurologic sequelae and 1 died.**

Conclusion. **The most important factor for hospital-acquired hyponatremia is the administration of hypotonic fluid. We suggest that hypotonic fluid not be given to children when they have a P_{Na} <138 mmol/L.** ***Pediatrics* 2004;113:1279–1284;** ***antidiuretic hormone, concentration of the urine, electrolyte-free water, intravenous fluids.***

ABBREVIATIONS. ECF, extracellular fluid; ADH, antidiuretic hormone secretion; P_{Na}, plasma sodium concentration; EFW, electrolyte-free water; TBW, total body water.

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Hyponatremia is the most frequently encountered electrolyte disorder in hospitalized patients[1,2] and suggests that there is a surplus of water and/or a deficit of Na^+ in the extracellular fluid (ECF) compartment. Hence, there must be a source of water and actions of antidiuretic hormone secretion (ADH) to impair its excretion.[3] In children, the source of water is frequently the administration of hypotonic intravenous fluids. When the plasma sodium concentration (P_{Na}) falls acutely to <130 mmol/L, brain cell swelling may develop and be sufficient to lead to a devastating neurologic outcome. The most frequent clinical setting for acute hyponatremia is after elective surgery.[4–6] In this situation, the stimuli for the release of ADH are usually nonosmotic (pain, anxiety, nausea, and the use of pharmacologic agents such as narcotics and inhalational anesthetics). The problem is compounded when hypotonic fluids are given while the excretion of hypotonic urine is impaired.[7]

We recently reported on the development of acute hyponatremia in children who received hypotonic intravenous fluids.[6] We identified during a 10-year period 23 patients who had a rapid reduction in P_{Na} after surgery or in association with the administration of large amounts of hypotonic fluids. There was a 30% adverse outcome rate (death or neurologic injury). However, because that study was based on either a hospital discharge diagnosis of acute hyponatremia or patients who were referred to the critical care unit because of cerebral edema and brainstem herniation, it is unlikely to be an accurate reflection of the numbers at risk for an adverse neurologic event. We therefore conducted the present study to determine the importance of intravenous fluid therapy and the underlying diseases in its development.

METHODS

Approval was obtained from the Institutional Research Ethics Board to conduct a retrospective review of patients who were seen in or admitted through our hospital emergency department.

Study Group

Hyponatremia was defined as a P_{Na} <136 mmol/L. During the 3-month period from November 2000 to February 2001, there were 13 506 visits to the emergency department at the Hospital for Sick Children in Toronto. Those who had at least 1 P_{Na} value <136 mmol/L were identified. We then focused on patients who had a fall in P_{Na} in hospital—the hospital-acquired hyponatremia group.

The following general clinical data were included in our analysis: age, gender, weight, diagnosis, and medications. We looked for possible central nervous system symptoms of acute hyponatremia (headache, nausea, vomiting, seizures, and changes in sen-

sorium) as well as the volume of oral and intravenous fluid intake. Output values were also included when data were recorded. Data suggestive of a contracted ECF volume were included when documented in the chart (low blood pressure, rapid heart rate, and reduced capillary refill time). For each patient, the volume and type of fluid administered were compared with those recommended for maintenance fluid requirements in children based on the formula using body weight originally published by Holliday and Segar.[8] Cases in which deficits were replaced (eg, a contracted ECF volume) were incorporated into the final analysis.

Analysis of the Basis for a Fall in P_{Na}

Patients who developed hyponatremia in hospital were analyzed in greater detail because we could evaluate risk factors that contributed to its development. We calculated the amount of electrolyte-free water (EFW) input using the tonicity and volume of the administered fluid.[9] For example, the commonly used solution for maintenance fluids in our institution is 3.3% dextrose in 0.3% NaCl (51 mmol of Na^+ per liter), which is one third of the amount present in an isotonic saline. Therefore, two thirds of the volume of this solution can be thought of as EFW.[10] In our calculations, we included potassium (K^+) in defining tonicity.[11] These calculations were also performed for oral solutions.

The influence of EFW on the P_{Na} was analyzed using the initial measured P_{Na} and total body water (TBW) estimated as 60% of body weight, except for neonates in whom TBW was calculated as 70% of body weight. If, for example, the P_{Na} fell from 140 to 135 mmol/L as a result of a positive balance for EFW, then the TBW in a 10-kg person would have to increase from 6000 mL to 6220 mL (positive balance of 220 mL of EFW). Included in calculations for output were insensible losses, using an average of 14 mL/kg/day in the absence of fever.[12] Finally, we recorded likely reasons for high ADH levels from data in the history (disease, symptoms, drugs, and surgery) and physical examination (ECF contraction).

We also compared the patients with hospital-acquired hyponatremia with a control group of age-, gender-, and weight-matched patients who had ≥2 P_{Na} measurements in which the P_{Na} was >136 mmol/L, using a 1:3 match. Cases with a reason for a shift of water from the intracellular fluid to the ECF compartment (eg, hyperglycemia) or those who were given hypertonic mannitol were excluded from this analysis. We identified all patients who had ≥1 serum electrolyte measurements from the hospital laboratory database.

Analytical Methods and Calculations

A retrospective case-control study was performed using a *t* test and a χ^2 test. Correction for multiple variable testing included using the Bonferroni correction.[13]

RESULTS

Patients

A total of 432 patients had ≥2 P_{Na} measurements, 97 of which had a P_{Na} <136 mmol/L. The remaining 335 patients were not hyponatremic and formed the basis of our control group. Sixty-two patients were hyponatremic on presentation, whereas 35 of 97 developed hyponatremia after presentation. In 12 of 62 of these patients, the P_{Na} remained <136 mmol/L, whereas in 50 of 62, it increased to >136 mmol/L but then fell again to <136 mmol/L in 5 patients on a subsequent measurement. Thus, the total number of patients who developed hospital-acquired hyponatremia was 40 of 432. The P_{Na} in these 40 patients with hospital-acquired hyponatremia fell from a mean of 139 ± 3 mmol/L to 133 ± 2 mmol/L, a decline of 6 ± 1 mmol/L in 19 ± 10 hours.

Our next step was to relate the amount of EFW given (orally and/or intravenously) to that needed to cause their observed fall in P_{Na}; there were 2 near-equal groups (Fig 1): 1 received sufficient (or more) EFW to explain their fall in P_{Na} (all points on or above the line of identity), and the other did not receive enough EFW to explain their fall in P_{Na} (points below the line of identity). The source of this EFW load was predominantly the infusion of hypotonic fluids (66%), whereas in the remainder, the fall in P_{Na} could be attributed to the oral intake of EFW; these latter patients could have had an occult source of water intake, a reason to shift EFW out of cells (eg, a catabolic state,[14] the excretion of hypertonic urine[7,15]). The main reason for this ECF volume expansion may have been the bolus infusion of more isotonic saline than needed to reexpand the ECF volume.

We identified 16 patients with insufficient EFW to cause the observed degree of fall in their P_{Na} (Fig 1); 11 received a bolus of 0.9 NaCl (45 ± 42 mL/kg/hour; 15% expansion of ECF if all retained) on the basis of the presumption that they had ECF contraction. None of the patients on or above the line of identity received boluses of fluid.

Case-Control Study

The in-hospital group with a fall in their P_{Na} received 3-fold more EFW and had a greater positive fluid balance than the control group ($P < .001$ and $P = .02$, respectively; Table 1). Although this in-hospital group received less Na^+ per kilogram of body weight, this difference was not statistically significant. The amount of fluid infused was not only significantly higher in this in-hospital group but also well above that recommended by the standard formula for maintenance fluid administration[8] and well above what we now calculate for maintenance fluids.[16] Our analysis showed that there were no significant differences related to the underlying disease, that the symptoms of nausea and vomiting were significantly more prevalent in the in-hospital group, and that patients in the in-hospital group underwent surgery more frequently ($P < .05$). Finally, likely reasons for high levels of ADH in patients with hospital-acquired hyponatremia were found to be mainly of nonosmotic origin (symptoms, drugs, and disease; Table 1).

DISCUSSION

The principal results in this study confirm that it was not uncommon for hyponatremia to develop in the first 48 hours of admission to hospital, related in large part to intravenous fluid administration. The level of P_{Na} that we used for eligibility criterion is consistent with previously published definitions[17] and was the median level found in a large published series of children who presented to a hospital with acute medical illnesses.[18] Groups of children who previously have been reported to be at risk are those with meningitis, encephalitis, head injury, bronchiolitis, gastroenteritis, and chronic lung disease of prematurity and in association with chemotherapy.[19–27] This list was not all-inclusive because other nonosmotic stimuli were present in our population with hospital-acquired hyponatremia (Table 1). Hyponatremia is also a common event after elective surgery[2,28–30] and when acute (<48 hours) can lead to catastrophic neurologic sequelae.[5,6,31] Children

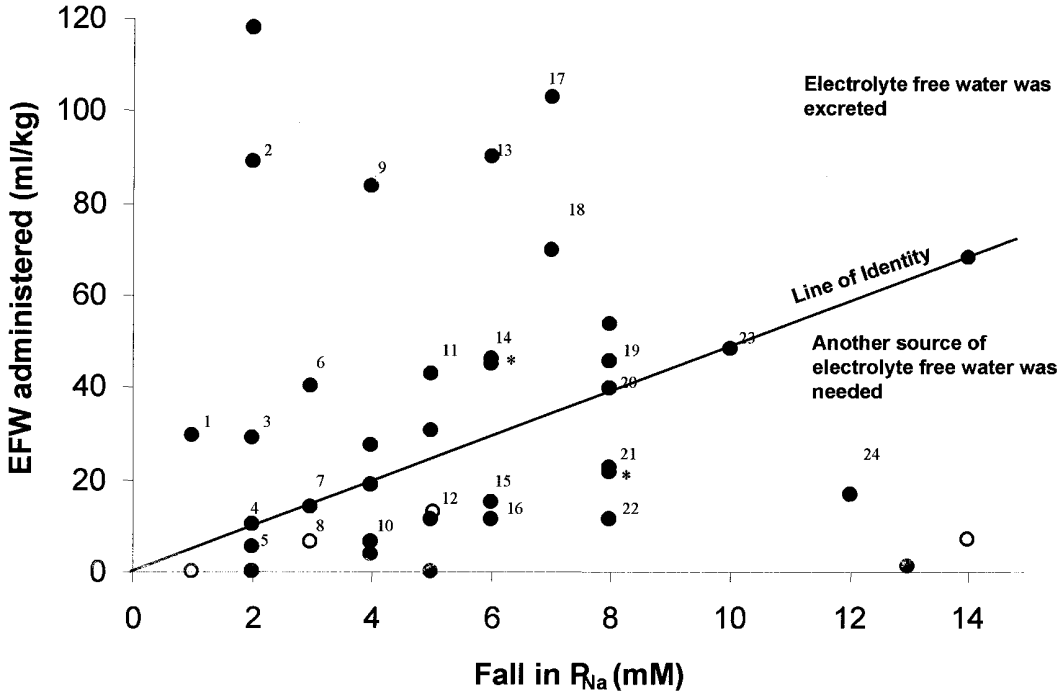

Fig 1. The relationship between EFW administration and the fall in P_{Na}. *Overlap of 2 points. Points represent individual patients with hospital-acquired hyponatremia ($n = 37$). The case numbers next to the dots refer to patients whose urine output is known and correspond with those in Fig 2. The solid line represents the amount of EFW that would need to be retained to cause the observed fall in P_{Na}. The patients whose points fell on or above the line of identity could have retained enough EFW to explain their fall in P_{Na}; any extra water either was excreted in the urine or sweat or was turned into an isotonic saline as a result of a positive balance for Na^+ . In the patients whose points fell below the line of identity, the amount of EFW given can be only a partial explanation for their fall in P_{Na}. These patients required a concurrent excretion of hypertonic Na^+ (+ K^+) and/or an occult source of EFW to achieve their observed fall in P_{Na}.

TABLE 1. Results 1:3 Age- and Gender-Matched Case-Control Study

Category	Variable	Cases ($n = 37$)	Controls ($n = 111$)	*P* Value
Demographics	Age, y	7 ± 6	7 ± 6	1.0
	Gender, number (%)	15 (41) F, 22 (60) M	45 (41) F, 66 (60) M	1.0
	Weight, kg	25 ± 18	28 ± 21	.4
	Surgery, number (%)	6 (16)	6 (5)	.04
Water and sodium	P_{Na}	139 ± 3 → 133 ± 2 mM	140 ± 2 mM	—
	Decrease in P_{Na}, mmol	6 ± 3 in 19 ± 10 h	—	—
	EFW, mL/kg/h	2 ± 2	1 ± 1	<.001
	Na^+, mmol/kg/h	0 ± 1	1 ± 1	.3
	Positive water balance, ml/kg/h*	4 ± 5	2 ± 3	.02
IV-fluid regimen	Amount of fluid, ml/h	98 ± 77	47 ± 46	<.001
	% that received more than recommended maintenance†	73	23	<.001
Main disease categories	GI disorders, number (%)	11 (30)	19 (17)	1.0
	Neoplasia	8 (22)	14 (13)	1.0
	Respiratory infections	5 (14)	28 (25)	1.0
	Renal disease	1 (3)	6 (5)	1.0
Reason for elevated ADH	Disease, number (%)	5 (14)	—	—
	Symptoms	23 (62)	—	—
	Drugs	9 (24)	—	—
	Hypovolemia	0 (0)	—	—
Possible symptoms	Nausea, number (%)	10 (27)	3 (8)	.008
	Headache	2 (5)	11 (10)	.5
	Vomiting	25 (68)	46 (41)	.008
	Seizures	1 (3)	6 (5)	.7
	Sensorium changes	7 (19)	13 (12)	1.0

* Data were available for all cases and 43 controls.
† As described by the formula of Holliday and Segar.[8]

with chronic hyponatremia are not at risk for the development of cerebral edema.[32,33]

There are 2 requirements for a fall in P_{Na}: the presence of ADH and a source of water input. Although it should not be surprising to find elevated ADH levels in acutely ill patients,[18] this will not cause hyponatremia in the absence of water input. The major source for water input in our study was the infusion of a large amount of hypotonic fluid. Because close to half of the cases received a higher

amount of intravenous fluid than recommended for maintenance on the basis of the formula of Holliday and Segar,[8] the amount given was a contributing causative factor. The infusion of a large volume of saline was likely attributable to the belief that the ECF volume was contracted. For the group that did not have a recorded input of sufficient water to explain their fall in P_{Na} (Fig 1, points below line of identity), one would suspect that they had an occult water intake (eg, ice chips, water residing in the lumen of the gastrointestinal tract after admission, electrolyte-free water generation by the kidney secondary to the excretion of hypertonic urine; open dots in Fig 2). For this latter mechanism, one needs the combination of an infusion of isotonic saline and the excretion of hypertonic urine.[7] It is possible that this desalination process may have been triggered by the acute expansion of the ECF volume as a result of the administration of isotonic saline, because we could find recorded evidence that the ECF volume was contracted in only 10% of these patients. We emphasize that the clinical assessment of the degree of ECF volume contraction is a method of limited sensitivity and specificity.[34–37]

Dangers of Acute Hyponatremia

Previous studies have shown that children with acute hyponatremia have an appreciable risk for neurologic damage.[5,6,38,39] With respect to the potential dangers of acute hyponatremia in our patient population, it is possible that the observed fall in P_{Na} led to serious severe neurologic outcomes in 2 of 40 patients. One of these (Fig 1; fall in P_{Na} of 14 mmol/L) had an underlying seizure disorder and had a convulsion during the hyponatremic period. This highlights the need to be more vigilant about the fall in P_{Na} when an underlying medical condition places the patient at risk. We also emphasize a diagnostic caveat: that a seizure may raise the P_{Na} transiently by an average of 13 mmol/L, masking the original degree of hyponatremia.[40] The second patient (fall in P_{Na} of 13 mmol/L from 142 to 128 mmol/L in 1.5 hours) had a cardiac arrest. Although she was resuscitated initially, she ultimately died. Postmortem examination revealed brain cell swelling. The high incidence of nausea and vomiting (Table 1) may indicate more cases of symptomatic hyponatremia; however, because these symptoms are also known to be potent stimuli of ADH release, this deduction is not possible from this retrospective study.

Rationale of the Choice of Intravenous Fluid: Hypotonic Versus Isotonic

The almost universal practice of the use of hypotonic fluids in children is based on calculations that linked energy expenditure to water and electrolyte losses, published nearly 50 years ago. Applying this formula results in the administration of large amounts of EFW, which then has to be excreted by the kidney. We believe that linking energy expenditure to water losses in hospitalized patients significantly overestimates the need for maintenance fluid. In a recent commentary,[16] we reevaluated the factors used to calculate water and electrolyte requirements in Holliday and Segar's original paper. Moreover, these calculations did not factor in the unpredictable effect of nonosmotic stimuli for ADH secretion in the acutely ill child, which can result in retention of water and hyponatremia.[18] Our conclusion was that

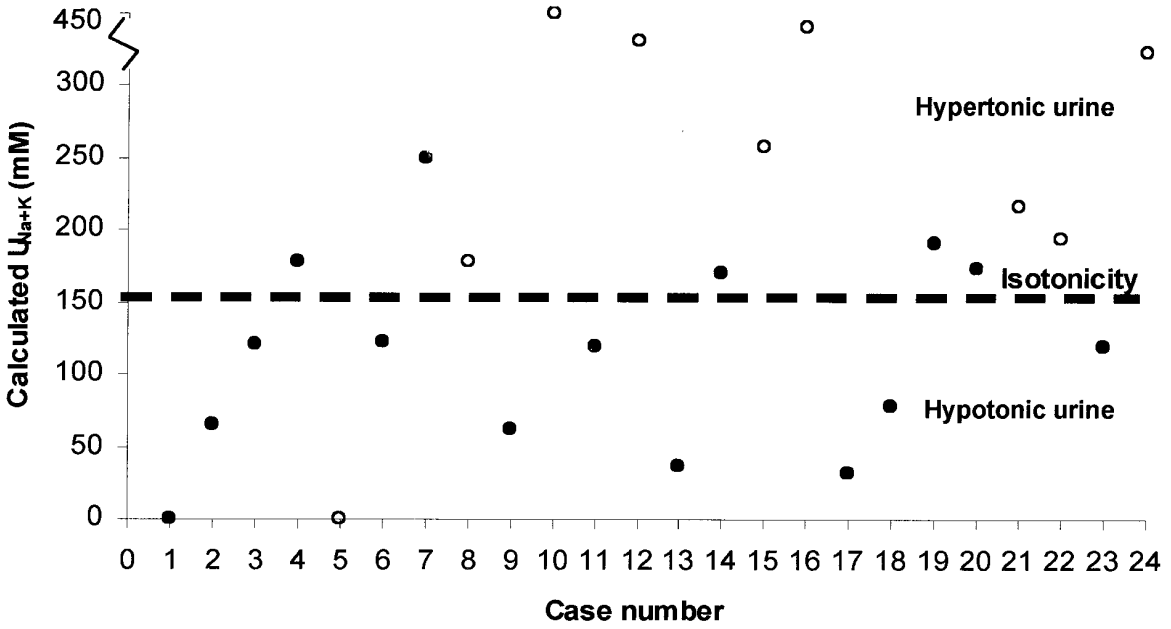

Fig 2. Calculated urine Na^+ concentration. Dots represent the urine Na^+ concentration for patients with known urine outputs. The case numbers correspond to the case numbers in Fig 1. Open dots refer to patients whose points fall under the line of identity in Fig 1. Patients whose points fell below the line representing isotonicity have urine Na^+ concentrations exceeding 150 mmol/L. In those patients, ADH levels should be high. In 2 patients, urine outputs were noted to be small, which explains their values close to 0 mmol/L. (For validation of this method, see Carlotti et al.[46])

the water requirements and the renal ability to excrete hypotonic urine were overestimated. Therefore, our general recommendation was that the P_{Na} be measured once the ECF volume is expanded >10% (30 mL/kg); and if the P_{Na} is <138 mmol/L, then do not infuse hypotonic fluids.[16]

The option of selecting isotonic rather than hypotonic for maintenance fluid in children has been advocated by some authors.[6,41–43] In a recent publication, Moritz and Ayus[43] drew attention to this idea, and our data support this position. This generally has not been accepted because of concerns about excessive administration of Na^+ and the development of hypernatremia. The comparative studies in children, although few, do not support this perceived danger. In a randomized trial of different fluid protocols in children with meningitis, Powell et al[20] compared a fluid-restricted group who received hypotonic saline with a fluid-deficit replacement plus maintenance regimen using predominantly isotonic solutions. Children in the isotonic group received an average of 6 mmol Na^+/kg/day and had normal P_{Na} levels, whereas those in the hypotonic group received an average of 2 mmol Na^+/kg/day and became hyponatremic. Likewise, in the study by Gerigk et al[18] of acutely ill children in which the median P_{Na} was 136 mmol/L at the time of admission to hospital, those who were given isotonic fluid had a more rapid fall in their ADH levels than those who received hypotonic fluids.

