Witness Statement Ref. No. 292/2

NAME OF CHILD: RAYCHEL FERGUSON (LUCY CRAWFORD)

Name: Peter Crean

Title: Doctor

Present position and institution:

Consultant Paediatric Anaesthetist, Royal Belfast Hospital for Sick Children

Previous position and institution: Consultant in Paediatric Anaesthesia and Intensive Care
[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 2000 - September 2012]

In N Ireland:

Chairman of the Paediatric Anaesthetic Group in N Ireland 1999-2004

Member of N Ireland Working Group on Hyponatraemia in Children 2001-2002

Member of the Human Organs Enquire Implementation Sub-group on the guidance to the HPSS and consent 2002-2004.

Member of the Human Organs Enquiry Implementation Sub-group on Public Information and Communication 2003.

Northern Ireland Regional Paediatric Fluid Therapy Working Group 2006.

Member of 'Pediatric Surgery Working Group Phase 1', Department of Health, N Ireland. 2008

Member of the Paediatric ENT Surgery Group, Department of Health, N Ireland, 2008-9

Guideline and Audit Implementation Network (GAIN). Member of Guideline

Development Group on Hyponatraemia in Adults. 2008-9

National:

Member of Working Group on Paediatric Anaesthesia and Emergency Care in District General Hospitals 2004-6.

"Care of the acutely ill or injured child: a team response" published 2006

Member of External Reference Group, Children's Hospital Service Pilot Improvement

Review, Healthcare Commission. 2004-2005

Member of the Children's Surgical Forum, Royal College of Surgeons, England 2005-07

President of the Association of Paediatric Anaesthetists of Great Britain and Ireland 2005-7

'Joint statement on the provision of general paediatric surgery provision in the District General Hospital', 2006. Member of the working group and co-signatory as President of the APA.

Member of working group revising 'Children's Surgery: a first class service'. 2006-07. 'Surgery for children – delivering a first class service' published July 2007

NICE Guideline Development Group on Sedation in Children 2008 - 2010

NCEPOD Advisor 2009 - 2011 on deaths following surgery in children. 'Are We There Yet?' Published October 2011.

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:

Ref:	Date:	
WS-292/1	07-11-2012	Statement to the Inquiry

IMPORTANT INSTRUCTIONS FOR ANSWERING:

Please attach additional sheets if more space is required. Please identify clearly any document to which you refer or rely upon for your answer. If the document has an Inquiry reference number, e.g. Ref: 049-001-001 which is 'Chart No.1 Old Notes', then please provide that number.

If the document does not have an Inquiry reference number, then please provide a copy of the document attached to your statement.

(1) Please confirm that you were the consultant under whose care Lucy Crawford was admitted to PICU?
Lucy was admitted under the care of Dr Seamus McKaigue.

(2) Who was in charge of Lucy's care when she was a patient in PICU?
She was jointly managed by the consultant anaesthetists in PICU and Dr Hanrahan, consultant paediatric neurologist.

(3) Arising out of your answer to question 2 of WS-292/1, please clarify the arrangements which were in place at RBHSC in April 2000 for receiving patient notes by fax from another hospital and for delivering them to relevant clinicians in PICU? Were the notes sent directly to an office within PICU, and did a member of admin staff place the notes on the patient's chart?
I am not sure that there were specific arrangements other than that faxes were sent to the fax machine in the Secretary's office, PICU. It is likely that these would have been brought to the attention of the clinicians, on arrival. It is also likely that a member of the administrative staff would have filed these notes in the patient's chart.

(4) Arising out of your answer to question 8(b) of WS-292/1, please address the following matters:

(a) List the potential causes of the acute neurological deterioration which you were aware of at the time of Lucy's death.
I now have no specific recollection of the potential causes of the acute neurological deterioration that I was aware of at the time of Lucy's death but they are likely to have been the list of differential diagnoses entered into the chart by Dr Hanrahan (061-018-063).

(b) You have indicated that Dr. Hanrahan took the lead with investigating these potential causes of the acute neurological deterioration. Insofar as you are aware, how was this matter investigated?
From the notes it would appear various blood tests were carried out as part of the investigation. A CT scan was also performed.

(c) You have indicated that you remember having concerns about Lucy's fluid management at the time. What do you think those concerns were?
Although I have difficulty in remembering what my specific concerns were at this far removed from that time, I anticipate that my concerns would have been in relation to the lack of a fluid prescription with appropriate calculations documented, the

administration of volumes of hypotonic fluid in excess of maintenance requirements (my calculated maintenance fluid requirement for Lucy would have been 40 ml/hr), and the lack of clarity around the volume of fluid infused, as recorded in the fluid balance sheet.

(d) **You have said that it is difficult to separate your memory of having contemporaneous concerns regarding Lucy's fluid management, with what you have come to know subsequently.**

Explain what it is that you came to know subsequently about her fluid management which you did not know at the time of her death.

What I came to know subsequently is that Lucy received 400 ml of 1/5 normal saline over a four hour period.