Children who undergo surgical procedures are particularly at risk from hyponatremia because of the association between anesthetic agents and opiates and nonosmotic ADH secretion. Moreover, the syndrome of inappropriate ADH secretion has been frequently reported in association with spinal surgery.[30,44] Burrows et al[30] compared hypotonic with isotonic intravenous fluids in children who underwent surgery for scoliosis. Both groups had a fall in their P_{Na} in the postoperative period, but the reduction was greater in those who received the hypotonic solution.

Patients who have findings of hyponatremia, with impaired excretion of EFW as a result of actions of ADH in the absence of obvious stimuli for ADH release (an ECF volume contraction of at least 8%), or either adrenal insufficiency or hypothyroidism are said to have the syndrome of inappropriate ADH secretion.[45] In this syndrome, the urine usually contains an appreciable quantity of Na^+. Therefore, we could have said that hyponatremia developed in our patients as a result of the syndrome of inappropriate ADH secretion. Notwithstanding, we have used a different way to describe the basis of hyponatremia in our population. Our description begins with the pathophysiology. Our patients had multiple nonosmotic stimuli for the release of ADH. The source of the EFW was hypotonic fluids given by the physician (hypotonic intravenous solutions), health care workers (eg, ice chips), and/or the family of the patient (oral drinks containing water). In addition, EFW could be generated by the kidneys when the urine has a higher $Na^+ + K^+$ concentration than the net of all inputs.[7] Regardless of the terminology, the most important factor is the net input of EFW in this setting because ADH is likely to be present for the nonosmotic reasons described above. Moreover, although patients have this type of ADH release, they need not develop a significant degree of hyponatremia because as their P_{Na} falls, thirst is suppressed and there is no longer a physiologic stimulus causing a large input of water. In contrast, in hospital, the physician rather than the patient determines the water intake.

Study Limitations

This study was retrospective and hence has the imperfections that characterize such studies. By evaluating every patient who arrived in our emergency department in a 3-month period, we attempted to minimize this limitation. Our actual incidence of hyponatremia is probably an overestimation because the P_{Na} was measured in only ~10% of the total population, a group that had indications for this measurement. In addition to these limitations, there was the problem of not measuring urine electrolytes and plasma ADH levels. Also, some of the patients and especially those who received insufficient EFW to explain their fall in P_{Na} could have had an occult source of water. Occult sources of water include water in the gastrointestinal tract that was not absorbed before the first measurement of the P_{Na}, the use of ice chips, or a parent's giving his or her child a drink without informing the nurse so that there is no record of that input in the hospital chart. We think that a prospective study to answer some of the obvious questions would be helpful.

CONCLUSIONS

The development of hyponatremia is unacceptably high in hospitalized children. This is attributable in large part to the administration of excessive amounts of water as hypotonic saline in situations in which ADH is secreted for nonosmotic reasons. The original guidelines for maintenance fluid may not be applicable in an era when the complexity and the severity of illness seen in hospitalized children who receive intravenous fluid therapy has radically changed (eg, leukemia, complex congenital heart disease) and irregularities of ADH secretion are more likely to be commonplace. We believe that hospital-acquired hyponatremia unnecessarily puts children at risk for the development of adverse neurologic events and is largely preventable. We suggest that the current recommendations for intravenous fluid therapy in hospitalized children be revised. Hypotonic fluids should not be used routinely in the intraoperative or postoperative period or when a patient has a P_{Na} in the low-normal or distinctly hyponatremic range (<138 mmol/L). In addition, boluses of isotonic saline should be given only when there are clear hemodynamic indications for that infusion.

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Pediatrics 2004;113;1279

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Acute Hyponatremia Related to Intravenous Fluid Administration in Hospitalized Children: An Observational Study

Ewout J. Hoorn, MD*; Denis Geary, MB‡§; Maryanne Robb, MD‡§‖; Mitchell L. Halperin, MD¶; and Desmond Bohn, MB*#

ABSTRACT. *Objective.* **To develop hyponatremia (plasma sodium concentration [P_{Na}] <136 mmol/L), one needs a source of water input and antidiuretic hormone secretion release to diminish its excretion. The administration of hypotonic maintenance fluids is common practice in hospitalized children. The objective of this study was to identify risk factors for the development of hospital-acquired, acute hyponatremia in a tertiary care hospital using a retrospective analysis.**

Methods. **All children who presented to the emergency department in a 3-month period and had at least 1 P_{Na} measured (n = 1586) were evaluated. Those who were admitted were followed for the next 48 hours to identify patients with hospital-acquired hyponatremia. An age- and gender-matched case-control (1:3) analysis was performed with patients who did not become hyponatremic.**

Results. **Hyponatremia (P_{Na} <136 mmol/L) was documented in 131 of 1586 patients with ≥1 P_{Na} measurements. Although 96 patients were hyponatremic on presentation, our study group consisted of 40 patients who developed hyponatremia in hospital. The case-control study showed that the patients in the hospital-acquired hyponatremia group received significantly more EFW and had a higher positive water balance. With respect to outcomes, 2 patients had major neurologic sequelae and 1 died.**

Conclusion. **The most important factor for hospital-acquired hyponatremia is the administration of hypotonic fluid. We suggest that hypotonic fluid not be given to children when they have a P_{Na} <138 mmol/L.** ***Pediatrics* 2004;113:1279–1284;** ***antidiuretic hormone, concentration of the urine, electrolyte-free water, intravenous fluids.***

ABBREVIATIONS. ECF, extracellular fluid; ADH, antidiuretic hormone secretion; P_{Na}, plasma sodium concentration; EFW, electrolyte-free water; TBW, total body water.

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Hyponatremia is the most frequently encountered electrolyte disorder in hospitalized patients[1,2] and suggests that there is a surplus of water and/or a deficit of Na^+ in the extracellular fluid (ECF) compartment. Hence, there must be a source of water and actions of antidiuretic hormone secretion (ADH) to impair its excretion.[3] In children, the source of water is frequently the administration of hypotonic intravenous fluids. When the plasma sodium concentration (P_{Na}) falls acutely to <130 mmol/L, brain cell swelling may develop and be sufficient to lead to a devastating neurologic outcome. The most frequent clinical setting for acute hyponatremia is after elective surgery.[4–6] In this situation, the stimuli for the release of ADH are usually nonosmotic (pain, anxiety, nausea, and the use of pharmacologic agents such as narcotics and inhalational anesthetics). The problem is compounded when hypotonic fluids are given while the excretion of hypotonic urine is impaired.[7]

We recently reported on the development of acute hyponatremia in children who received hypotonic intravenous fluids.[6] We identified during a 10-year period 23 patients who had a rapid reduction in P_{Na} after surgery or in association with the administration of large amounts of hypotonic fluids. There was a 30% adverse outcome rate (death or neurologic injury). However, because that study was based on either a hospital discharge diagnosis of acute hyponatremia or patients who were referred to the critical care unit because of cerebral edema and brainstem herniation, it is unlikely to be an accurate reflection of the numbers at risk for an adverse neurologic event. We therefore conducted the present study to determine the importance of intravenous fluid therapy and the underlying diseases in its development.

METHODS

Approval was obtained from the Institutional Research Ethics Board to conduct a retrospective review of patients who were seen in or admitted through our hospital emergency department.

Study Group

Hyponatremia was defined as a P_{Na} <136 mmol/L. During the 3-month period from November 2000 to February 2001, there were 13 506 visits to the emergency department at the Hospital for Sick Children in Toronto. Those who had at least 1 P_{Na} value <136 mmol/L were identified. We then focused on patients who had a fall in P_{Na} in hospital—the hospital-acquired hyponatremia group.

The following general clinical data were included in our analysis: age, gender, weight, diagnosis, and medications. We looked for possible central nervous system symptoms of acute hyponatremia (headache, nausea, vomiting, seizures, and changes in sen-

sorium) as well as the volume of oral and intravenous fluid intake. Output values were also included when data were recorded. Data suggestive of a contracted ECF volume were included when documented in the chart (low blood pressure, rapid heart rate, and reduced capillary refill time). For each patient, the volume and type of fluid administered were compared with those recommended for maintenance fluid requirements in children based on the formula using body weight originally published by Holliday and Segar.[8] Cases in which deficits were replaced (eg, a contracted ECF volume) were incorporated into the final analysis.

Analysis of the Basis for a Fall in P_{Na}

Patients who developed hyponatremia in hospital were analyzed in greater detail because we could evaluate risk factors that contributed to its development. We calculated the amount of electrolyte-free water (EFW) input using the tonicity and volume of the administered fluid.[9] For example, the commonly used solution for maintenance fluids in our institution is 3.3% dextrose in 0.3% NaCl (51 mmol of Na^+ per liter), which is one third of the amount present in an isotonic saline. Therefore, two thirds of the volume of this solution can be thought of as EFW.[10] In our calculations, we included potassium (K^+) in defining tonicity.[11] These calculations were also performed for oral solutions.

The influence of EFW on the P_{Na} was analyzed using the initial measured P_{Na} and total body water (TBW) estimated as 60% of body weight, except for neonates in whom TBW was calculated as 70% of body weight. If, for example, the P_{Na} fell from 140 to 135 mmol/L as a result of a positive balance for EFW, then the TBW in a 10-kg person would have to increase from 6000 mL to 6220 mL (positive balance of 220 mL of EFW). Included in calculations for output were insensible losses, using an average of 14 mL/kg/day in the absence of fever.[12] Finally, we recorded likely reasons for high ADH levels from data in the history (disease, symptoms, drugs, and surgery) and physical examination (ECF contraction).

We also compared the patients with hospital-acquired hyponatremia with a control group of age-, gender-, and weight-matched patients who had ≥2 P_{Na} measurements in which the P_{Na} was >136 mmol/L, using a 1:3 match. Cases with a reason for a shift of water from the intracellular fluid to the ECF compartment (eg, hyperglycemia) or those who were given hypertonic mannitol were excluded from this analysis. We identified all patients who had ≥1 serum electrolyte measurements from the hospital laboratory database.

Analytical Methods and Calculations

A retrospective case-control study was performed using a *t* test and a χ^2 test. Correction for multiple variable testing included using the Bonferroni correction.[13]

RESULTS

Patients

A total of 432 patients had ≥2 P_{Na} measurements, 97 of which had a P_{Na} <136 mmol/L. The remaining 335 patients were not hyponatremic and formed the basis of our control group. Sixty-two patients were hyponatremic on presentation, whereas 35 of 97 developed hyponatremia after presentation. In 12 of 62 of these patients, the P_{Na} remained <136 mmol/L, whereas in 50 of 62, it increased to >136 mmol/L but then fell again to <136 mmol/L in 5 patients on a subsequent measurement. Thus, the total number of patients who developed hospital-acquired hyponatremia was 40 of 432. The P_{Na} in these 40 patients with hospital-acquired hyponatremia fell from a mean of 139 ± 3 mmol/L to 133 ± 2 mmol/L, a decline of 6 ± 1 mmol/L in 19 ± 10 hours.

Our next step was to relate the amount of EFW given (orally and/or intravenously) to that needed to cause their observed fall in P_{Na}; there were 2 near-equal groups (Fig 1): 1 received sufficient (or more) EFW to explain their fall in P_{Na} (all points on or above the line of identity), and the other did not receive enough EFW to explain their fall in P_{Na} (points below the line of identity). The source of this EFW load was predominantly the infusion of hypotonic fluids (66%), whereas in the remainder, the fall in P_{Na} could be attributed to the oral intake of EFW; these latter patients could have had an occult source of water intake, a reason to shift EFW out of cells (eg, a catabolic state,[14] the excretion of hypertonic urine[7,15]). The main reason for this ECF volume expansion may have been the bolus infusion of more isotonic saline than needed to reexpand the ECF volume.

We identified 16 patients with insufficient EFW to cause the observed degree of fall in their P_{Na} (Fig 1); 11 received a bolus of 0.9 NaCl (45 ± 42 mL/kg/hour; 15% expansion of ECF if all retained) on the basis of the presumption that they had ECF contraction. None of the patients on or above the line of identity received boluses of fluid.

Case-Control Study

The in-hospital group with a fall in their P_{Na} received 3-fold more EFW and had a greater positive fluid balance than the control group ($P < .001$ and $P = .02$, respectively; Table 1). Although this in-hospital group received less Na^+ per kilogram of body weight, this difference was not statistically significant. The amount of fluid infused was not only significantly higher in this in-hospital group but also well above that recommended by the standard formula for maintenance fluid administration[8] and well above what we now calculate for maintenance fluids.[16] Our analysis showed that there were no significant differences related to the underlying disease, that the symptoms of nausea and vomiting were significantly more prevalent in the in-hospital group, and that patients in the in-hospital group underwent surgery more frequently ($P < .05$). Finally, likely reasons for high levels of ADH in patients with hospital-acquired hyponatremia were found to be mainly of nonosmotic origin (symptoms, drugs, and disease; Table 1).

DISCUSSION

The principal results in this study confirm that it was not uncommon for hyponatremia to develop in the first 48 hours of admission to hospital, related in large part to intravenous fluid administration. The level of P_{Na} that we used for eligibility criterion is consistent with previously published definitions[17] and was the median level found in a large published series of children who presented to a hospital with acute medical illnesses.[18] Groups of children who previously have been reported to be at risk are those with meningitis, encephalitis, head injury, bronchiolitis, gastroenteritis, and chronic lung disease of prematurity and in association with chemotherapy.[19–27] This list was not all-inclusive because other nonosmotic stimuli were present in our population with hospital-acquired hyponatremia (Table 1). Hyponatremia is also a common event after elective surgery[2,28–30] and when acute (<48 hours) can lead to catastrophic neurologic sequelae.[5,6,31] Children

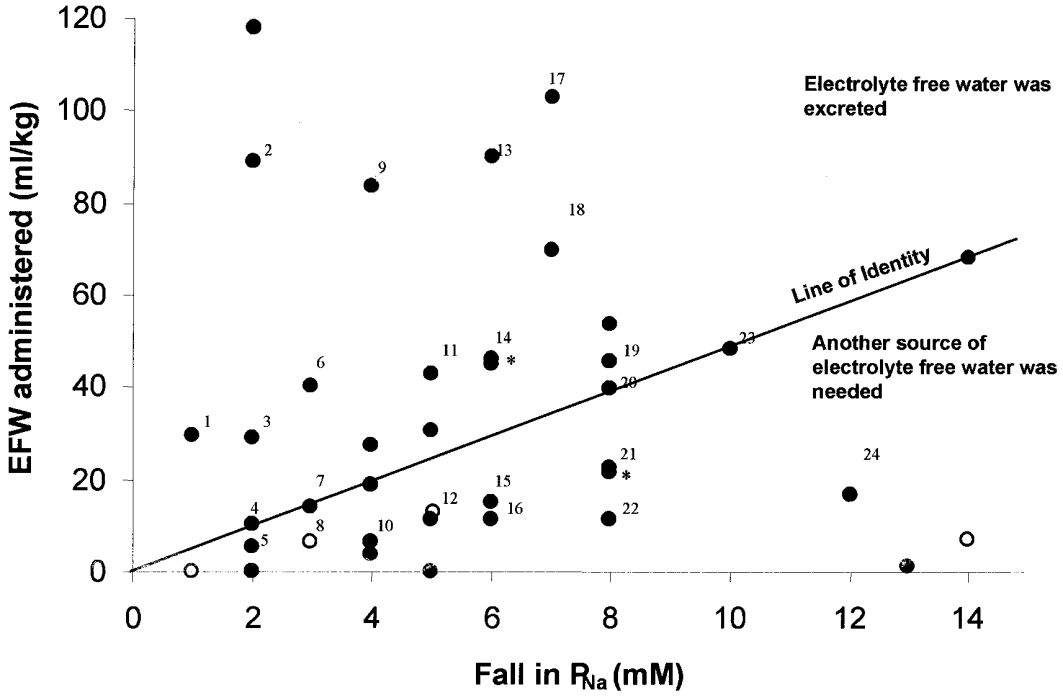

Fig 1. The relationship between EFW administration and the fall in P_{Na}. *Overlap of 2 points. Points represent individual patients with hospital-acquired hyponatremia ($n = 37$). The case numbers next to the dots refer to patients whose urine output is known and correspond with those in Fig 2. The solid line represents the amount of EFW that would need to be retained to cause the observed fall in P_{Na}. The patients whose points fell on or above the line of identity could have retained enough EFW to explain their fall in P_{Na}; any extra water either was excreted in the urine or sweat or was turned into an isotonic saline as a result of a positive balance for Na^+ . In the patients whose points fell below the line of identity, the amount of EFW given can be only a partial explanation for their fall in P_{Na}. These patients required a concurrent excretion of hypertonic Na^+ (+ K^+) and/or an occult source of EFW to achieve their observed fall in P_{Na}.

TABLE 1. Results 1:3 Age- and Gender-Matched Case-Control Study

Category	Variable	Cases ($n = 37$)	Controls ($n = 111$)	*P* Value
Demographics	Age, y	7 ± 6	7 ± 6	1.0
	Gender, number (%)	15 (41) F, 22 (60) M	45 (41) F, 66 (60) M	1.0
	Weight, kg	25 ± 18	28 ± 21	.4
	Surgery, number (%)	6 (16)	6 (5)	.04
Water and sodium	P_{Na}	139 ± 3 → 133 ± 2 mM	140 ± 2 mM	—
	Decrease in P_{Na}, mmol	6 ± 3 in 19 ± 10 h	—	—
	EFW, mL/kg/h	2 ± 2	1 ± 1	<.001
	Na^+, mmol/kg/h	0 ± 1	1 ± 1	.3
	Positive water balance, ml/kg/h*	4 ± 5	2 ± 3	.02
IV-fluid regimen	Amount of fluid, ml/h	98 ± 77	47 ± 46	<.001
	% that received more than recommended maintenance†	73	23	<.001
Main disease categories	GI disorders, number (%)	11 (30)	19 (17)	1.0
	Neoplasia	8 (22)	14 (13)	1.0
	Respiratory infections	5 (14)	28 (25)	1.0
	Renal disease	1 (3)	6 (5)	1.0
Reason for elevated ADH	Disease, number (%)	5 (14)	—	—
	Symptoms	23 (62)	—	—
	Drugs	9 (24)	—	—
	Hypovolemia	0 (0)	—	—
Possible symptoms	Nausea, number (%)	10 (27)	3 (8)	.008
	Headache	2 (5)	11 (10)	.5
	Vomiting	25 (68)	46 (41)	.008
	Seizures	1 (3)	6 (5)	.7
	Sensorium changes	7 (19)	13 (12)	1.0

* Data were available for all cases and 43 controls.
† As described by the formula of Holliday and Segar.[8]

with chronic hyponatremia are not at risk for the development of cerebral edema.[32,33]

There are 2 requirements for a fall in P_{Na}: the presence of ADH and a source of water input. Although it should not be surprising to find elevated ADH levels in acutely ill patients,[18] this will not cause hyponatremia in the absence of water input. The major source for water input in our study was the infusion of a large amount of hypotonic fluid. Because close to half of the cases received a higher

amount of intravenous fluid than recommended for maintenance on the basis of the formula of Holliday and Segar,[8] the amount given was a contributing causative factor. The infusion of a large volume of saline was likely attributable to the belief that the ECF volume was contracted. For the group that did not have a recorded input of sufficient water to explain their fall in P_{Na} (Fig 1, points below line of identity), one would suspect that they had an occult water intake (eg, ice chips, water residing in the lumen of the gastrointestinal tract after admission, electrolyte-free water generation by the kidney secondary to the excretion of hypertonic urine; open dots in Fig 2). For this latter mechanism, one needs the combination of an infusion of isotonic saline and the excretion of hypertonic urine.[7] It is possible that this desalination process may have been triggered by the acute expansion of the ECF volume as a result of the administration of isotonic saline, because we could find recorded evidence that the ECF volume was contracted in only 10% of these patients. We emphasize that the clinical assessment of the degree of ECF volume contraction is a method of limited sensitivity and specificity.[34–37]

Dangers of Acute Hyponatremia

Previous studies have shown that children with acute hyponatremia have an appreciable risk for neurologic damage.[5,6,38,39] With respect to the potential dangers of acute hyponatremia in our patient population, it is possible that the observed fall in P_{Na} led to serious severe neurologic outcomes in 2 of 40 patients. One of these (Fig 1; fall in P_{Na} of 14 mmol/L) had an underlying seizure disorder and had a convulsion during the hyponatremic period. This highlights the need to be more vigilant about the fall in P_{Na} when an underlying medical condition places the patient at risk. We also emphasize a diagnostic caveat: that a seizure may raise the P_{Na} transiently by an average of 13 mmol/L, masking the original degree of hyponatremia.[40] The second patient (fall in P_{Na} of 13 mmol/L from 142 to 128 mmol/L in 1.5 hours) had a cardiac arrest. Although she was resuscitated initially, she ultimately died. Postmortem examination revealed brain cell swelling. The high incidence of nausea and vomiting (Table 1) may indicate more cases of symptomatic hyponatremia; however, because these symptoms are also known to be potent stimuli of ADH release, this deduction is not possible from this retrospective study.

Rationale of the Choice of Intravenous Fluid: Hypotonic Versus Isotonic

The almost universal practice of the use of hypotonic fluids in children is based on calculations that linked energy expenditure to water and electrolyte losses, published nearly 50 years ago. Applying this formula results in the administration of large amounts of EFW, which then has to be excreted by the kidney. We believe that linking energy expenditure to water losses in hospitalized patients significantly overestimates the need for maintenance fluid. In a recent commentary,[16] we reevaluated the factors used to calculate water and electrolyte requirements in Holliday and Segar's original paper. Moreover, these calculations did not factor in the unpredictable effect of nonosmotic stimuli for ADH secretion in the acutely ill child, which can result in retention of water and hyponatremia.[18] Our conclusion was that

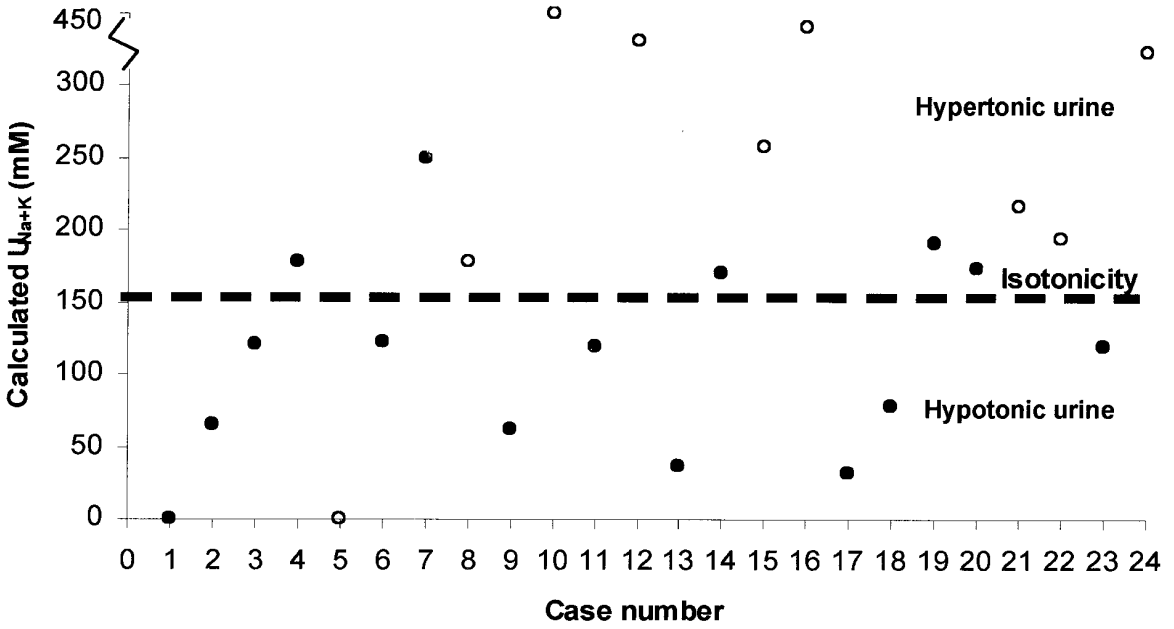

Fig 2. Calculated urine Na^+ concentration. Dots represent the urine Na^+ concentration for patients with known urine outputs. The case numbers correspond to the case numbers in Fig 1. Open dots refer to patients whose points fall under the line of identity in Fig 1. Patients whose points fell below the line representing isotonicity have urine Na^+ concentrations exceeding 150 mmol/L. In those patients, ADH levels should be high. In 2 patients, urine outputs were noted to be small, which explains their values close to 0 mmol/L. (For validation of this method, see Carlotti et al.[46])

the water requirements and the renal ability to excrete hypotonic urine were overestimated. Therefore, our general recommendation was that the P_{Na} be measured once the ECF volume is expanded >10% (30 mL/kg); and if the P_{Na} is <138 mmol/L, then do not infuse hypotonic fluids.[16]

The option of selecting isotonic rather than hypotonic for maintenance fluid in children has been advocated by some authors.[6,41–43] In a recent publication, Moritz and Ayus[43] drew attention to this idea, and our data support this position. This generally has not been accepted because of concerns about excessive administration of Na^+ and the development of hypernatremia. The comparative studies in children, although few, do not support this perceived danger. In a randomized trial of different fluid protocols in children with meningitis, Powell et al[20] compared a fluid-restricted group who received hypotonic saline with a fluid-deficit replacement plus maintenance regimen using predominantly isotonic solutions. Children in the isotonic group received an average of 6 mmol Na^+/kg/day and had normal P_{Na} levels, whereas those in the hypotonic group received an average of 2 mmol Na^+/kg/day and became hyponatremic. Likewise, in the study by Gerigk et al[18] of acutely ill children in which the median P_{Na} was 136 mmol/L at the time of admission to hospital, those who were given isotonic fluid had a more rapid fall in their ADH levels than those who received hypotonic fluids.

Children who undergo surgical procedures are particularly at risk from hyponatremia because of the association between anesthetic agents and opiates and nonosmotic ADH secretion. Moreover, the syndrome of inappropriate ADH secretion has been frequently reported in association with spinal surgery.[30,44] Burrows et al[30] compared hypotonic with isotonic intravenous fluids in children who underwent surgery for scoliosis. Both groups had a fall in their P_{Na} in the postoperative period, but the reduction was greater in those who received the hypotonic solution.

Patients who have findings of hyponatremia, with impaired excretion of EFW as a result of actions of ADH in the absence of obvious stimuli for ADH release (an ECF volume contraction of at least 8%), or either adrenal insufficiency or hypothyroidism are said to have the syndrome of inappropriate ADH secretion.[45] In this syndrome, the urine usually contains an appreciable quantity of Na^+. Therefore, we could have said that hyponatremia developed in our patients as a result of the syndrome of inappropriate ADH secretion. Notwithstanding, we have used a different way to describe the basis of hyponatremia in our population. Our description begins with the pathophysiology. Our patients had multiple nonosmotic stimuli for the release of ADH. The source of the EFW was hypotonic fluids given by the physician (hypotonic intravenous solutions), health care workers (eg, ice chips), and/or the family of the patient (oral drinks containing water). In addition, EFW could be generated by the kidneys when the urine has a higher $Na^+ + K^+$ concentration than the net of all inputs.[7] Regardless of the terminology, the most important factor is the net input of EFW in this setting because ADH is likely to be present for the nonosmotic reasons described above. Moreover, although patients have this type of ADH release, they need not develop a significant degree of hyponatremia because as their P_{Na} falls, thirst is suppressed and there is no longer a physiologic stimulus causing a large input of water. In contrast, in hospital, the physician rather than the patient determines the water intake.

Study Limitations

This study was retrospective and hence has the imperfections that characterize such studies. By evaluating every patient who arrived in our emergency department in a 3-month period, we attempted to minimize this limitation. Our actual incidence of hyponatremia is probably an overestimation because the P_{Na} was measured in only ~10% of the total population, a group that had indications for this measurement. In addition to these limitations, there was the problem of not measuring urine electrolytes and plasma ADH levels. Also, some of the patients and especially those who received insufficient EFW to explain their fall in P_{Na} could have had an occult source of water. Occult sources of water include water in the gastrointestinal tract that was not absorbed before the first measurement of the P_{Na}, the use of ice chips, or a parent's giving his or her child a drink without informing the nurse so that there is no record of that input in the hospital chart. We think that a prospective study to answer some of the obvious questions would be helpful.

CONCLUSIONS

The development of hyponatremia is unacceptably high in hospitalized children. This is attributable in large part to the administration of excessive amounts of water as hypotonic saline in situations in which ADH is secreted for nonosmotic reasons. The original guidelines for maintenance fluid may not be applicable in an era when the complexity and the severity of illness seen in hospitalized children who receive intravenous fluid therapy has radically changed (eg, leukemia, complex congenital heart disease) and irregularities of ADH secretion are more likely to be commonplace. We believe that hospital-acquired hyponatremia unnecessarily puts children at risk for the development of adverse neurologic events and is largely preventable. We suggest that the current recommendations for intravenous fluid therapy in hospitalized children be revised. Hypotonic fluids should not be used routinely in the intraoperative or postoperative period or when a patient has a P_{Na} in the low-normal or distinctly hyponatremic range (<138 mmol/L). In addition, boluses of isotonic saline should be given only when there are clear hemodynamic indications for that infusion.

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Acute Hyponatremia Related to Intravenous Fluid Administration in Hospitalized Children: An Observational Study

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Iatrogenic hyponatremia in hospitalized children: Can it be avoided?

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Iatrogenic hyponatremia in hospitalized children is a common problem. It is usually caused by the administration of free water, either orally or through the prescription of hypotonic intravenous fluids. It can result in cerebral edema and death, and is most commonly reported in healthy children undergoing minor surgery. The current teachings and practical guidelines for maintenance fluid infusions are based on caloric expenditure data in healthy children that were derived and published more than 50 years ago. A re-evaluation of these data and more recent recognition that hospitalized children are vulnerable to hyponatremia, with its resulting morbidity and mortality rates, suggest that changes in paediatricians' approach to fluid administration are necessary. There is no single fluid therapy that is optimal for all hospitalized children. A thorough assessment of the type of fluid, volume of fluid and electrolyte requirements based on individual patient requirements, plus rigorous monitoring, is required in any child receiving intravenous fluids. The present article reviews how hyponatremia occurs and makes recommendations for minimizing the risk of iatrogenic hyponatremia.

Key Words: *Antidiuretic hormone; Children; Complications; Fluids; Hyponatremia; Therapy*

L'hyponatrémie iatrogène chez les enfants hospitalisés : Peut-on l'éviter?

L'hyponatrémie iatrogène est un trouble courant chez les enfants hospitalisés. En général, elle est provoquée par l'administration d'eau sans restriction par voie orale ou par la prescription de liquides hypotoniques par voie intraveineuse. Elle peut entraîner un œdème cérébral et la mort, et on la constate surtout chez des enfants en santé qui subissent une intervention chirurgicale mineure. L'enseignement et les guides de pratique en vigueur relatifs à l'infusion de liquides d'entretien dépendent de données sur la dépense calorifique d'enfants en santé, dérivées et publiées il y a près de 50 ans. Une réévaluation de ces données et la prise en compte plus récente du fait que les enfants hospitalisés sont vulnérables à l'hyponatrémie, avec les taux de morbidité et de mortalité qui en résultent, laissent supposer la nécessité d'apporter des modifications dans la démarche des pédiatres à l'égard de l'administration de liquides. Il n'existe pas de thérapie liquidienne unique optimale pour tous les enfants hospitalisés. Une évaluation approfondie du type et du volume de liquide et des besoins électrolytiques de chaque patient, associée à une surveillance rigoureuse, s'impose pour tout enfant qui reçoit des liquides intraveineux. Le présent article analyse l'apparition de l'hyponatrémie et contient des recommandations pour réduire au minimum le risque d'hyponatrémie iatrogène.

One of the most common tasks ascribed to paediatricians is prescribing fluids for hospitalized children. There are many indications for fluid administration in hospitalized children. While the need for administration of isotonic fluids to restore intravascular volume and correct hypotension is accepted, the choice of maintenance fluids in hospitalized children requires some scrutiny.

The traditional guideline for maintenance fluid infusion focuses on the need to replace insensible loss of water for heat dissipation, and is based on caloric expenditure data and deductions that were published more than 50 years ago (1,2). However, the assumptions and deductions are based on the requirements of healthy children, and have recently been challenged (3,4). Indeed, Holliday et al (5) recently modified their initial recommendations based on the recent controversy. The traditional approach to prescribing maintenance fluids in children should be re-evaluated based on the following:

- Hyponatremia is the most common electrolyte disorder in hospitalized patients (both adult and paediatric) (6-8);
- Danger is posed by iatrogenic hyponatremia in otherwise normal children (cerebral edema and death) (9); and
- Administration of hypotonic intravenous (IV) fluids is a major risk factor for developing hyponatremia (10).

In the current article, two cases are presented to illustrate iatrogenic hyponatremia, and some suggestions are provided on how to avoid it in hospitalized children.

CASE PRESENTATIONS

Case 1

A newborn baby weighing 2.2 kg developed chylothorax following repair of coarctation of the aorta, which was treated with chest drainage. Her feeds were changed to two-third strength Portagen (Mead Johnson Nutritionals, USA),

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(sodium content at full strength of 2.2 mmol/100 mL) at 150 mL/kg/day for six days. Her sodium level five days before the change in feed was 140 mmol/L. Her next serum sodium level, which was measured six days after the diagnosis and change to Portagen feed, was 111 mmol/L. By this time, she had also lost 250 g of her birth weight, but was otherwise asymptomatic.

Why did this baby develop severe hyponatremia? In six days, the patient's intake (oral and IV) was 168 mL of free water (dextrose 5% in water to maintain patency of the IV line) and 1453 mL of two-third strength Portagen. Her output consisted of 450 mL of chylous chest drainage (electrolyte concentration similar to serum) and 734 mL of stool and urine combined. Her total sodium balance consisted of an intake of sodium (Portagen = 22 mmol) minus losses (chyle = 58 mmol), plus at least 36 mmol in urine and stools. Case 1 demonstrated unusually large losses of a body fluid; in this case, chest tube drainage. The principles of fluid and electrolyte balance discussed can be applied to losses of any body fluid, such as nasogastric drainage or ostomy losses.

Case 2

A 13-day-old baby weighing 3.18 kg was admitted to hospital because of poor feeding, constipation and failure to thrive. There was no clinical evidence of dehydration. The patient's admission serum electrolytes were sodium 132 mmol/L, potassium 4.6 mmol/L, urea 5 mmol/L and creatinine 18 µmol/L. An IV infusion was commenced at 20 mL/h of dextrose 5% in water with 2.5 mmol sodium chloride added. During hospitalization, the baby had a low-grade fever, poor feeding and infrequent bowel movements. The baby's usual feeds were continued in hospital (Similac Advanced [Abbott Laboratories, USA] – sodium content 0.7 mmol/100 mL) prescribed at 100 mL/kg/day to 150 mL/kg/day in addition to the IV fluids. On day 4 of admission, the baby developed increasing abdominal distension with bilious vomiting. Feeds were stopped; IV fluids were changed to dextrose 5% in 0.45% sodium chloride and increased to 130 mL/kg/h. Urinary and stool losses to this point had not been measured. The following day, and after a surgical consultation, the baby was taken to the operating room where a diagnosis of Hirschsprung disease was made. Serum electrolytes on the day of surgery (five days after admission) were as follows: sodium 120 mmol/L, potassium 5.2 mmol/L, urea 3.6 mmol/L and creatinine 15 µmol/L. The last serum electrolyte blood test had been performed four days previously. The baby was transferred postoperatively to the paediatric intensive care unit for analgesia and correction of electrolyte disturbances.

Why did this baby develop severe hyponatremia? The patient's total sodium and fluid balance during hospitalization could not be calculated because the baby's losses were not recorded. However, it is clear the child received hypotonic fluids in excess of requirements in the face of nonosmotic stimuli to antidiuretic hormone (ADH) secretion as a result of the acute illness.

TABLE 1
Standard intravenous solutions

Solution	Sodium, mmol/L	Glucose, g/L	Osmolarity, mOsm/L	EFW, %
0.9% NaCl	154	0	308	0
0.45% NaCl, 5% dextrose	77	50	406	50
Ringer's lactate	130	0	272	16
0.3% NaCl, 3.3% dextrose	53	33	269	66
0.2% NaCl, 5% dextrose	35	50	321	78
5% dextrose	0	50	252	100
3% NaCl	513	0	1027	0

EFW Electrolyte-free water; NaCl Sodium chloride

Table 1 lists commonly prescribed IV fluids, and their electrolyte and free water contents.

Factors leading to hyponatremia in these children included failure to monitor and adjust for excessive losses of body fluids, administration of electrolyte-free water through scheduled IV flushes and hypotonic fluids (oral or IV), excessive total fluid administration and failure to regularly monitor serum electrolytes.

PHYSIOLOGICAL BASIS FOR HYPONATREMIA

The above two cases represent failure to appreciate the physiological basis for iatrogenic hyponatremia. There are three requirements for the development of hyponatremia, not all of which are required in any individual patient (11). Most commonly, free water has to be administered and its excretion has to be impaired. In addition, greater urine losses of sodium and potassium relative to serum sodium may also exist. The primary source of electrolyte-free water in hospitalized children is the administration of hypotonic fluids, either intravenously or orally. Impaired free water excretion and greater urinary losses of sodium in hospitalized patients occur because they may have multiple nonosmotic stimuli for ADH secretion, even when the serum sodium level is less than 135 mmol/L (12-14). Some hyponatremic children may be both free water and sodium overloaded. These children require both water and sodium restriction, and careful diuresis and monitoring.

Traditional maintenance IV fluid rates may be excessive for sick hospitalized children due to nonosmotic ADH secretion, and thus they need to be individualized. A recent report (15) documented that the development of hyponatremia is unacceptably high in hospitalized children. The paper reviewed the literature and studied children who presented to the emergency department in a single institution over a three-month period and who had at least one serum sodium level measured (n=1586). The authors argue persuasively that the most important factor for hospital-acquired hyponatremia is iatrogenic. Release of ADH due to nonosmotic reasons may result in a small fall in serum sodium level, which leads to a suppression of thirst. In a

nonhospitalized child, this limits free water intake by the child. In contrast, in hospitalized children, once IV fluids are administered, it is the physician rather than the patient who determines the patient's water intake. The authors suggested that the original guidelines for maintenance fluid may not be applicable in the population of acutely ill children seen today because the complexity and the severity of illness seen in hospitalized children who receive IV fluid therapy (eg, leukemia and complex congenital heart disease) has radically changed; they further suggested the need for a revision of the current recommendations for IV fluid administration in hospitalized children (15). A systematic review of evidence from studies evaluating the safety of administering hypotonic versus isotonic IV maintenance fluids in hospitalized children has been performed (16). A meta-analysis of six studies, which met rigorous criteria, revealed that hypotonic solutions significantly increased the risk of developing acute hyponatremia (OR 17.22; 95% CI 8.67 to 34.2) and resulted in greater morbidity (16). Despite knowledge of the risks, symptomatic hyponatremia and deaths continue to occur (17,18).

POPULATIONS AT RISK FOR HYPONATREMIA

Linking energy expenditure to water losses in hospitalized children overestimates the need for maintenance fluid (19,20). A recent commentary (21) re-evaluated the factors used to calculate water and electrolyte requirements in Holliday and Segar's article (2), and pointed out that the original calculations did not factor in the unpredictable effect of nonosmotic stimuli for ADH secretion in the acutely ill child (13,22). Those with meningitis, encephalitis, head injury, bronchiolitis, gastroenteritis and chronic lung disease of prematurity, and in association with chemotherapy (essentially any ill child), are at risk for excessive ADH secretion (23-31). Of special relevance in otherwise healthy children, the risk of hyponatremia in postsurgical patients is well recognized (13,22,32,33), and is compounded by the administration of hypotonic solutions. Anesthetic agents, pain, nausea and opiates are also associated with nonosmotic ADH secretion, and contribute to the development of hyponatremia in these children. Compounding this, the inconsistencies of perioperative fluid administration have been recognized as a cause for concern in the anesthesia literature (34).

DANGERS POSED BY HYPONATREMIA

While not all hospitalized children develop hyponatremia, age and skeletal muscle mass relative to body weight are important risk factors (19). Skeletal muscle contains close to 50% body water. The brain is 80% water, of which two-thirds is in the cells, which swell during hyponatremia. Children have a greater brain cell volume to skull volume than teenagers and adults (35). The combination of a smaller muscle mass, and a greater brain cell volume is believed to account for the greater risk of increased intracranial pressure and neurological damage occurring in children who develop hyponatremia (15,36-38).

Hyponatremia is not merely of cosmetic interest. The number of reported deaths and cases of significant neurological damage from hospital-acquired hyponatremia in children receiving hypotonic maintenance solution has increased over the past 10 years (36,39-42). Indeed, several reviews (12,20) have suggested the potential harm associated with the use of these solutions and recommend that their routine use in children be reconsidered. There is an ongoing public enquiry in Northern Ireland into the deaths of three children with hyponatremia (17). There are warnings on Royal College Web sites in the United Kingdom about the dangers of prescribing hypotonic IV fluids to children (43). IV guidelines were recently developed in Ontario in response to the Paediatric Death Review Committee of the Office of the Chief Coroner for Ontario (18). Despite these developments, standard paediatric medicine and anaesthesia texts and guidelines continue to recommend hypotonic maintenance solutions for paediatric patients (44-46).

RISKS ASSOCIATED WITH THE USE OF ISOTONIC FLUID

There have been several concerns raised with regard to the use of isotonic maintenance fluid. The belief that 0.9% saline may cause hypernatremia is not supported (13,14,33,47). To the contrary, 0.9% saline administration as a maintenance fluid does not eliminate the risk of hyponatremia. When large volumes of 0.9% saline are given due to high circulating levels of ADH, such as when restoring intravascular volume or during routine anesthesia, hyponatremia is well described. The subsequent diuresis results in a disproportionate excretion of sodium rather than free water, the so-called urinary desalination (48). Another cited risk of administering large volumes of 0.9% saline is hyperchloremic metabolic acidosis. This is common after large volumes of 0.9% saline are given during acute resuscitation, and mild degrees of hypernatremia can be seen. Several prospective studies (21) in children and adults attest to the safety of 0.9% saline, and a strong case can be made for the prophylactic use of 0.9% saline in all hospitalized children, unless they have demonstrated hypernatremia, rather than waiting for hyponatremia to develop with the traditional maintenance regimen. Considering the well-documented dangers of iatrogenic hyponatremia in hospitalized children, the risk benefit of 0.9% saline versus hypotonic solutions in our opinion falls strongly in favour of 0.9% saline. In addition, because traditional maintenance IV fluid rates may be excessive for sick hospitalized children due to nonosmotic ADH secretion, fluid restriction should be implemented after restoring intravascular volume until the child is stable. This will also significantly reduce the risk of iatrogenic hyponatremia.

RECOMMENDATIONS

- Every hospitalized child requires a thorough assessment of ongoing fluid and electrolyte requirements. Fluid balance should be rigorously monitored by regular weighing and

daily monitoring of urea, creatinine and electrolyte levels. Less frequent serum sodium monitoring may be appropriate in a child with a stable medical condition, and after normal free water and sodium balance has been confirmed with daily serum sodium monitoring.

- Fluid prescription orders need to be individualized.
- Electrolyte content of body fluid losses may need to be evaluated.
- Children receiving enteral fluid or nutrition are also at risk of iatrogenic hyponatremia, and must have their serum electrolytes monitored, recognizing that all commercial enteral formulas are hypotonic.

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ERRATUM

Canadian Paediatric Society position statement – Management of the infant at increased risk for sepsis. Paediatr Child Health 2007;12(10):893-8.

On page 895, in the section titled, Well-appearing infant of a GBS-negative mother who had risk factors at delivery, the last sentence should read:

"If a GBS-negative woman with risk factors delivers a baby who remains well, the infant does not require evaluation for GBS (recommendation grade B)".

The Canadian Paediatric Society regrets this error. To access this statement, visit <www.cps.ca/english/publications/FetusAndNewborn.htm>.

Document de principes de la Société canadienne de pédiatrie – La prise en charge du nourrisson plus vulnérable à la septicémie. Paediatr Child Health 2007;12(10):899-905.

À la page 902, dans la section intitulé *Le nourrisson qui semble en santé et qui est né d'une mère négative au SGB qui présentait des facteurs de risque à l'accouchement*, la dernière phrase devrait se lire comme suit :

« Si une femme dont la culture de SGB est négative et qui présente des facteurs de risque accouche d'un bébé qui demeure en santé, le nourrisson n'a pas besoin de subir d'évaluation de SGB (catégorie de recommandation B). »

La Société canadienne de pédiatrie est désolée de cet inconvénient. Pour accéder à ce document de principes, rendez-vous à < www.cps.ca/francais/publications/FetN.htm >.

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An audit of intravenous fluid prescribing and plasma electrolyte monitoring; a comparison with guidelines from the National Patient Safety Agency

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Summary

Objectives: To audit past practice of intravenous (i.v.) fluid prescribing and electrolyte monitoring, prior to the publication of guidelines by the National Patient Safety Agency (NPSA, Ref. NPSA/2007/22) in March 2007, highlighting areas of discrepancy, in a specialist children's hospital.

Methods: We performed a retrospective case note review of 100 appendectomy patients between February 2004 and March 2007, recording; fluid type and volumes given as maintenance therapy, resuscitation boluses and nasogastric replacement; the frequency and timing of plasma electrolyte measurement; the relationship between plasma sodium [Na] concentration and i.v. fluid prescribed; and patient weight recordings.

Results: Ninety-eight acute appendectomies and two interval elective appendectomies. Median age 10 years (interquartile range: 8–11.25). Before surgery, hypotonic maintenance fluid was prescribed for 94% patients. During surgery, maintenance fluid was predominantly isotonic. After surgery, hypotonic maintenance fluid was prescribed for 92% patients. All maintenance fluid volumes were appropriately calculated according to weight using the Holliday and Segar formula (*Paediatrics*, **19**, 1957, 823). Fluid boluses were isotonic on 128/129 occasions and all accurately calculated according to weight. Nasogastric losses were replaced with 0.9% sodium chloride. No patient had daily plasma electrolyte measurements whilst administered i.v. fluid. Twenty-seven patients had recorded hyponatremia ([Na] <135 mmol·l^{-1}; 21 at presentation, six subsequently after admission). Hypotonic maintenance fluid was continued in 26/27 patients with hyponatremia. No patient had daily weight recorded.

Conclusions: Our practice of i.v. fluid prescribing and electrolyte monitoring in children, prior to the publication of guidelines by the NPSA in March 2007, did not fully meet the recommended standards.

Keywords: hyponatremia; hypotonic; isotonic; intravenous fluid; pediatric

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Introduction

Over the past 8 years in the United Kingdom (UK), there have been four reported hospital deaths in previously healthy children, from the neurological sequelae of hyponatremia, associated with intravenous (i.v.) fluid therapy (1). Many more cases have been reported worldwide, often after only minor surgery (2). Subsequently, the National Patient Safety Agency (NPSA) for England and Wales published guidelines (1) in March 2007 for clinicians prescribing i.v. fluid for pediatric patients in an attempt to reduce the associated risks.

The guidelines from the NPSA apply to children aged 1 month to 16 years and are summarized in Table 1. There are five broad aims:

- Remove 0.18% sodium chloride + 4% glucose solutions from general use.
- Prescribe fluid appropriately and monitor plasma electrolytes carefully.
- Provide adequate staff training.
- Audit practice rigorously.
- Report significant incidences of hyponatremia.

We aimed at determining if our past clinical practice of i.v. fluid prescribing and electrolyte monitoring in a specialist children's hospital prior to March 2007, concurred with the newly published guidelines from the NPSA (1). We restricted our audit strictly to surgical patients undergoing appendectomy for four reasons:

- All these patients received i.v. fluids at some point during their hospital admission.
- Most of them had no significant co-morbidity.
- The NPSA categorize them as susceptible to hyponatremia.
- We would be able to review the practice of doctors from several disciplines including emergency department clinicians, surgeons and anesthetists.

Table 1
Summary of guidelines published by National Patient Safety Agency, March 2007

1	If shock present, administer 20 ml·kg^{-1} 0.9% sodium chloride (NaCl) fluid boluses
2	Check plasma electrolytes before commencing i.v. maintenance infusion
3	Children should be weighed before commencing i.v. fluids and daily thereafter
4	Volumes of i.v. fluids should be accurately calculated; the Holliday and Segar (3) formula is considered appropriate
5	Monitor plasma glucose if using i.v. solutions without glucose/dextrose
6	Recheck plasma electrolytes every 24 h whilst receiving i.v. fluids
7	If the plasma sodium concentration is below 130 mmol·l^{-1} recheck electrolytes within 4–6 h
8	Fluid balance charts should be accurately documented
9	The majority of children may safely be administered 0.45% NaCl with 5% dextrose or 0.45% NaCl with 2.5% dextrose for maintenance fluid. In some circumstances only isotonic fluid should be administered (0.9% NaCl, NaCl 0.9% with 5% dextrose, or Hartmann's solution). These circumstances are; peri- and postoperative children, children with sodium levels at the lower end of normal or below 135 mmol·l^{-1}, children with central nervous system infections, head injury, bronchiolitis, excessive gastrointestinal losses and children with salt wasting conditions
10	Fluids used to replace ongoing losses should reflect the electrolyte composition of fluid lost. 0.9% NaCl is appropriate in most cases. (±KCl)
11	Fluid deficits should be replaced over 24 h with isotonic fluid ±5% dextrose
12	Those requiring maintenance fluid and replacement of ongoing losses should receive a single isotonic fluid. (0.9% NaCl or 0.9% NaCl with 5% dextrose)
13	0.18% NaCl + 5% dextrose should not be administered except in very specialized clinical areas and should not be available in regular wards
14	Some acutely unwell children with increased antidiuretic hormone secretion may benefit from restriction of fluids volumes to two-thirds recommended
15	If plasma sodium >160 mmol·l^{-1} children should receive isotonic solutions for maintenance therapy

Methods

After registering the project with the hospital's audit committee, a single researcher reviewed the clinical records of the last 100 consecutive patients who had undergone appendectomy between March 2007 and February 2004. Patients were excluded from the audit if their case notes were not immediately available in the medical records department. We cross referenced blood results recorded in the case notes with those from the Hospital Information System and used a structured questionnaire, based on recent recommendations from the NPSA (1), to record clinical data.

The questionnaire was divided into three time periods: (i) from admission to surgery, (ii) during surgery and (iii) after surgery. For each we determined:

- The type of i.v. fluid given as boluses for resuscitation.
- The type of i.v. fluid prescribed for maintenance requirements.

- The volumes of fluid administered.
- The duration of maintenance fluid administration.

In addition, it was noted whether the following was performed as recommended by the NPSA guidelines (see Table 1):

- Plasma electrolyte concentrations checked before starting i.v. maintenance fluids.
- Plasma electrolyte concentrations monitored daily during i.v. therapy and repeated within 6 h if the plasma [Na] was <130 mmol·l^{-1}.
- Isotonic fluids prescribed if the plasma [Na] was <135 mmol·l^{-1}.
- Isotonic maintenance fluid prescribed during surgery and postoperatively.
- The patient weighed before starting i.v. therapy and daily thereafter.
- Nasogastric losses replaced with 0.9% sodium chloride (NaCl).

Intravenous fluids classified as isotonic included 0.9% NaCl, 0.9% NaCl + 5% dextrose, Hartmann's solution, 4.5% human albumin solution (PPS), fresh frozen plasma (FFP). Fluids classified as hypotonic included 0.45% NaCl + 5% dextrose, 0.45% NaCl + 5% dextrose + 20 mmol·l^{-1} potassium chloride (KCl), 0.18% NaCl + 5% dextrose, 5% dextrose and 10% dextrose.

Results

We reviewed 100 appendectomy patients aged 2–14 years (median 10, interquartile range: 8–11.25 years), 49% male and 51% female. Ninety-eight patients presented with acute appendicitis and two patients had interval elective appendectomies. Twenty-six appendectomies were performed laparoscopically and 73 were open procedures. One patient had a laparoscopic approach converted to an open procedure.

Intravenous fluid management from admission to surgery

Maintenance fluid therapy was commenced on admission to hospital in 97/98 of the acute appendectomies. The two elective cases received no i.v. fluids preoperatively. Baseline plasma electrolyte concentrations were obtained for 97/100 patients. Twenty-one children had an admission plasma [Na] <135 mmol·l^{-1}. Ninety-four patients were prescribed a single hypotonic solution for maintenance i.v. therapy (see Figure 1). All patients had volumes of maintenance fluid calculated appropriately according to the Holliday and Segar (3) formula. The median duration of maintenance fluid administration before surgery was 10 h (range 0–80 h, interquartile range: 6.25–18.25 h).

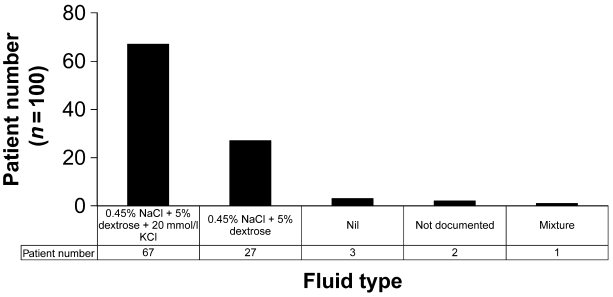

Figure 1
Chart title: Maintenance fluid prescribed before surgery. Mixture = a combination of; 0.9% NaCl solution and 0.45% NaCl + 5% dextrose solution (n = 1). Nil = no maintenance fluid administered.

Fifty-seven children required i.v. fluid boluses for resuscitation before surgery (a total of 66 boluses); these were all given as isotonic solutions, as recommended by the NPSA guidelines, either 0.9% NaCl (82%) or PPS 4.5% (18%). The bolus volumes were calculated appropriately according to weight and ranged from 10 to 20 ml·kg^{-1}.

Intravenous fluid management during surgery

Fifty-five patients were administered a single isotonic solution for maintenance i.v. fluid therapy during surgery but contrary to the NPSA recommendations 29 patients were administered a single hypotonic solution (see Figure 2). One patient received 10% dextrose and i.v. insulin because of clinical signs of malignant hyperpyrexia. The volumes of maintenance fluid administered during surgery varied considerably, and were calculated using one of the following methods: the Holliday and Segar (3) formula (52% of patients), 3, 5 or 10 ml·kg^{-1}·h^{-1}.

Thirty-five patients required i.v. fluid boluses for resuscitation during surgery (a total of 39 boluses). Of 39, 38 boluses were given as isotonic solutions (0.9% NaCl, PPS, Hartmann's solution or FFP). The volume of all boluses was calculated appropriately

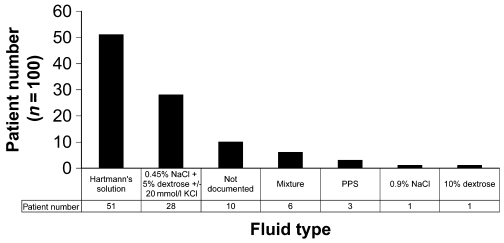

Figure 2
Chart title: Maintenance fluid prescribed during surgery. Mixture = a combination of one of: (i) Hartmann's solution and 0.45% NaCl + 5% dextrose + 20 mmol·l^{-1} KCl (n = 3). (ii) 0.9% NaCl and 0.45% NaCl + 5% dextrose (n = 1). (iii) 0.9% NaCl and 4.5% human albumin solution (n = 1). (iv) 4.5% human albumin solution and 0.45% NaCl + 5% dextrose + 20 mmol·l^{-1} KCl (n = 1). PPS = 4.5% human albumin solution.

according to weight and ranged from 5 to 20 ml·kg^{-1}. Blood glucose concentrations were not measured on any patient receiving i.v. fluids without dextrose.

Intravenous fluid management after surgery

All 100 patients were administered maintenance i.v. fluid therapy after surgery, of which 92 received a single hypotonic solution (see Figure 3), as opposed to the NPSA recommended isotonic solutions. Initial maintenance i.v. fluid volumes were prescribed appropriately in accordance with the Holliday and Segar (3) formula and gradually reduced as oral fluid intake increased. The median duration of maintenance fluid administration after surgery, to complete discontinuation, was 60 h (range: 15–216 h, interquartile range: 47.75–93 h).

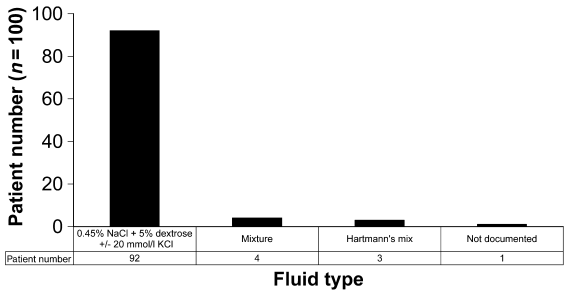

Figure 3
Chart title: Maintenance fluid prescribed after surgery. Hartmann's mix = a combination of; Hartmann's solution and 0.45% NaCl + 5% dextrose (n = 3). Mixture = a combination of (i) 0.9% NaCl and 0.45% NaCl + 5% dextrose (n = 2). (ii) 0.9% NaCl + 5% dextrose and 0.45% NaCl + 5% dextrose (n = 2).

Seventeen patients required resuscitation with fluid boluses (a total of 24 boluses). All boluses were given as isotonic solutions (0.9% NaCl, PPS or Hartmann's solution) in volumes calculated appropriately according to weight (5–20 ml·kg^{-1}). Nasogastric tubes were placed in six children at the discretion of the surgeon during surgery. Losses were significant in three patients, and in accordance with the guidelines were replaced each hour with equal volumes of 0.9% NaCl.

Biochemical monitoring

Plasma electrolytes were measured in 97 patients on admission to hospital. Three patients, two of which were interval elective appendectomies, did not have plasma electrolytes measured at any time during hospital stay. Despite the median duration of total maintenance fluid administration (i.e. before and after surgery combined) being 78.5 h (range: 19–264 h, interquartile range: 60.75–106.25 h), plasma electrolytes were only measured once in the majority of patients (54/100). No patient reached the standard of daily electrolyte monitoring as defined in the NPSA guidelines (1) whilst receiving maintenance i.v. fluids.

At the time of presentation, 21 patients had plasma [Na] <135 mmol·l^{-1}. A further six patients with [Na] >135 mmol·l^{-1} on admission subsequently developed hyponatremia. Overall, from these 27 patients we identified 46 electrolyte results with plasma [Na] <135 mmol·l^{-1} (see Table 2). Of these 46 results only 36 were re-measured and furthermore just 17 were within the recommended 24 h time period. Although all three results recording plasma [Na] <130 mmol·l^{-1} were repeated, on only one occasion was this performed within 6 h of the initial

Table 2
Total number of blood results recording plasma [Na] concentration <135 mmol·l^{-1}

Sodium plasma concentration (mmol·l^{-1}) (total 46)	*No. blood samples*
129	3
130	3
131	1
132	12
133	14
134	13

measurement, as is recommended by the NPSA guidelines (1). Additionally 26/27 patients with documented plasma [Na] <135 mmol·l^{-1} were prescribed hypotonic rather than isotonic solutions as i.v. maintenance fluid.

Monitoring of body weight

All 100 patients were weighed on admission to hospital but no patient had daily weights recorded whilst receiving maintenance i.v. fluid.

Intravenous fluid charts

Fluid balance charts (99%) and fluid prescription charts (98%) were completed clearly and possible to follow on retrospective review. Intraoperative fluid administration was clearly documented on the anesthetic chart in 90% of cases.

Discussion

We carried out a retrospective audit of our i.v. fluid prescription and electrolyte monitoring in pediatric appendectomies. We compared our clinical practice over 3 years from February 2004 to March 2007 with recommendations laid out by the NPSA guidelines (1) published in March 2007. We found several practices consistent with these guidelines: accurate calculation of fluid volumes; choice of fluid for i.v. bolus resuscitation and nasogastric aspirate replacement; and good record keeping. However, we identified significant discrepancies in two main aspects: firstly, in the choice of i.v. maintenance fluids, both during and after surgery, and for children with hyponatremia; and secondly, in the frequency of biochemical monitoring.

The NPSA worked in collaboration with an external working group, representative of several professional bodies (including the Royal Colleges of Surgery, Paediatrics and Child Health, and Anaesthetics) and invited opinions from consultant specialists and pharmacists to compile their guidelines. They apply to all pediatric patients aged 1 month to 16 years old [apart from a few exclusions (1)] receiving intravenous fluid therapy with the intent to reduce the risk of hyponatremia. The guidelines state that in most circumstances children can be safety administered 0.45% NaCl + 5% dextrose or 0.45% NaCl + 2.5% dextrose solutions (i.e. hypotonic) for i.v. maintenance therapy. Crucially, there are exceptions (1) and particularly relevant to our audit, children in the peri and postoperative period, and all patients with a plasma [Na] <135 mmol·l^{-1} should only receive isotonic maintenance fluid. Plasma electrolytes should be regularly monitored to alert clinicians to hyponatremia.

The normal range for plasma [Na] is often quoted as between 135 and 145 mmol·l^{-1} (4). The definition of hyponatremia varies (1,5,6) but the NPSA define it as a plasma [Na] <135 mmol·l^{-1} (1). Furthermore, the NPSA defines severe hyponatremia as a plasma [Na] <130 mmol·l^{-1} and severe acute hyponatremia as a decrease in plasma [Na] concentration from normal to <130 mmol·l^{-1} in <48 h (1). In severe acute hyponatremia, the brain may be unable to adapt to the rapid accumulation of intracerebral free water within the constraints of the rigid skull resulting in hyponatremic encephalopathy (2,5,7). Intravenous fluid therapy, particularly with hypotonic solutions, has been associated with acute hyponatremia, (2,5,7–12). Typically patients initially develop nonspecific symptoms such as headache, nausea, vomiting and lethargy, progressing to loss of consciousness, seizures, brainstem herniation and death (5,7). Children are more at risk than adults of hyponatremic encephalopathy, especially after surgery, and encephalopathy occurs at higher plasma [Na] than in adults (2,7–9,12,13).

There have been no definitive clinical trials providing conclusive evidence to support a particular choice of fluid for maintenance therapy in pediatric patients. There is growing support found in the literature to change conventional practice and routinely prescribe isotonic rather than hypotonic solutions to reduce the incidence of hyponatremia (2,5–13) . Many authors discuss the potential limitations in the original paper by Holliday and Segar (3) and question the appropriateness of their formula in acutely unwell children. Nevertheless, there remains opposition to this proposal. Some authors believe there is a lack of evidence to support the routine prescription of isotonic solutions with unknown safety implications associated with the administration of large sodium loads (14–17). These differing views have been considered carefully and have particular bearing on the NPSA recommendations.

In our audit, plasma electrolyte concentrations were measured much less frequently than recommended in the NPSA guidelines, even in children with documented hyponatremia. Venepuncture in children can be challenging and is generally avoided as much as possible. However, the early signs of hyponatremia are nonspecific and difficult to diagnose clinically without biochemical analysis. Although nearly all patients (97%) had blood sent for laboratory analysis on admission (correlating with i.v. cannulation), the frequency of electrolyte measurement subsequently was variable and no patient had daily analysis whilst receiving i.v. fluid therapy. Possible ways of improving compliance with the recommendations include obtaining blood for laboratory analysis and siting i.v. sampling cannulae during anesthesia.

Positive findings from our audit included the almost universal practice of using isotonic solutions for fluid bolusing and accurate calculation of all fluid volumes (bolus and maintenance) based on body weight. Medical staff from emergency medicine, surgery and anesthetics were all involved in this management. Further good practice was found in choice of fluid for nasogastric losses. Significant losses were replaced with equal volumes of 0.9% NaCl as recommended by the NPSA.

In our audit, despite a surprisingly high incidence of hyponatremia, no patient suffered any serious harm. It was noted, however, a few patients had prolonged symptoms of nausea, vomiting and drowsiness in the post operative period. Unfortunately, it is difficult to be certain if this was secondary to hyponatremia or the more likely result of resolving sepsis and morphine administration because of the absence of further biochemical monitoring for clarification.

The primary aims of clinical guidelines are to improve the care of patients and to provide consistency of management regardless of where or by whom they are treated (18). The NPSA guidelines will hopefully have several positive outcomes: alert clinicians to the importance of individualizing fluid administration; improve patient safety; increase biochemical monitoring and awareness of hyponatremia; stop non evidence based practice; clarify beneficial management; and stimulate debate, audit and further research.

In conclusion, our past practice, in a specialist children's hospital, of i.v. fluid prescribing and electrolyte monitoring, prior to the publication of guidelines by the NPSA in March 2007, was not fully consistent with their new recommendations. The audit has highlighted specific areas of discrepancy in our practice and alerted us to the surprisingly high incidence of hyponatremia in appendectomy patients. Now a local policy based on the NPSA guidelines has been agreed and recently implemented into our clinical practice for all children admitted to our hospital. We plan to re-audit our practice again in the 2010 to determine our improvement in patient care.

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CURRENT TOPIC

Non-traumatic coma in children

F J Kirkham

Many acutely ill children are not fully conscious. Most make a full neurological recovery as the underlying cause is treated, but considerable skill is required to distinguish the group at high risk of further deterioration, potentially leading either to death or to severe handicap. This article is an attempt to guide the worried paediatrician in casualty or on the ward faced with a child in non-traumatic coma who may need intensive care. The most effective method of deciding the order of priorities in this emergency situation is to ask oneself a series of questions.

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Is the child unconscious and if so, how deeply?

This is the most important question of all and may well be the most difficult to answer. The Glasgow Coma Scale was designed to assess depth of coma after head injury in adults and has been used in paediatric non-traumatic coma.[1–3] Although alternatives such as the Seshia scale have less interobserver variability, probably because there are fewer choices,[4] the Glasgow scale is very familiar to nursing staff and casualty officers and works well down to the age of 5. In those below that age, the motor and eye opening scales may be used (except that children below the age of 9 months cannot localise pain), but a modification of the verbal scale is needed. The modified James scale (table 1) has been used successfully in several UK centres, can be consistently reproduced between observers,[5] and has therefore been endorsed by the British Paediatric Neurology Association. The response to pain should be examined both with a supraocular stimulus (for localisation, flexion, and extension) and with nailbed pressure, for example with a pencil (for withdrawal). There may be a need for flexibility in terms of the overlap between the age groups. Thus, children of any age who are restless and talking unintelligibly have a verbal score of 2 and are therefore deeply unconscious; they are at high risk of further deterioration. At initial presentation, it is preferable to err on the side of recording too low a score, as it is easier to withdraw treatment from a child who is improving than to resuscitate one who deteriorates.

Table 1 Modified Glasgow coma scale

	>5 years	<5 years
Eye opening		
4	Spontaneous	
3	To voice	
2	To pain	
1	None	
Verbal		
5	Orientated	Alert, babbles, coos, words or sentences—normal
4	Confused	Less than usual ability, irritable cry
3	Inappropriate words	Cries to pain
2	Incomprehensible sounds	Moans to pain
1	No response to pain	No response to pain
Motor		
6	Obeys commands	Normal spontaneous movements
5	Localises to supraocular pain (>9 months)	
4	Withdraws from nailbed pressure	
3	Flexion to supraocular pain	
2	Extension to supraocular pain	
1	No response to supraocular pain	

Is the intracranial pressure raised?

The initial priorities are to establish an airway to ensure adequate gas exchange and to measure the mean arterial pressure (MAP), maintaining it as high as possible acutely. For an unconscious patient, the time to ask oneself whether or not there is intracranial hypertension is as soon as this basic triage is done, as irreversible brain damage may supervene long before it is possible to measure the intracranial pressure (ICP). The answer for all non-traumatic encephalopathies, whether infectious[6–9] or not,[9–12] is almost certainly "yes"; whatever the controversies about the benefits of monitoring, appropriate management in the acute situation prevents death and handicap.

Intracranial hypertension is thought to cause brain damage by at least two mechanisms. Firstly, reduced cerebral perfusion pressure (CPP = MAP − ICP) causes cerebral ischaemia, particularly in the borderzones between the main arterial territories; this may be associated with seizures, for example in hypertensive encephalopathy,[13] but is often clinically silent. Secondly, if there are differences in pressure between the forebrain compartment and the posterior fossa, one (uncal herniation) or both (diencephalic and midbrain/upper pontine herniation syndromes) temporal lobes may herniate through the tentorium. Similarly, if there is a pressure differential between the posterior fossa and the spinal canal, the brain may herniate through the foramen magnum (lower pontine and medullary herniation syndromes). Brain herniation causes direct mechanical damage and also ischaemia and haemorrhage secondary to vascular distortion. Central or uncal herniation through the tentorium is compatible with intact survival; herniation through the foramen magnum is not. These syndromes, and the changes from one to the next which signify progressive herniation, are

Table 2 Brain stem examination[120]

Response to pain	**Flexion to supraocular pain**	**Diencephalic**
	Extension to supraocular pain	**Midbrain/upper pontine**
	None	Lower pontine
Posture	Normal	Brainstem intact
	Hemiparesis	**Uncal herniation**
	Decorticate	**Diencephalic**
	Decerebrate	**Midbrain/upper pontine**
	Flaccid	Lower pontine
Tone/reflexes/plantars	Normal	Brainstem intact
	Unilateral pyramidal	**Uncal herniation**
	Bilateral pyramidal	**Diencephalic**
	Flaccid/extensor plantars	Lower pontine
Oculocephalic (doll's eye)	Saccadic eye movements	Normal forebrain control
Exclude cord injury	**Full deviation eyes away**	**Diencephalic**
Turn head from side to side, watch eyes	**Minimal deviation eyes**	**Midbrain/upper pontine**
	No movement eyes	Lower pontine
Oculovestibular (calorics)	Nystagmus	Normal forebrain control
Exclude perforated eardrum	**Full deviation eyes towards**	**Diencephalic**
Head in midline and 30° back	**Minimal deviation eyes**	**Midbrain/upper pontine**
Inject 20 ml ice cold water into ear canal	No movement eyes	Lower pontine
Pupil size	**Normal midpoint**	**Midbrain/upper pontine**
	Small	**Diencephalic**
	Unilaterally large	**Uncal herniation**
	Bilaterally large	Lower pontine
Pupil response to light	Brisk	Brainstem intact
Bright torch	**Unresponsive**	**Midbrain/upper pontine**
Respiratory pattern	Normal	Brainstem intact
	Cheyne–Stokes	**Diencephalic**
	Hyperventilation	**Midbrain/upper pontine**
	Ataxic, shallow	Lower pontine
	Gasping, slow, irregular	Medullary

Bold refers to clinical signs of potentially reversible cerebral herniation.

recognisable clinically[7 8] (tables 2 and 3), although appropriate clinical testing of the brain stem reflexes is often not performed routinely (table 2). Emergency management of intracranial hypertension at the time of presentation is potentially life saving in all encephalopathies. The important steps are: (i) to memorise the stages of progressive herniation which are compatible with intact survival (in **bold** in tables 2 and 3); (ii) to acquire the habit of serially examining the patient's conscious level (table 1) and brain stem reflexes (table 2) with these concepts in mind, so that progression is recognised immediately; and (iii) to learn the management algorithm so that action is taken as swiftly as possible.

The examination of the brain stem is best carried out with the possibility of uncal or central herniation in mind. It is therefore essential to examine the posture, response to pain, tone, peripheral reflexes, and plantar response as well as the oculocephalic (doll's eye) reflexes, pupil size and response to light, and respiratory pattern (table 2). If it is not possible to perform oculocephalic testing, for example, if there is any suspicion of a cervical injury, or if there is any doubt over the findings, oculovestibular or caloric testing should be undertaken using ice cold water (table 2). The most important use of these brain stem signs is in the recognition of progressive uncal and central transtentorial herniation (table 3), so that the early stages may be recognised and appropriately managed before irreversible herniation has occurred. The signs of the diencephalic stage of central herniation may be mimicked by drugs, toxins, and metabolic abnormalities, as well as occurring intra- and post-ictally. In the acute situation, however, it is always better to assume that central herniation is imminent and take appropriate action, rather than waiting for clear evidence of progression through the stages, which may occur very rapidly. Recovery is extremely unlikely if the patient has reached the lower pontine or medullary stage, so that if children are seen with some or all of the signs, either of uncal herniation or of the diencephalic or mid-brain/upper pontine phases of central herniation, emergency management of presumed raised ICP is mandatory.

Table 3 Herniation sydromes

Uncal	**Unilateral fixed dilated pupil** **Unilateral ptosis** **Minimal deviation of eyes on oculocephalic/oculovestibular testing** **Hemiparesis**
Diencephalic	**Small or midpoint pupils reactive to light** **Full deviation of eyes on oculocephalic/oculovestibular testing** **Flexor response to pain and/or decorticate posturing** **Hypertonia and/or hypereflexia with extensor plantars** **Cheyne–Stokes respiration**
Midbrain/upper pontine	**Midpoint pupils, fixed to light** **Minimal deviation of eyes on oculocephalic/oculovestibular testing** **Extensor response to pain and/or decerebrate posturing** **Hyperventilation**
Lower pontine	Midpoint pupils, fixed to light No response on oculocephalic/oculovestibular testing No response to pain or flexion of legs only Flaccidity with extensor plantars Shallow or ataxic respiration
Medullary	Pupils dilated and fixed to light Slow, irregular, or gasping respiration Respiratory arrest with adequate cardiac output

Bold refers to clinical signs of potentially reversible cerebral herniation.

Papilloedema is very rarely seen in acute encephalopathies, even if the intracranial pressure is very high.[8 14 15] Corneal, gag, and cough reflexes may also be elicited, but do not provide essential additional information and are therefore omitted here. If the lateral ventricles are small on the computed tomography (CT) scan in a child in coma it is likely that the ICP is raised; but such a scan is often reported as normal, and raised ICP should be assumed even if there is no evidence of brain swelling on the CT scan.[7 16 17] Figure 1 shows CT scan abnormalities commonly seen in unconscious children.

What is the emergency management of the unconscious patient?

The potentially life saving manoeuvres required in an unconscious child who has just arrived in casualty can be considered separately from the long term management of the comatose patient, which is rather more controversial. The main priority in these extremely sick children is to maintain the airway and the systemic circulation and to correct significant metabolic derangements. Shock is a commonly associated finding, particularly when the aetiology is meningitis[18]; it should be treated rapidly with plasma and if necessary, inotropic support. Adrenaline is relatively contraindicated, as there is evidence for an associated lactic acidosis, at least in septic shock.[19] Hypoglycaemia, which is common in association with any serious illness in the developing world,[20] must be treated, but salt wasting is an important association with conditions such as meningitis; initial fluid therapy should aim to slowly replace salt and water losses[21–23] as well as maintain

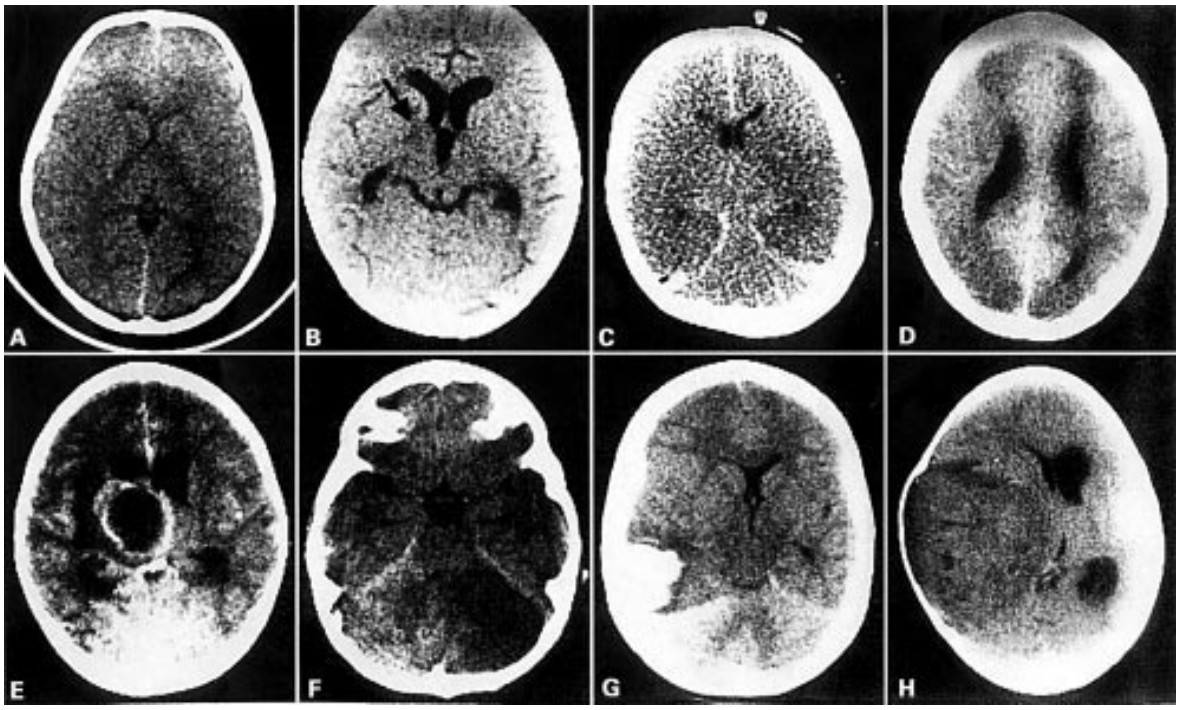

Figure 1 CT scan abnormalities commonly seen in unconscious children (A) Small ventricles suggestive of acute brain swelling in a patient in acute coma. (B) Acute hydrocephalus in a patient with a reduced level of consciousness after status epilepticus. There is a small infarct in the basal ganglia on the left, indicated by the arrow. CSF showed a pleiocytosis and acid fast bacilli; the child responded to antituberculous therapy. (C) Low density in the cerebral hemispheres compared with the posterior fossa, suggestive of widespread ischaemia. There is high density in the falx suggestive of blood and it is likely that this child has been shaken. (D) Bilateral anterior and posterior watershed infarcts in a child with hypertensive encephalopathy in whom blood pressure had been reduced precipitously. (E) Contrast enhanced CT scan showing a cerebral abscess in a child with a hemiparesis, a reduced level of consciousness, and a fever. (F) Low density in the right cerebellum compatible with an infarct in a child with an acute vertebrobasilar dissection. (G) CT scan without contrast showing a left sided intracerebral haematoma in a child with an arteriovenous malformation. (H) Large supratentorial tumour and acute hydrocephalus.

adequate nutrition. Resuscitation and maintenance of systemic homoeostasis are the priorities in the acute situation and there is no case for fluid restriction; however hypo-osmolar fluids such as 5 or 10% dextrose are contraindicated because of the risk of delayed cerebral oedema.

In a drowsy child (Glasgow coma score 12 or more), with an adequate airway, a well maintained blood pressure and no signs of brain stem compromise, a single dose of 0.25–0.5 g/kg 20% mannitol is often associated with rapid improvement in conscious level. Although not contraindicated,[24] if the aetiology is intracranial haemorrhage, there is a risk that as the brain oedema is reduced, the rate of bleeding will increase; an emergency CT scan is therefore mandatory if the patient does not regain full consciousness immediately after the dose has been given. If the level of consciousness is deteriorating or there is evidence of reversible brain stem compromise (signs in **bold** in tables 2 and 3), the child must be immediately ventilated. This has at least two benefical effects: firstly, the airway is protected, making respiratory arrest less likely; and secondly, ICP will decrease because cerebral blood flow and therefore blood volume are directly related to pCO_2.[25] Clinical experience suggests that mannitol may also help in this situation, at least in the short term, although there is little evidence available.[8 24 26 27] Mannitol should not be administered in renal failure

Table 4 Emergency management of the unconscious patient

Establish airway and give high flow oxygen by mask
Measure blood pressure and resuscitate with salt containing fluids/inotropes if low; do *not* reduce immediately if high
Perform Dextrostix testing and simultaneous true blood sugar and give dextrose if low
Assess level of consciousness using the modified Glasgow coma scale (table 1)
Assess brain stem function (table 2) and decide whether the patient has evidence of central or uncal herniation (table 3)
Lift the eyelids and look for tonic deviation of the eyes or nystagmus
Examine the fundi for papilloedema (rarely seen in acute encephalopathy; absence does not exclude intracranial hypertension), retinal haemorrhages, and macular star suggestive of hypertension
If modified Glasgow coma score is less than 12 or there is evidence of herniation, intubate and ventilate
If modified Glasgow coma score is between 12 and 14, or intubation is not possible immediately and there is evidence of progressive uncal or central herniation (table 3), give mannitol 0.25 g/kg
If there is tonic deviation of the eyes or nystagmus, assume subtle status epilepticus and give a benzodiazepine and/or phenytoin
If the child is febrile and is either under the age of 12 months or is older than 12 months and has a Glasgow coma score greater than 12, undertake a lumbar puncture (table 5) after checking that the child is not in subtle status. The CSF pressure should be measured with a transducer or a manometer. A dose of mannitol 0.25 g/kg should be given if the pressure is greater than 15 cm H_2O or if there is evidence of deterioration in the modified Glasgow coma score or the brain stem signs after the lumbar puncture. If the CSF is cloudy, dexamethasone may be given before starting a third generation cephalosporin
If the child is afebrile or febrile with a deteriorating level of consciousness, do not perform lumbar puncture, but start a third generation cephalosporin and aciclovir and ring the nearest paediatric intensive care unit with access to a neurosurgical unit to request transfer by their transport team for CT scan and further management

as it is excreted by the kidneys and makes dialysis difficult.

Clinical seizures should be treated immediately, as they are usually accompanied by an increase in ICP,[28] may precipitate with cerebral herniation,[29] and may be associated with excitotoxic[30] and ischaemic[31] mechanisms of secondary brain damage. Generalised tonic–clonic seizures occur, but subtle seizures, including unilateral clonus, eye deviation, nystagmus, and eyelid twitching are characteristic of prolonged status epilepticus, which is common in non-traumatic coma,[31 32] but often remains undetected, particularly in ventilated patients. Lifting up the eyelids to look for tonic deviation of the eyes or nystagmus is therefore worthwhile. It is sensible to control fever, as high body temperature tends to lower the seizure threshold. The standard protocol for the management of status epilepticus may be followed.[33] A benzodiazepine should be used initially, but it is essential to have access to a ventilator if more than one bolus dose is required in an unconscious patient. There are few data on the pharmokinetics and efficacy of rectal paraldehyde (0.4 ml/kg mixed with an equal volume of olive oil), but it is cheap, is often associated with the cessation of seizures, and is said to have less effect on respiratory drive than either benzodiazepines or barbiturates. Intravenous phenytoin (18 mg/kg) may be given over 20 minutes with ECG monitoring. Intramuscular phenobarbitone is commonly used in the developing world, but one study showed that a dose of 10 mg/kg was often ineffective[34]; a recent controlled trial showed that mortality was higher in unventilated patients with cerebral malaria treated with the usually effective dose of 20 mg/kg,[33–35] probably because of associated respiratory depression.[35] This drug cannot therefore be recommended unless ventilation is feasible.

Table 4 summarises the emergency management of the unconscious patient.

What is the cause and which possible underlying causes should be treated immediately?

The cause may be apparently obvious in, for example, a child who has just been resuscitated after a cardiac arrest, a known diabetic presenting in coma, a hypertensive patient with a macular star, or a patient with severe viral hepatitis. In diabetic coma, if serum sodium does not increase in parallel with the reduction in plasma glucose, there is a serious risk of cerebral oedema and herniation[36]; this is the commonest cause of death in diabetic children.[37] This is probably preventable if fluid losses are replaced over a 48 hour period with at least 125 mmol of sodium per litre over the first 24 hours.[38 39] The prognosis for hypertensive encephalopathy is excellent if an ischaemic insult is not superimposed,[40] so if blood pressure is raised in an unconscious patient, it should be reduced extremely slowly. Hepatic transplantation is life saving in fulminant liver failure with progressive deterioration in conscious level,[41] but the prognosis is better in those who do not have cerebral oedema on CT scan[42] or require ventilation.

The previously well child presenting in coma can prove more difficult diagnostically. Routine haematology, biochemistry, and microbiology may be helpful, and specific tests, including blood ammonia, lactate, and urine toxicology screen should also be performed (table 5). Reye's syndrome[14] has become very rare nowadays, probably in association with the warnings not to give aspirin to children under 12, but ornithine carbamoyl transferase deficiency still presents, often with unilateral cerebral oedema in a manifesting heterozygote.[43] Occasionally, other metabolic conditions may present as coma in a previously well child and accidental or deliberate poisoning is a possibility; plasma and urine should therefore be saved at the time of the acute presentation in case later investigation is required. Careful examination of thick and thin blood films for *Plasmodium falciparum* is essential in children who live in or have travelled from endemic areas, but negative studies do not exclude the diagnosis; either quinine or arthemether must be given if there is any doubt.[44]

If the child is deeply unconscious, afebrile, or has focal signs, the top diagnostic priority is a CT scan rather than a lumbar puncture, as likely diagnoses include intracerebral haemorrhage, ischaemic stroke, hydrocephalus, and brain tumour. As this will inevitably mean some delay, a third generation cephalosporin and aciclovir must be given to cover the possibility of infection. There is a good case for immediate ventilation and transfer of the afebrile comatose child to a paediatric intensive care unit with access to neurosurgery; if there is a space occupying lesion and/or acute hydrocephalus, timely decompression may prevent brain herniation. In addition, if the CT scan is normal, magnetic resonance imaging may be warranted, as the posterior fossa is better shown (for example, for the diagnosis of cerebellar inflammation,[45] tumour, or ischaemia which may cause life threatening acute hydrocephalus). In addition, evidence of focal pathology may suggest ischaemic stroke or an alternative aetiology (for example, frontotemporal pathology in herpes simplex encephalitis,[46] or thalamic involvement in Japanese B[47] or Epstein–Barr[48] encephalitis). There may be a case for additional sequences, for example, fluid attenuated inversion recovery,[49 50] diffusion weighted imaging, magnetic resonance angiography or venography. It is important to remember that children who have been non-accidentally injured may present in unexplained coma with or without seizures.[51] Careful examination of the fundi for retinal haemorrhages is mandatory and it is important to remember that cranial ultrasound does not exclude subdural haemorrhage or effusion, so that CT or magnetic resonance imaging is an essential investigation, even in those with an open fontanelle; magnetic resonance imaging is particularly useful in dating the injury and therefore deciding whether the child has been serially abused.

Table 5 Investigation of non-traumatic coma

Investigations	*Indication/clinical clues*	*Possible abnormality*	*Further investigation if abnormal*	*Possible diagnoses*	*Action*
Dextrostix	All	Low	Blood glucose	Hypoglycaemia secondary to:	Intravenous dextrose
Blood glucose			Liver function tests	• Fasting	Fluids/insulin
			Blood ammonia	• Severe illness	
			Blood lactate	• Reye's syndrome	
			Blood and urine amino acids	• Organic aciduria	
			Urine organic acids	• Fatty acid oxidation defect	
				• Haemorrhagic shock and encephalopathy	
	Previous polydipsia/polyuria	High		Diabetic ketoacidosis	
Blood sodium	All	Low	Urinary sodium	Hypo/hypernatraemia +/− dehydration	Appropriate fluids
		High			
Blood urea	All	High	Blood creatinine	Dehydration	Rehydrate
			Blood film	Haemolytic-uraemic syndrome	Dialysis, plasmapheresis
Aspartate transaminase	All	High	Blood ammonia	Reye's syndrome	
				Hypoxic-ischaemic	
Blood ammonia	All (unless cause known)	High	Blood orotic acid	Urea cycle defect	Sodium benzoate
			Urine organic acids	Organic acidaemia	
Full blood count and film	All	Low Hb	Hb electrophoresis	Anaemia	Transfusion
		High WBC		Infection	3rd generation cephalosporin
		Low platelets		DIC, infection	
		Sickle cells		Sickle cell disease	
		Burr cells		Haemolytic-uraemic syndrome	Dialysis, plasmapheresis
	Residence in endemic area	Parasites on thick/thin films		Malaria	Quinine
	Pica	Basophilic stippling	Wrist *x* ray—lead line	Lead encephalopathy	Chelation
Blood culture	All				Appropriate antibiotics
Stool culture	All	Shigella, enteroviruses			
Mycoplasma IgG, IgM	All (unless cause known)		Chest *x* ray	Mycoplasma encephalitis	Erythromicin, ?prednisolone
Viral titres	Analyse if unexplained		Repeat at discharge		
Urine for toxin screen	Analyse if unexplained		Blood film—basophilic stipling, wrist *x* ray—lead line	Poisoning	Antidote
Blood lead	Analyse if unexplained				Chelation
CT scan without contrast	All (after resuscitation, afebrile patients should ideally be transferred for CT scan to a unit with neurosurgical facilities)	Blood			
		• Subdural	Skull *x* ray/skeletal survey/clotting screen	Non-accidental injury	Neurosurgical referral Child protection
		• Extradural			Neurosurgical referral
		• Intracerebral			
		Space occupying lesion		Tumour	Neurosurgical referral
		Hydrocephalus			
		• Obstructive		?Space occupying lesion	Antituberculous cover
		• Communicating	CSF examination	?Meningitis, especially tuberculous	Neurosurgical referral
		Abscess	Culture aspirate Contrast CT/MRI		Neurosurgical referral Anaerobic cover
		Swelling			Mannitol 0.25 g/kg
		Focal low density		Cerebral abscess, herpes simplex, stroke, ADEM	
		Abnormal basal ganglia	Plasma/CSF lactate, blood gas	Leigh's syndrome, hypoxic-ischaemic, striatal necrosis	
Lumbar puncture	In febrile if no clinical or radiological evidence of raised ICP (delay and treat if doubt)				
• Pressure measurement		High	CT scan		Mannitol, ventilate
• Microscopy		High WCC		Meningitis/encephalitis	3rd generation cephalosporin, aciclovir
• Gram, bacterial culture		High RBC	CT scan (traumatic tap should clear by 3rd bottle)	Haemorrhage/encephalitis/ non-accidental injury	Neurosurgical referral, aciclovir, child protection
• Glucose		Low		Tuberculous meningitis	Immediate and prolonged antituberculous therapy
• Protein		High			
• PCR for viruses, TB					
• Prolonged search for acid fast bacilli, culture for TB on Lowenstein–Jensen	Prodrome > 7 days, optic atrophy, focal signs, abnormal movements, CSF polymorphs < 50%, hydrocephalus and/or basal enhancement on contrast CT			Tuberculous meningitis	Immediate and prolonged antituberculous therapy
• Antibodies e.g. herpes simplex, Mycoplasma				Encephalitis	Aciclovir, erythromycin
• Lactate	Abnormal breathing/eye movements, basal ganglia lucencies		Muscle biopsy	Leigh's syndrome	
EEG	All, especially if ventilated or evidence of subtle seizures (nystagmus, tonic deviation of eyes, clonic jerking limbs)	Epileptiform discharges		Status epilepticus	IV benzodiazepines, phenytoin, thipentone
		Asymmetrical foci of spikes or periodic lateralising epileptiform discharges on slow background		Herpes simplex encephalitis (many patients do not have characteristic EEG)	High dose IV aciclovir for 2 weeks
MRI	Unexplained encephalopathy	Frontotemporal abnormality	CSF for herpes simplex PCR	Herpes simplex encephalitis	High dose IV aciclovir for 2 weeks
		Thalamic abnormality	CSF for Epstein–Barr virus (arboviruses in endemic area)		

If the child is febrile, CSF should be obtained once the level of consciousness is starting to improve after resuscitation. This is crucial in the developing world where children commonly have both malaria parasitaemia and meningitis,[52] and it is not possible to distinguish between them clinically[53]; infants, in whom cerebral herniation is exceptional because of the open fontanelle, very commonly have both.[52] In the developed world, there is also a risk of suboptimal management if CSF is not obtained[54]; this may become increasingly important as antibiotic resistance increases.[55] Although there is a risk of cerebral herniation,[7 29] a normal CT scan does not exclude intracranial hypertension[7] and may not be essential if there are no focal signs.[56] Diagnosis and treatment of subtle seizures is essential prior to lumbar puncture,[29] however, and the procedure must be postponed in children over 12 months who have a Glasgow coma score less than 12 (table 1) or signs of herniation (table 3). The pressure should be measured with a transducer (a device designed to measure blood pressure may be used) rather than by displacement into manometer tubing. Ideally, if the child is not fully conscious, he or she should be in the intensive care unit and ventilated during the lumbar puncture; if this is not possible, a dose of mannitol should be available, to be given if the pressure is high.

For measurement of cerebral perfusion pressure (CPP), it is important that CSF pressure is measured in mm Hg (if obtained in cm H_2O, the pressure should be divided by 1.35). The CSF should be sent for a cell count, protein, glucose, and a Gram stain. If there are white cells but no organisms on the Gram stain, a careful search for acid fast bacilli after Ziehl–Nielssen staining should be performed and the CSF should be put up for culture for *Mycobacterium tuberculosis*. This is particularly important if there are clinical or radiological features, specifically hydrocephalus or ventricular enhancement, suggestive of tuberculous meningitis.[57 58] Viral antibodies should also be requested, particularly looking for herpes simplex. The polymerase chain reaction (PCR) may be used to suggest the diagnosis in tuberculous meningitis, enteroviral, or herpes simplex[59] infection, but it is technically difficult to avoid contamination. PCR is also available for other organisms, including meningococcus and pneumococcus, and may be useful in confirming the diagnosis in partially treated infections, provided that the limitations of sensitivity and specificity are taken into account. It is essential to liaise closely with the local microbiology laboratory, as the range of likely diagnoses varies considerably with location.[60–63]

There is no doubt that a seriously ill child in non-traumatic coma should be covered with a broad spectrum antibiotic which is also appropriate to treat meningitis, should this prove to be the underlying cause. Recent studies have suggested that the third generation cephalosporins, cefotaxime, ceftazidine, and ceftriaxone used alone give good antibiotic cover for meningitis, but the combination of chloramphenicol and penicillin is still used in the developing world. The emergence of resistant organisms means that microbiological advice should always be sought, particularly if the patient is in a high risk group, for example, a child with sickle cell disease or splenectomy on prophylactic penicillin. There is some evidence that dexamethasone, given before the antibiotic, reduces the incidence of deafness and possibly neurological handicap,[64] although the data were collected when *Haemophilus influenzae* was a common pathgen, and the benefit is less certain for pneumococcal or tuberculous meningitis.[65–67] A child presenting with acute seizures should be treated with aciclovir to cover the possibility of herpes simplex encephalitis and if the diagnosis is likely, this drug should be continued at high dose for two weeks because of the risk of relapse.[68] If there is any suspicion of tuberculous meningitis, for example, if there is hydrocephalus on the CT scan or the CSF sugar is low, treatment with antitubercular therapy should be considered. The treatment of other possible infections such as *Mycoplasma pneumoniae* remains controversial, but most physicians use erythromicin in idiopathic coma until the results of antibody testing are known.[69]

There is little evidence that specific management improves outcome in ischaemic encephalopathy,[70] but carbon monoxide poisoning should be treated with hyperbaric oxygen.[71]

What is the management if the child remains unconscious?

MONITORING OF INTRACRANIAL PRESSURE

After admission to intensive care locally or transfer to the regional centre, the next few hours are usually spent in establishing the cause of coma and improving the child's general condition. If the child remains unconscious for more than six hours and the blood pressure can be maintained, ICP monitoring should be considered. If there is irreversible brain stem damage clinically, or an electroencephalogram (EEG) predictive of very poor outcome, ICP monitoring is unlikely to be of benefit. Great care should be taken if there is a bleeding diasthesis. Extradural ICP monitoring has been undertaken safely in patients with liver disease with a prolonged prothrombin time, but a platelet count of below 50×10^9/l is an absolute contraindication. Bleeding may be more likely in patients with meningitis in whom the vessels may be inflamed. Although various techniques for monitoring ICP have been described, the Camino system, which has a fibreoptic sensor, and may be placed subdurally, intracerebrally, or intraventricularly is used very widely now. The catheters are expensive but the technique appears to be very safe, can be performed at the bedside, and gives reliable measurements over several days, even at high ICP.

MAINTENANCE OF AN ADEQUATE CEREBRAL PERFUSION PRESSURE

The baseline ICP may be normal or high and in addition there are often plateaus or spikes of very much higher ICP which are probably secondary to autoregulatory vasodilatation. There

is evidence that in non-traumatic coma, outcome is related more to minimum CPP than to maximum ICP,[9 72] although there is controversy over the ideal CPP to aim for, which may depend on the age of the child. In adults with head injury there is some evidence that the cerebral circulation is unstable at a CPP of less than 70 mm Hg and that outcome is poor for patients whose CPP cannot be maintained at or above this level.[73] The small amount of data available in non-traumatic coma in children suggests that outcome is poor if mean CPP is consistently lower than 65–70 mm Hg,[9 74] but there may be a number of confounding factors, including CO_2 tension; current advice is to maintain CPP above a minimum of 50 mm Hg. The main priority is to maintain the systemic circulation, with plasma if the circulation is underfilled, and otherwise with inotropic support. There is some evidence that maintenance of the systemic circulation in this way may prevent ICP spikes.

MANAGEMENT OF PERSISTENT INTRACRANIAL HYPERTENSION

Management of the intracranial hypertension is rather more controversial. A mass may require surgical management and acute hydrocephalus may need emergency drainage. The child should be nursed flat with the head in the midline, so that venous drainage from the head is not obstructed, and with the head either flat or tilted up to 30°. The patient should be handled as little as possible and nursing procedures such as suction should be performed with great caution. There is considerable controversy over the use of hyperventilation in unconscious patients. There is no evidence that prophylactic hyperventilation prevents intracranial hypertension, and there is evidence that it is possible to reduce cerebral blood flow below the ischaemic threshold in unconscious patients.[75] The current recommendation is to ventilate to normocapnia; the patient can then be hyperventilated or bagged during ICP spikes. It is essential to wean patients from the ventilator slowly.

Fluid management can be very difficult and should be tailored for the individual patient's needs. There is considerable controversy over fluid restriction, which has been shown to be potentially harmful in patients with subarachnoid haemorrhage and meningitis.[21–23] The syndrome of inappropriate secretion of ADH, for which fluid restriction is indicated, is relatively rare; instead cranial diabetes insipidus may require careful management.[76] It is essential that the systemic circulation is well filled and that large volumes of hypo-osmolar fluids are not given. To manage these patients properly it is essential to monitor blood pressure, central venous pressure, urine output, weight, core and peripheral temperature, plasma and urine electrolytes, and osmolality at least six hourly and to make appropriate management decisions with the same frequency. Mannitol may reduce spikes of ICP very rapidly and acts either as an osmotic diuretic or by reducing cerebral blood volume. As with hyperventilation, there is no evidence that regular prophylactic mannitol is of benefit.

A few years ago there was a vogue for using anaesthetic agents which reduce ICP by reducing cerebral metabolic demand and therefore cerebral blood flow and blood volume. There is no evidence that barbiturates and other sedatives are of any benefit in global cerebral ischaemia. Although there may be an intermediate group of patients in coma from other causes who might benefit from barbiturate therapy, the risk of hypotension probably outweighs any useful effect in reducing ICP. In addition, drug levels may remain high several days after the drug has been discontinued, making the diagnosis of brain death impossible. Reducing the body temperature by 1°C can reduce cerebral metabolic rate considerably and there is evidence for an additional beneficial effect on ischaemic brain tissue. Those units using profound hypothermia have abandoned this management strategy because of neutropenia and infection,[77] but recent evidence suggests a benefit for mild hypothermia in head injury[78] (although a controlled trial in adults was negative), stroke, and neonatal hypoxic-ischaemic encephalopathy. There is, therefore, a case for maintaining normothermia or mild hypothermia in unconscious patients, although research is needed as fever may have an important antiparasitic effect in infectious encephalopathies. One major advantage is that hypothermia is easily reversible.

As some of the pharmacological interventions discussed above may be definitely harmful, it is often worth considering simple mechanical manoeuvres such as CSF drainage if intracranial hypertension persists.[79] An intraventricular cannula may be placed, although this is difficult if the ventricles cannot be seen on CT scan. If it is impossible to maintain an adequate cerebral perfusion pressure in a child with a treatable cause for coma in whom neurophysiology is preserved, it may well be worth considering surgical decompression.[80–82]

MONITORING OF ELECTROENCEPHALOGRAPHIC SEIZURE ACTIVITY

Once an unconscious patient is ventilated, it is usually impossible to detect clinical evidence of seizures, but a substantial proportion have ongoing status epilepticus.[83] A 1–4 channel cerebral function monitor can be used to detect the majority of electrical discharges,[84 85] but requires considerable neurophysiological back up, including regular full 16-channel EEG,[86] so that the data are interpreted correctly and focal discharges are not missed. The pathophysiology of epilepsy occurring in the context of coma is poorly understood. There are a number of reasons for seizures to occur, for example, fever, ischaemia in the anterior and posterior cortical borderzones, release of excitotoxic neurotransmitters after ischaemia, particularly in the hippocampal region of the temporal lobe, direct cortical invasion and thrombophlebitis in meningitis, small vessel vasculitis in conditions such as haemolytic-uraemic syndrome, vasospasm, stenosis or

occlusion of the basal cerebral vessels in meningitis, and perhaps venous thrombosis in conditions such as cerebral malaria where the venous system is the site of parasitic invasion. One benefit of neurophysiological monitoring is to give early warning of potentially treatable complications, presenting either as deterioration in the background pattern or as seizure discharges.

It has been argued that prolonged seizures and status epilepticus in unconscious patients simply reflect the degree of brain damage already sustained, but there is evidence that poor outcome is associated with the presence of prolonged seizures in a number of encephalopathies.[87–92] In a study using CFAM monitoring, outcome (but not mortality) was related to number and duration of electroencephalographic seizures and to the duration of the longest seizure.[92] There is therefore an argument for monitoring and aggressive management, but there have been no studies looking at the effect of treatment of subclinical seizure discharges on outcome. More research is needed in this area.

Are there any other potentially treatable secondary phenomena causing neuronal damage?

There is a large amount of experimental data available suggesting a role for substances such as free radicals, excitotoxins, and calcium, released during a cascade of biochemical reactions after ischaemia, in the causation of brain damage. In some patients, for example, those with meningitis, there is evidence for an inflammatory vasculopathy, with spasm, stenosis, and occlusion of the large (and perhaps the small) cerebral vessels.[93] Anticoagulation has been suggested, but these patients commonly have a bleeding diasthesis and there have been no randomised studies to date, so this treatment cannot be recommended.[94] It is possible that the next few years will bring appropriate drugs to antagonise these phenomena but none is available as yet.

What is the prognosis?

This becomes the most important question in the minds of parents and professionals. There is no doubt that prolonged coma after a hypoxic-ischaemic insult in childhood carries a very poor prognosis,[70 95] but most children surviving infectious encephalopathies have a good outcome,[89 96 97] with mild or moderate difficulties only, which are often subtle.[96 97] If global ischaemia has not occurred during the course of other encephalopathies, the prognosis may well be very much better than is obvious in the first few weeks after the child comes off the ventilator.[99 99] Cortical blindness often recovers.[100] A child with either a hemiparesis or a mild extrapyramidal disorder, such as chorea, in the first few weeks after coma, may well improve considerably, although those left with a dystonic[101] or spastic quadriparesis are less likely to do well. Later onset movement disorders are often difficult to treat, although some respond to drugs.[102 103] Cognitive function may recover sufficiently for children to return to their former schools, but concentration may be poor, processing speed is often reduced, and there may be subtle disorders of executive function, all of which may make learning new material difficult. Behavioural difficulties are very common and may be very difficult for families to deal with in the context of their child's life threatening illness.

The prediction of outcome in the acute stages requires considerable experience but is not shirked by good teams. It is obviously important to discuss the prognosis with the parents, but although it is essential to spell out the truth as clearly as possible, it can be as important not to be too gloomy, unless a poor outcome is beyond reasonable doubt, as most families fear the worst instinctively. Aetiology, depth, and duration of coma have all been shown to be associated with outcome in large series,[1–3 87–92 104–106] but have relatively limited utility for the individual patient, either because discrimination between good and poor is not good enough or because by the time the picture is clear, withdrawal of life support is no longer an option. Serial EEGs can be very helpful in giving an early idea of prognosis when the patient is still on intensive care,[86 107] especially when they are combined with multimodal evoked potentials.[107] Neuroimaging may also be useful; poor outcome is usual if there is widespread low density, suggesting global ischaemia.[108] It is, however, important to realise that recovery of consciousness is expected if the lesion (however large) is focal, and in many of these cases, the residual handicap is mild.[109] Brain death may be diagnosed clinically in the majority of patients, although training is required,[110] and in certain patients (for example, infants and those with uncertain aetiology), confirmatory tests are useful.[111] On transcranial Doppler ultrasound, a direction of flow index below 0.8 for more than two hours is very suggestive of irreversible brain stem death.[112 113]

What happens next?

Early rehabilitation, by a team comprising doctors, nurses, teachers, a physiotherapist, occupational and speech therapists, and a psychologist, is often very rewarding after childhood non-traumatic coma.[114] Reintegration into school often requires time, with considerable input from team members. It is essential to test hearing early,[115 116] particularly after meningitis, and to provide appropriate aids if necessary, although long term follow up is also required, as some patients change over time.[117] Many children who have had seizures acutely do not develop epilepsy at follow up, and may be weaned from their anticonvulsants after three to six months. Patients who do develop epilepsy require close supervision of their anticonvulsant drugs, as control can make a considerable difference to cognitive and behavioural outcome. Epilepsy surgery may be very successful if there is a unilateral temporal focus.[118 119]

Even if to the physician, the child has a relatively good outcome, for the family, subtle changes in personality or social perception

have often changed their much loved "normal" child into somebody with long standing problems. This is usually utterly devastating and families need considerable long term support from team members and from the appropriate parent support groups. Much more support will be required for those with severe handicap and for the relatively small group of children left in a vegetative state,[98] as the burden of caring often overwhelms parents and siblings. There is a need for more research so that outcome, rather than survival, can be improved for this important group of children.

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Hospital-Acquired Hyponatremia: Why Are There Still Deaths?

Michael L. Moritz and Juan Carlos Ayus

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rican American. I smiled when one doctor described the Nigerian father of a patient as an African American. The Nigerian father didn't smile.

The textbooks say that a patient's race can, and should, influence the doctor's thinking about possible diagnoses. An Ashkenazic Jewish infant might have Tay-Sachs disease. A black boy might have sickle cell anemia. A Southeast Asian girl might have thalassemia. Of course, I know that Ashkenazic Jews get Tay-Sachs, but the only infant I ever saw with Tay-Sachs was a Mexican child. I didn't misdiagnose the disease because he was Mexican instead of Jewish.

Do all Hispanics have the same genetic risk for asthma? Do Mexicans and Puerto Ricans eat the same diet? What about a patient from Spain—is he Hispanic in the same way that I am?

My childhood friend Lela wasn't diagnosed with cystic fibrosis until she was 8 years old. Over the years, her doctors had described her as a "2-year-old black female with fever and cough...4-year-old black girl with another pneumonia. Lela is back." Had she been a white child, or had no visible "race" at all, she would probably have gotten the correct diagnosis and treatment much earlier. Only when she was 8 did a radiologist, who had never seen her face to face, notice her chest radiograph and ask, "Who's the kid with CF?"

An emergency room physician referred a patient to me with this history: "A 14-year-old black male from South Central Los Angeles with a positive tox screen presents with headache. He's probably in a gang." I ordered a computed tomography scan of the patient's head and discovered a large cyst that had blocked the normal flow of cerebral spinal fluid until the fluid had backed up and squashed his brain against his skull. Yes, he had a headache, and he had smoked a joint before going to the hospital.

Those are just two examples of incorrect diagnoses caused by doctors who use racial assumptions to arrive at incorrect medical conclusions. As a physician, such misdiagnoses disturb me. I am also concerned as a father. I am Mexican from California, and my wife is black from Los Angeles. Our daughter is blonde with green eyes and pale skin. I have no known white ancestors, and that kind of heritage—even if it is just a legend—would not be left out of my family's stories. In my wife's case, her mother is now tracing their family's roots back through American history; as of 1843, she has not found a single white ancestor. But my wife's relatives generally have fair skin, and I suspect that my mother-in-law will eventually find a slave owner or overseer or some other white man who is responsible for that, and for my daughter's appearance.

What concerns me is that many years from now, when she is old enough to see a doctor with neither me nor my wife present, the doctor will use what he assumes is her race to misdiagnose her: "A 19-year-old white female presents with irritability."

Here is the crux of the problem: My daughter's race can never be known. Her genetic risk for this or that disease is necessarily imprecise because she is a person, not a race.

Americans used to define anyone who had "one drop of Negro blood" as a Negro, but we now know that definition makes no sense. We learn nothing if we group together as Asian Americans a man in Seattle who was born in the far-eastern portion of the former Soviet Union, a Korean woman living in Toronto, and a child in California with maternal grandparents who immigrated from China and a father whose ancestors came to New Jersey from Europe. There are almost as many definitions of Hispanic as there are Hispanics. Do I have the same genetic risk for sickle cell anemia as a Puerto Rican, a Spaniard, or a Mayan? What about my daughter, and the millions like her in this country, whose racial and ethnic ancestry defies geography and time?

If by using a patient's ancestry in medical discourse we can narrow the range of possible diagnoses, then at least we must be careful to describe accurately the genetic, ethnic, cultural, or geographical variables involved; guessing what category a person fits in is not acceptable. And when "race" cannot possibly matter, let us omit it. What difference does it make if it is an African American or an Asian who has an earache or ingrown toenail?

Medical school professors must teach students that a Hispanic is not real. That an Asian American doesn't exist. That whites exist only in America: They are Irish in Ireland, Italian in Italy, Spaniards in Spain. That harm—real, physical harm—can come from calling a child with cystic fibrosis an African American.

Race does exist in America, alas. It's why my daughter's history here starts in slavery. It's why my Mexican face identifies me to strangers before they know I'm an educated member of the middle class. It's why nobody dares to ask for details about anybody else's identity.

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Hospital-Acquired Hyponatremia: Why Are There Still Deaths?

Intravenous fluids are probably the most frequently prescribed medication for hospitalized children. The current practice of administering hypotonic fluids to children is based largely on recommendations of Holliday and Segar,[1] made almost 50 years ago and on their assumption that the electrolyte composition of intravenous fluids should approximate the composition of human and cow milk.

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The safety of these recommendations has never been established. There have been >50 cases of death or permanent neurologic injury in children over the past decade from hospital-acquired hyponatremia resulting from the administration of hypotonic fluid.[2–5] In a recent contribution to *Pediatrics*, we introduced the concept of administering isotonic saline (0.9% sodium chloride) in maintenance fluids to prevent hospital-acquired hyponatremia.[6] In an accompanying editorial, Holliday et al[7] argued that the administration of isotonic saline is unsafe and that hyponatremia results from egregious fluid management.

In this issue of *Pediatrics*, a study by Hoorn et al[8] supports our hypothesis that the routine administration of hypotonic fluids is dangerous and can result in unnecessary deaths. In this article, Hoorn et al assess the relationship of intravenous fluid administration and the development of hospital-acquired hyponatremia. They found that 10% of children with normal serum sodium at presentation to the emergency department go on to develop hyponatremia. Of the 40 patients with hospital-acquired hyponatremia, 2 had neurologic sequelae and 1 child died from cerebral edema due to an acute fall in serum sodium from 142 to 128 mmol/L. The main contributing factor for developing hospital-acquired hyponatremia was the administration of hypotonic fluids. Since their article was submitted for publication, there have been additional reports of death and hyponatremic encephalopathy resulting from hypotonic fluid administration.[9–11]

The data in this article, in conjunction with numerous previous reports of hospital-acquired hyponatremic encephalopathy in children, indicate that the current practice of administering hypotonic maintenance intravenous fluids in children is unsafe and should be abandoned. We disagree with the authors' recommendations that hypotonic fluids should be avoided only in postoperative patients and those with low normal serum sodiums ($P_{Na} < 138$ mmol/L). Their data do not support these recommendations, because the majority of patients who developed hyponatremia in their study had a serum sodium >137 mmol/L, and the 1 death occurred in a patient with a serum sodium of 142 mmol/L. The administration of intravenous fluids should be considered an invasive procedure, and all hospitalized patients should be considered at risk for developing hyponatremia. The current practice of routinely administering hypotonic fluids is unphysiologic, given the numerous stimuli for antidiuretic hormone production in hospitalized children. How many more children will die unnecessarily? One is too many. Many tragic deaths could be avoided by the administration of isotonic saline. Although no one parenteral fluid can be administered safely to all children, isotonic saline would seem to be the safest fluid for most children. The administration of hypotonic fluid is unnecessary unless there is a free-water deficit or ongoing free-water losses.[12] Until proof exists that the administration of isotonic saline could be harmful, the routine practice of administering hypotonic fluids should be abandoned.

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More Than a Matter of Time

Few topics in graduate medical education have provoked as much comment and controversy as the recent decision of the Accreditation Council for Graduate Medical Education to limit resident "duty hours," defined as all clinical and academic activities related to the residency program. Regulations that went into effect July 1, 2003, limit duty hours to 80 hours per week, averaged over a 4-week period. In addition, residents may spend no more than 24 consecutive hours on duty, although they may remain on duty for up to 6 additional hours, for a total of 30 hours, to participate in didactic activities, transfer care of patients, conduct conti-

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Hospital-Acquired Hyponatremia: Why Are There Still Deaths?

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PAEDIATRICS

Perioperative fluid therapy in children: a survey of current prescribing practice†

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Background. Fluid therapy in children may be associated with iatrogenic hyponatraemia. We surveyed anaesthetists' current fluid prescribing practice during the perioperative period, departmental fluid protocols and awareness of the concerns of the Royal College of Paediatrics and Child Health (RCPCH) about the use of dextrose 4%/saline 0.18% in children.

Methods. Questionnaire survey of 477 consultant anaesthetists in two training areas in the UK.

Results. Responses were received from 289 anaesthetists (60.6%)—responses from the 203 consultants that anaesthetized children were analysed. A total of 67.7% did not have a local departmental policy for fluid prescription, and 58.1% were unaware of the concerns of RCPCH. A total of 60.1% of anaesthetists said that they prescribed hypotonic dextrose saline solutions in the intraoperative period and 75.2% did so in the postoperative period. Anaesthetists working in specialist paediatric hospitals were 5.1 times more likely to prescribe isotonic fluids intraoperatively than those working in district hospitals (95% CI 1.48–17.65, P=0.01), but they all prescribed hypotonic dextrose saline solutions postoperatively. The Holliday and Segar formula for maintenance fluid was quoted by 81.8% of anaesthetists; only 5.9% of anaesthetists would restrict fluids in the immediate postoperative period. Anaesthetists working in specialist paediatric hospitals were 13.2 times more likely to restrict fluids postoperatively than those working in district hospitals (95% CI 2.8–61.8, P=0.001).

Conclusions. The prescription of hypotonic dextrose saline solutions by anaesthetists may be putting children at risk from iatrogenic hyponatraemia. Departmental protocols for perioperative fluid prescription in children are uncommon. We suggest that national guidance is required.

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There have been more than 50 case reports of serious morbidity or death in previously healthy children associated with the administration on i.v. fluids and hospital-acquired hyponatraemia.[1] Deaths have been reported after both major and minor surgery in children, including tonsillectomy, orchidopexy, reduction of fractures and appendicectomy.[2–5] The postoperative course in these children is typified by progressive lethargy, headache, nausea and vomiting, followed by rapid deterioration to respiratory arrest and coma.[2] Fatal cerebral oedema occurring during surgery has also been reported.[3] Children have usually had continued administration of large volumes of hypotonic i.v. fluid in the presence of a low plasma sodium.[2 6 7] The deaths of three children believed to be as a result of hospital-acquired hyponatraemia is currently the subject of a public enquiry in Northern Ireland.[8] Central to discussion in the literature and also to the enquiry is whether too much fluid is being given, or the wrong type of fluid.[2 8–12]

†This article is accompanied by Editorial II.

There are several i.v. fluid solutions in common use in paediatric practice in the UK. Dextrose 4%/saline 0.18% and dextrose 2.5%/saline 0.45% are isotonic when administered but effectively hypotonic once the glucose has been metabolized; these are referred to as hypotonic solutions hereafter. After a report of another death, the use of dextrose 4%/saline 0.18% in children was discussed by the Medical Control Agency/Committee on Safety of Medicines and by the Joint Royal College of Paediatrics and Child Health (RCPCH)/Neonatal and Paediatric Pharmacists Standing Committee on Medicines in 2002. They concluded that the problem was an issue of clinical practice rather than product regulation and that dextrose 4%/saline 0.18% could continue to be used but should be prescribed carefully, especially to children in the postoperative period. Their concerns were communicated to the Royal College of Anaesthetists for dissemination to members. A letter was sent to College Tutors and Heads of Departments of Anaesthesia and the issue featured as a news item on the Royal College of Anaesthetists website in 2002. The letter was published in the College Bulletin in 2003.[13]

It is our practice, as specialist paediatric anaesthetists, to only use solutions in the intraoperative period that are isotonic with plasma, compound sodium lactate solution (Hartmann's solution) being our standard intraoperative maintenance fluid. This solution is used for children of all ages, with or without added dextrose as required. However, in discussions with trainee anaesthetists and Operating Department Practitioners from non-specialist institutions, it seemed that the practice of non-specialist anaesthetists may vary.

We therefore conducted a survey of a sample of anaesthetists in the UK to find out about their perioperative fluid prescriptions for children, the existence of departmental protocols, whether they were aware of the concerns from the RCPCH and whether this had affected their prescribing practice.

Methods

We surveyed all the consultant anaesthetists in two training Schools of Anaesthesia in the UK, thus including anaesthetists working in a variety of different hospital settings, both specialist and non-specialist (Bristol School of Anaesthesia and the North Western School of Anaesthesia). Names and addresses of hospitals were obtained from the Royal College of Anaesthetists College Tutors website. The departmental administrator for each hospital was contacted and a survey sent to all 477 consultant anaesthetists in the two Schools in May 2004 with a numbered postage-paid reply envelope. An independent research fellow opened the replies. Anonymity was maintained by separating the completed surveys from the envelope, noting the identifying number. Non-respondents were contacted by telephone or email after 4 weeks and then 6 weeks.

The questionnaire included details of the setting in which the anaesthetist worked, their paediatric anaesthesia training, the frequency with which they anaesthetized children, whether they had a departmental protocol for perioperative fluid administration and whether they were aware of the warning letter from the RCPCH concerning the use of dextrose 4%/saline 0.18% in children. They were asked about their choice of fluid for routine intraoperative maintenance and postoperative maintenance, what type of fluid they would prescribe as a fluid bolus in case of hypovolaemia and the volume of postoperative maintenance fluid they would routinely prescribe. There were four fluid choices: saline 0.9% or Hartmann's solution, both isotonic with plasma; dextrose 2.5%/saline 0.45% or dextrose 4%/saline 0.18% (hypotonic dextrose saline solutions); and a chance to specify 'other'. A pilot study was performed to exclude ambiguous questions. Multi-centre Research Ethics Committee approval was obtained from the South West Multi-centre Research Ethics Committee.

Statistical analyses

We used logistic regression to compare the use of isotonic fluids (saline 0.9% or Hartmann's solution) intraoperatively and postoperatively within different hospital settings and between anaesthetists with differing years of practice as a consultant, training, frequency of anaesthetizing children and knowledge/response to the RCPCH warning. Univariate odds ratios are presented and multivariable models were used to investigate whether associations found were independent. Results are presented with 95% confidence intervals (95% CI).

Results

A total of 289 replies were received giving a response rate of 60.6%. Eighty-six of these anaesthetists indicated that they never anaesthetized children and their replies were not analysed further. The results are based on the remaining 203 respondents.

One hundred and twenty-three (60.6%) respondents worked in district hospitals, 67 (33.0%) in teaching hospitals and 13 (6.4%) in specialized paediatric units. A total of 25.6% indicated that they had not received any specific training in paediatric practice, 22.7% had received training in paediatric anaesthesia for 3 months or less, 23.6% for 6–12 months and 27.6% had more than 12 months training. A total of 59.1% of respondents currently anaesthetized children occasionally, 32.0% had regular paediatric sessions amounting to <50% of their workload ('interest' in paediatric anaesthesia) and 7.9% had >50% of their workload made up of paediatric anaesthetic sessions ('specialist' paediatric anaesthetists).

Eighty-five (41.9%) respondents were aware of the RCPCH warning of November 2002, and of these only 26 had changed their practice as a result. A total of 67.7% indicated that they had no departmental policy regarding perioperative fluids in children.

Table 1 Choice of fluids from questionnaire responses of 198 who gave details of their fluid prescribing practice out of the 203 respondents who anaesthetize children. *Numbers do not add up to 100% as some respondents would give a mixture of fluids

Operative period	Fluid choice	Number of anaesthetists (%)
Intraoperative fluid maintenance*	Hypotonic dextrose saline solutions	
	Dextrose 4%/saline 0.18%	99 (50%)
	Dextrose 2.5 or 5%/saline 0.45%	31 (15.7%)
	Isotonic solutions	
	Hartmann's solution	72 (36.4%)
	Saline 0.9%	48 (24.2%)
Bolus for hypovolaemia intraoperatively	Hypotonic dextrose saline solutions	22 (11.1%)
	Isotonic solutions (saline 0.9%, Hartmann's or colloid)	161 (81.3%)
Postoperative fluid maintenance*	Hypotonic dextrose saline solutions	
	Dextrose 4%/saline 0.18%	130 (65.7%)
	Dextrose 2.5 or 5% with saline 0.45%	43 (21.7%)
	Isotonic solutions	
	Hartmann's solution	25 (12.6%)
	Saline 0.9%	24 (12.1%)

Intraoperative fluids

One hundred and ninety-eight of the 203 responders regularly anaesthetizing children provided information on the fluid they gave in the perioperative period, the remaining anaesthetists stating that they did not prescribe perioperative fluids for children. The most common choice for routine intraoperative fluid maintenance was dextrose 4%/saline 0.18% (50%) (Table 1). Other choices included Hartmann's solution (36.4%), saline 0.9% (24.2%) or dextrose 2.5 or 5% with saline 0.45% (15.7%). Several respondents indicated that they would give a mixture of fluids. Overall, 60.1% respondents indicated that they would give hypotonic dextrose saline solutions intraoperatively, 34.9% indicated that they would only give Hartmann's solution or saline 0.9%.

Isotonic fluids were the most common choice of fluid to be used as a bolus in the event of hypovolaemia (saline 0.9%, Hartmann's or colloid). A total of 11.1% respondents indicated that they would use their standard maintenance fluid (hypotonic dextrose saline) as a bolus to correct intraoperative hypovolaemia.

Postoperative fluids

The most commonly prescribed fluid for postoperative maintenance was dextrose 4%/saline 0.18% (65.7% of respondents), or dextrose 2.5 or 5% with saline 0.45% (21.7% of respondents). Isotonic fluids were not commonly prescribed (24.7% of respondents). Several respondents indicated that they would give a mixture of fluids: overall, 75.2% of respondents indicated they would only give hypotonic dextrose saline solutions postoperatively, 14.1% indicated that they would only give Hartmann's solution or saline 0.9%. No respondent indicated that they would give dextrose containing physiological saline fluids postoperatively (e.g. dextrose 5%/saline 0.9%).

In the intraoperative period (Table 2), there were significant associations between the prescribing practices of the anaesthetist and the type of hospital they worked in, the extent of their specialist training and the frequency with which they anaesthetized children. Those within specialist paediatric hospitals were 5.1 times more likely to use only isotonic solutions than the anaesthetists within district hospitals (95% CI 1.48–17.65, P=0.01). Similarly, they were more likely to use only isotonic solutions if they had more specialist training [odds ratio >12 months *vs* none 2.40 (1.08–5.33), P=0.03] or >50% of their workload was with children [cf. occasional work with children, odds ratio 3.86 (1.30–11.44), P=0.015]. After taking account of hospital type, none of the other variables was independently significant.

Use of isotonic saline solutions in the postoperative period (Table 3) was not significantly associated with hospital type, years of practice, training or experience, or with awareness of the 2002 correspondence. All anaesthetists working in specialist paediatric hospitals used hypotonic dextrose saline solutions postoperatively. However, those who were aware of the 2002 correspondence were 4.1 times more likely to use dextrose 2.5 or 5%/saline 0.45% (95% CI 1.6–10.4, P=0.003), and not to use dextrose 4%/saline 0.18%, than those not aware of the correspondence.

One hundred and ninety-four respondents provided information on how they calculated postoperative maintenance fluids. The majority (81.8%) based the calculation on the formula originally described by Holliday and Segar formula (Table 4).[9 14] Nineteen (9.3%) respondents quoted an approximate but incorrect formula. One hundred and seventy-six respondents provided information on how much of the calculated fluid volume they would prescribe postoperatively: only 5.9% would fluid restrict, 72.4% would prescribe 100% of predicted maintenance fluid and 2% would give volumes in excess of the amount calculated. Those within specialist paediatric hospitals were 13.2 times more likely to restrict postoperative fluids than those working in district hospitals (95% CI 2.8–61.8, P=0.001). Ten respondents said that the amount of fluid prescribed would depend on the type of surgery.

Discussion

The most striking finding of this survey of a sample of more than 200 anaesthetists who anaesthetize children was that >60% were using hypotonic dextrose saline solutions in the intraoperative period. The practice of specialist paediatric anaesthetists differed significantly from non-specialists for intraoperative fluid prescription (isotonic fluids significantly more likely to be used). However, specialist paediatric

Table 2 Intraoperative fluid prescription practice amongst the 198 respondents who gave details of their prescribing. Some fields do not total to 198 because of missing values. *Odds ratio given is per additional year of practice

	Only isotonic fluid given (number of anaesthetists, % total in that category)	Univariate odds ratio for the use of isotonic solutions (95% confidence interval)	*P*-value
Type of hospital			
District hospital (*n*=121)	37 (30.6%)	1	
Teaching hospital (*n*=64)	25 (39.1%)	1.46 (0.77–2.74)	0.246
Specialist paediatric hospital (*n*=13)	9 (69.2%)	5.11 (1.48–17.65)	0.01
Years of practice as a consultant anaesthetist*		1.004 (0.96–1.05)	0.87
Specialist training in paediatric anaesthesia			
None (*n*=51)	15 (29.4%)	1	
<3 months (*n*=44)	12 (27.3%)	0.9 (0.37–2.21)	0.82
6 to <12 months (*n*=46)	16 (34.8%)	1.28 (0.54–3.01)	0.57
12 months or more (*n*=56)	28 (50%)	2.40 (1.08–5.33)	0.03
Frequency of anaesthetizing children			
Occasional (less than once a month) (*n*=116)	35 (30.2%)	1	
Interest (<50% workload) (*n*=65)	25 (38.5%)	1.45 (0.76–2.74)	0.26
Specialist (>50% of workload) (*n*=16)	10 (62.5%)	3.86 (1.30–11.44)	0.015
November 2002 correspondence			
Not aware of correspondence (*n*=13)	38 (33.6%)	1	
Aware but did not change practice (*n*=56)	22 (39.3%)	1.23 (0.51–2.98)	0.64
Changed practice as a result (*n*=26)	10 (38.5%)	1.27 (0.66–2.48)	0.47

Table 3 Postoperative fluid prescription practice amongst the 198 respondents who gave details of their prescribing. Some fields do not total to 198 because of missing values. *Odds ratio given is per additional year of practice. †All of the specialist paediatric hospital staff used dextrose products and a confidence interval could therefore not be calculated

	Only isotonic fluid given (number of anaesthetists, % total in that category)	Univariate odds ratio (95% confidence interval)	*P*-value
Type of hospital			
District hospital (*n*=121)	16 (13%)	1	
Teaching hospital (*n*=64)	12 (19.4%)	1.61 (0.71–3.65)	0.258
Specialist paediatric hospital (*n*=13)	0	0†	0.999
Years of practice as a consultant anaesthetist*		0.98 (0.93–1.05)	0.58
Specialist training in paediatric anaesthesia			
None (*n*=51)	12 (23.5%)	1	
<3 months (*n*=44)	5 (11.4%)	0.42 (0.13–1.30)	0.13
6 to <12 months (*n*=46)	5 (10.6%)	0.39 (0.13–1.20)	0.10
12 months or more (*n*=56)	6 (10.9%)	0.40 (0.14–1.16)	0.09
Frequency of anaesthetizing children			
Occasional (less than once a month) (*n*=116)	16 (13.9%)	1	
Interest (<50% workload) (*n*=65)	10 (15.4%)	1.13 (0.48–2.65)	0.79
Specialist (>50% of workload) (*n*=16)	1 (6.3%)	0.41 (0.05–3.34)	0.41
November 2002 correspondence			
Not aware of correspondence (*n*=13)	17 (15.2%)	1	
Aware but did not change practice (*n*=56)	4 (6.9%)	0.41 (0.13–1.29)	0.13
Changed practice as a result (*n*=26)	6 (23.1%)	1.68 (0.59–4.78)	0.33

anaesthetists were just as likely to prescribe hypotonic dextrose saline postoperatively as non-specialists. 74% of anaesthetists prescribed full volume maintenance fluids postoperatively (or more), according to the formula described by Holliday and colleagues,[9] but specialist paediatric anaesthetists were significantly more likely to restrict fluids postoperatively. A total of 67.7% of anaesthetists did not have a local departmental policy for fluid prescription, and 58.1% were unaware of the correspondence from the RCPCH regarding iatrogenic hyponatraemia in children and the use of dextrose 4%/saline 0.18%.

There have been more than 50 case reports of neurological injury as a result of hospital-acquired hyponatraemia in children, many cases after routine surgery for the common conditions of childhood.[15] Concerns have focused on the use of hypotonic fluids for maintenance therapy, in particular, the use of dextrose 4%/saline 0.18%. These concerns have been relayed to anaesthetists via the RCPCH and Royal College of Anaesthetists.[13] Although there is some debate,[9 12] and only a few, very small randomized studies in children in the perioperative period,[15] the weight of expert opinion favours the use of isotonic fluids for maintenance therapy in children at risk of hyponatraemia.[1 7 10 11 15 16] It has been suggested that most cases of hospital-acquired hyponatraemia would be prevented by the use of isotonic saline in the perioperative period.[15]

Table 4 The Holliday and Segar formula: the average maintenance requirement for fluid[9 14]

Body weight (kg)	Average maintenance allowance for fluid	
	ml day^{-1}	ml h^{-1}
0–10	100 ml kg^{-1}	4 ml kg^{-1}
10–20	1000 ml + 50 ml kg^{-1} for each kg more than 10 kg	40 ml + 2 ml kg^{-1} for each kg more than 10 kg
20–30	1500 ml + 20 ml kg^{-1} for each kg more than 20 kg	60 ml + 1 ml kg^{-1} for each kg more than 20 kg

Table 5 Sodium content and osmolality of commonly used crystalloid solutions

Intravenous fluid	Sodium (mmol litre^{-1})	Osmolality (mosm kg^{-1} H_2O)	% electrolyte-free water
Dextrose 5%	0	252	100
Saline 0.18%/dextrose 4%	30	282	80
Saline 0.45%/dextrose 2.5%	75	293	50
Hartmann's solution	131	278	16
Dextrose 5%/Ringer's solution	130	525	16
Saline 0.9%	150	308	0
Dextrose 5%/saline 0.9%	150	560	0

Children are particularly vulnerable to the effects of acute hyponatraemia and become symptomatic at higher plasma sodium concentrations than adults. More than 50% of children with serum sodium <125 mmol litre^{-1} develop hyponatraemic encephalopathy.[15]

Dilutional hyponatraemia occurs when there is a source of electrolyte-free water and an inability to excrete free water in the kidney. The i.v. fluids include those that are isotonic with plasma or hypotonic when compared with plasma, the differences being most clearly illustrated by the relative proportions of electrolyte-free water (Table 5). The excretion of water in the kidney is controlled by vasopressin (antidiuretic hormone, ADH). Vasopressin release is controlled by osmotic stimuli so that healthy individuals are able to excrete large volumes of dilute urine in response to a water load by suppression of vasopressin release. Plasma osmolality is thus regulated within narrow limits despite wide variations in fluid intake. Vasopressin release is also controlled by a variety of non-osmotic stimuli. These include factors commonly encountered in the perioperative period—decreased extracellular fluid volume, hypovolaemia, pain, nausea, stress and drugs such as morphine, also CNS and pulmonary disturbances. These non-osmotic stimuli override the osmotic control so that the perioperative period is characterized by high concentrations of vasopressin and an inability to excrete a free water load. Administration of hypotonic fluids in this situation will lead to hyponatraemia.[2 15–17] A recent observational study in a tertiary children's hospital indicated a 10% incidence of hospital-acquired hyponatraemia in children presenting to the emergency department. Children in the hospital-acquired hyponatraemia group received significantly more electrolyte-free water in the form of hypotonic i.v. fluids.[7]

I.V. fluids are used as 'replacement' fluids to expand the extracellular fluid volume, maintain arterial pressure or replace abnormal fluid losses, and 'maintenance' fluid to replace insensible and urinary losses when oral intake is suspended.[18] The rationale for fluid administration needs to be carefully considered during the intraoperative and postoperative periods.

During the intraoperative period, the stress response to surgery causes maximal vasopressin release and urinary losses will be low. Insensible losses (sweating/respiratory water losses) will also be low—the requirement for maintenance water is low. However, there is a need to maintain arterial pressure to counter the effect of anaesthetic agents, and to replace fluid deficits because of fasting and ongoing losses associated with surgery. These deficits/losses are from the extracellular compartment and should logically be replaced by a solution approximating to the composition of extracellular fluid. Hypotonic solutions would be expected to result in a decrease in plasma sodium. Balanced salt solutions have been recommended for fluid replacement during surgery in standard paediatric texts for many years,[19 20] in line with adult practice. Of note, much of the published work concerning fluids in children in the paediatric anaesthetic literature has been concerned with the need for glucose during surgery,[21–23] rather than consideration of the sodium content of maintenance fluids. In one study, children undergoing elective minor surgery were randomized to receive either dextrose 2.5%/saline 0.43% or dextrose 5%/saline 0.33%. In both groups there was a decrease in plasma sodium, significantly greater in the group receiving more electrolyte-free water.[24] A small study in children undergoing scoliosis surgery randomized patients to receive either Hartmann's solution or hypotonic dextrose saline intraoperatively and postoperatively. Patients receiving hypotonic fluid had significantly lower plasma sodium at all time points up to 48 h, including the first postoperative sample.[17] Intraoperative dilutional hyponatraemia and fatal cerebral oedema has been reported.[3]

It was surprising that 60% of anaesthetists in this survey indicated that they give hypotonic dextrose saline intraoperatively. This practice may be related to concerns about intraoperative hypoglycaemia, especially in small infants undergoing prolonged surgery. Children requiring preoperative dextrose infusion or parenteral nutrition are especially vulnerable.[24] However, for routine surgery, these concerns may be exaggerated as fasting times have been liberalized in recent years, and even healthy infants have been shown to maintain blood glucose concentrations within normal limits during surgery, with or without added dextrose.[25] Use of dextrose 0.9 or 1% is sufficient to avoid hypoglycaemia and prevent ketosis in infants but fluids containing dextrose 4 or 5% are associated with

hyperglycaemia, which may have deleterious effects.[21 22] We think that there is no justification to use either dextrose 4%/saline 0.18% or dextrose 2–5%/saline 0.45% as maintenance during surgery as this fluid will be associated with dilutional hyponatraemia and hyperglycaemia. Intraoperative fluid should be an isotonic solution with or without low-dose dextrose (0.9–1%).[22]

A survey of intraoperative glucose administration by two specialist paediatric anaesthetic groups, the Association of Paediatric Anaesthetists (APA) and the French Language Society of Paediatric Anaesthesiologists (ADARPEF) indicated that the majority of anaesthetists use glucose containing solutions in neonates and infants, less frequently in older children.[23] Ninety-seven per cent of APA members used glucose concentrations >4% whilst only 59% of ADARPF members used glucose concentrations in this range. It was suggested that the differences were related to commercial availability; solutions containing low-dose dextrose have been available in European countries for many years.[22] It seems likely that anaesthetists in the UK (including one third of specialist paediatric anaesthetists in this survey) are using commonly available 'off the shelf' fluids containing dextrose to avoid the possibility of intraoperative hypoglycaemia (dextrose 4%/saline 0.18%, or dextrose 2.5 or 5%/saline 0.45%). We recommend that an isotonic solution containing low-dose dextrose should be available in the UK to address these concerns.

A few anaesthetists in the survey stated that they only anaesthetized children for minor surgery and therefore did not administer fluids to children. Recent studies in adults have demonstrated that preoperative i.v. fluid therapy (Hartmann's solution) decreases postoperative nausea and pain in high-risk patients undergoing gynaecological surgery,[26] and that liberal *vs* restrictive fluid administration improves recovery after laparoscopic surgery.[27] Children undergoing minor surgery such as tonsillectomy are at particularly high risk of postoperative nausea and vomiting. Administration of intraoperative fluids and withholding oral fluids for 4–6 h has been shown to reduce vomiting in children undergoing day surgery, particularly those receiving opioids.[28] A small study in children undergoing tonsillectomy showed that perioperative saline infusion was associated with significantly lower postoperative ADH concentrations compared with control children who did not receive intraoperative fluids, the difference presumed to be as a result of correction of hypovolaemia.[29] Many anaesthetists give intraoperative fluid such as Hartmann's solution, even for minor surgery in children, to ensure adequate hydration and to allow children to take oral fluids on demand postoperatively. Excessive fluids should be avoided—hyponatraemia secondary to hypervolaemia inducing desalination has been reported.[30] The I.V. fluids should only be started after minor surgery if the child is unable to tolerate oral fluids—much better to allow the child to control their own water balance postoperatively.

In the postoperative period, maintenance fluids are required to replace insensible losses, urinary losses and provide a source of dextrose when oral intake is precluded or inadequate. In addition, isotonic replacement fluids may be required for ongoing or abnormal losses (such as gastrointestinal losses). Holliday and Segar proposed a formula to estimate the maintenance need for water in parenteral fluid therapy in 1957 and this formula has been in common use to calculate maintenance postoperative fluids since then (Table 4). The requirement for water was related to the caloric expenditure in healthy children, with estimations for average insensible losses and average urinary losses.[9 14] However, they pointed out that caloric expenditure is reduced in hospitalized children and urinary losses may vary according to the clinical situations and the effects of ADH; thus maintenance fluid requirements should be restricted postoperatively. The authors suggested that the ideal maintenance fluid in children was hypotonic dextrose saline but that volume deficits should be replaced with a 20–40 ml kg^{-1} bolus of isotonic saline.[9]

The syndrome of inappropriate ADH (SIADH) was described in 1957; production of inappropriately concentrated urine in the presence of hyponatraemia and low plasma osmolality (in the absence of hypovolaemia and with normal renal and adrenal function).[31] Experts have emphasized the dangers of administration of hypotonic saline solution in the presence of elevated ADH concentrations in a child who is acutely unwell, either advocating only isotonic solutions (with dextrose) in the postoperative patient,[15] or avoiding hypotonic solutions if the plasma sodium decreases below 138 mmol $litre^{-1}$.[2 7] Holliday argued against the use of isotonic saline for routine maintenance but highlighted the importance of correcting volume deficits with isotonic fluid boluses. He suggested that isotonic maintenance fluids would be associated with hypernatraemia or fluid overload and possible desalination as a consequence. However, in the presence of elevated ADH concentrations, Holliday and others recommend fluid restriction to 50% of maintenance requirements.[9–12] Specialist paediatric anaesthetists in this study appear to follow this pattern, and restrict fluids postoperatively, although we did not obtain information as to the degree of fluid restriction. Many of the cases of iatrogenic hyponatraemia have been associated with administration of hypotonic fluids in excess of maintenance values recommended by Holliday and Segar.[2]

It is surprising that in this era of evidence-based medicine there have been very few studies to compare the use of isotonic or hypotonic maintenance fluids in children in the postoperative period. The majority of anaesthetists in this survey would prescribe hypotonic dextrose saline postoperatively and all anaesthetists working in specialist paediatric hospitals indicated that they would prescribe hypotonic dextrose saline postoperatively. Some authors have suggested that only isotonic fluids should be used postoperatively and have questioned the ethics of

conducting a randomized study of hypotonic *vs* isotonic maintenance fluids in postoperative children.[11] Our survey shows that a carefully conducted trial may be justified, as the exclusive use of isotonic saline in the postoperative period would be a major change in current practice, including by specialist paediatric anaesthetists. A recent randomized study has investigated replacement fluids in children with gastroenteritis. This showed that saline 0.9% was preferable to saline 0.45% and protected against hyponatraemia. Urinary sodium excretion increased appropriately in normonatraemic children given saline 0.9%, and hypernatraemia did not occur.[32]

There are clearly limitations in a questionnaire survey of practice, but we feel that a 60% response rate and the opinions of more than 200 consultants who anaesthetize children allow useful conclusions to be drawn. There were very few specialist anaesthetists who contributed to the survey, but we estimate that this is an accurate reflection of the ratio of specialist to non-specialist paediatric anaesthetist in the UK, and in general, the views expressed by the specialist anaesthetists reflects that of expert opinion. Respondents to a questionnaire survey may not be able to qualify their responses—but we were looking at routine practice, not exceptions to practice such as the neonate or child in the intensive care setting. Although most major surgery in children will be in the specialist centres, the majority of children undergoing routine minor surgery are operated on outside specialist centres,[33] and thus the prescribing practices of non-specialists are important to the general welfare of children. It is important to reiterate that many of the case reports of iatrogenic hyponatraemia occur in previously healthy children undergoing routine surgery.

A quarter of the anaesthetists indicated that they did not have any specific training in paediatric anaesthesia—the survey included clinicians who had been in practice for more than 20 yr, before the trend for centralization of paediatric services and modular training in paediatric anaesthesia. Worryingly, clinicians appeared to have low awareness of the concerns of the RCPCH concerning iatrogenic hyponatraemia and departmental policies for fluid management in children were uncommon. Unfortunately, communication between colleges does not appear to be an effective way of notifying risk to clinicians. Guidance is available in the BNF for children[34] and from the Department of Health in Northern Ireland,[35] the latter as a consequence of a number of high profile deaths in the province. Others have suggested that dextrose 4%/saline 0.18% should be labelled to highlight the risk of iatrogenic hyponatraemia.[36] It would seem sensible to address these issues with national guidance through an organization such as the National Patient Safety Authority.

In summary, this survey has indicated that the current prescribing practices of large numbers of anaesthetists may be putting children at risk from iatrogenic hyponatraemia, namely the use of hypotonic fluid intraoperatively and prescription of full volume hypotonic maintenance fluid postoperatively. Departmental policies are uncommon, as is awareness of the correspondence from the RCPCH regarding iatrogenic hyponatraemia in children and the use of dextrose 4%/saline 0.18%.

Simple measures could be taken to reduce the risk of death from iatrogenic hyponatraemia. We recommend that clinicians consider whether fluids are being given for 'replacement', to expand the extracellular fluid compartment, or as 'maintenance'. All replacement fluids should be with isotonic solutions; this includes all intraoperative fluids. Maintenance i.v. fluids should only be administered postoperatively if the child is unable to take fluids by mouth. If i.v. fluids are administered, especially if hypotonic fluids are given, fluid balance and electrolytes must be monitored. Fluid restriction should be considered in a child who is acutely unwell (elevated ADH). Children who are hyponatraemic should only receive isotonic fluids.

Appendix

Perioperative fluid survey in paediatric practice

Please tick the box next to your answer and write in more detail where asked. Please be as specific as you can. All responses are strictly confidential. Thank you for taking time to complete this questionnaire.

1. Do you work in a Specialist paediatric hospital? ☐
   Teaching hospital? ☐
   District general hospital? ☐
2. How many years have you been practicing as a consultant anaesthetist?
3. Have you had any specialist training in paediatric anaesthesia?
4. If you answered yes to Q3 please give details.....
5. How frequently do you anaesthetize children, elective or emergency cases?
   Never ☐
   Less than once a month ☐
   Once a month ☐
   Once a fortnight ☐
   More than once per week ☐

(If you answer 'never' please stop here and return survey)

6. How many elective paediatric sessions (or equivalent) do you anaesthetize for each week?
   No regular sessions ☐
   One to two sessions per week ☐
   Three or more sessions per week ☐
7. Do you have a standard practice for **perioperative** fluid management in your department?
   YES ☐ NO ☐ DON'T KNOW ☐
   Comments.....
   .....
8. What **type** of maintenance fluid would you give to a child requiring fluid **intraoperatively, assuming no rapid volume losses?**

Saline 0.9% ☐ Saline 0.18%/dextrose 4% ☐
Hartmann's solution ☐
Saline 0.45%/dextrose 2.5% ☐
Other (please specify).....

9. If you considered a bolus of fluid was required **intraoperatively**, what **type** of fluid would you give? For example, saline 0.9%
For a bolus of 10 ml kg^{-1} .....
For a bolus of 20 ml kg^{-1} .....
For a bolus of 30 ml kg^{-1} .....

10. What **type** of maintenance fluid would you give to a child requiring fluid postoperatively, assuming **no major ongoing volume losses?**
Saline 0.9% ☐ Saline 0.18%/dextrose 4% ☐
Hartmann's solution ☐
Saline 0.45%/dextrose 2.5% ☐
Other (please specify).....

11a. What **formula** would you use to calculate the postoperative fluid volume requirements? For example, 100 ml kg^{-1} per day

11b. What **proportion** of this calculated volume would you prescribe?
Full daily requirements ☐ i.e. 100% of the calculated volume
Above daily requirements ☐ please specify percentage.....%
Below daily requirements ☐ please specify percentage.....%

12. Have you changed your practice with respect to the correspondence from the Royal College of Paediatrics and Child Health/Royal College of Anaesthetists of December 2002?
YES ☐ NO ☐ Not aware of correspondence ☐
If yes, what is the nature of the change?.....

13. Please add any further comments about this issue.....
.....

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