(e) **You have said that you knew at the time of Lucy's death that acutely developing hyponatraemia could cause neurological decompensation.**

In your evidence to the Inquest you acknowledged that the sodium level in Lucy's case "dropped 10 to 127 within a short period of time" [Ref: 013-021-074].

Did Lucy suffer acutely developing hyponatraemia?

I used this term to differentiate acutely developing hyponatraemia from hyponatraemia which develops chronically. With Lucy, the hyponatraemia that developed was an acute event.

(5) **Arising out of your answer to question 8(c) of WS-292/1, you have explained the developments which led you to conclude that Lucy's care in the Erne Hospital should be further reviewed (in 2003), particularly the use of hypotonic fluids.**

Please explain what consideration was given at the time of Lucy's death to the concern that the administration of hypotonic fluids could have caused dilutional hyponatraemia to develop. If consideration was given to this issue, what conclusions were reached?

If you or your colleagues did not give consideration to this issue at the time of her death, please explain why this was not done.

I am unable to recollect what my considerations were at the time of Lucy's death. However, I would like to reflect on what I consider my knowledge of dilutional hyponatraemia to have been at the time of Lucy's admission.

Hyponatraemia occurs commonly in children. Children admitted to hospital can have sodium levels in the high 120's; these levels are not uncommon to see and do not necessarily cause harm.

At the time of Lucy's admission to PICU, I knew of the 1992 Arieff paper in the BMJ and his editorial in the journal Paediatric Anaesthesia in 1998. I also knew that Adam Strain died of acute dilutional hyponatraemia. So it would be fair to say that I was aware of the problems associated with the infusion of hypotonic fluids in children and the potential for dilutional hyponatraemia to develop. At the time of Lucy's admission, Adam was the only child that I was aware of who had died from this condition in the Children's Hospital. His lowest sodium level was 119. I am now aware of Claire's admission in 1996 and the details of her care.

In the Arieff paper in the BMJ in 1992 the majority of children had sodium levels of 120 or less, the highest level being 123. Also, I note that the sodium levels in relation to both Claire and Raychel were 121 and 118 respectively, when they became acutely unwell.

Since Lucy's death there has been a great deal of debate regarding dilutional hyponatraemia in the medical literature. It became clear that, although the majority of children who developed neurological symptoms due to dilutional hyponatraemia had sodium levels of around 120 or less, this problem could also be seen in children with higher sodium levels. Moritz and Ayus reviewed this subject in their articles in 2005 (Pediatr Nephrology 20: 1687-1700) and 2010 (Pediatr Nephrology 25: 1225-1238). They highlighted the fact that the average sodium level in children who developed hyponatraemic encephalopathy was 120. Moritz and Ayus also reviewed cases in the literature and, in their 2005 article, presented reports from 1992 to 2004 of more than 50 children with this condition. Only a small number of these children developed hyponatraemic encephalopathy with sodium levels of above 125. Of those who did develop this condition, the only case report in their review to have appeared in the literature before Lucy's death had been published in 1997 (Pediatrics 99: 625-630). In their 2010 review, nine additional reports in the literature from 2005 to 2009 were presented; none of these had sodium levels above 125.

With the knowledge available to me at the time of Lucy's admission to PICU, I do not think I would have considered a sodium level of 127 to have been low enough for me to have formed the opinion that dilutional hyponatraemia had caused Lucy's acute collapse.

(6) In your answer to question 8(c) of WS-292/1, you have said that the Coroner asked you to review Lucy's chart.

Please describe the steps that you took as part of this review, the conclusions which you reached, and the factors that you took into account when reaching these conclusions.

I reviewed Lucy's chart at the request of the Coroner.

Having been involved in the care of Raychel Ferguson in 2001, and with the knowledge gained as a member of the N Ireland Working Group on Hyponatraemia in Children 2001-2002, I believe I was reminded of distinct similarities in the management and subsequent collapse of both Lucy and Raychel. I believe the issue that caused me concern was Lucy's fluid management in the Erne Hospital and I was unable to exclude this as a potential cause of her acute deterioration. I expressed my concern to the Coroner.

(7) Also at 8(c) you have cited a reference for a document as 006-061. Please check this reference and provide a copy of the document to which you refer.
006-011-295/6

(8) Arising out of your answer to question 8(d) of WS-292/1, please clarify whether you discussed the possible causes of Lucy's death with clinical colleagues at the time of her death?
I have no recollection of this.

If this issue was discussed, who was it that it was discussed with and what conclusions were reached?

If you did not discuss the possible causes of Lucy's death with clinical colleagues at the time of her death, please explain why not?

As I am unable to recall whether it had been discussed or not I am unable to answer this question.

(9) In your answer to question 13 of WS-292/1 you have said that the writing of a discharge letter would normally be undertaken by the consultant paediatrician or consultant surgeon in charge of the case. You have noted that an Inpatient/Outpatient Advice Note was completed. Arising out of that answer please address the following matters:

(a) Who was the clinician in charge of Lucy's case?
Dr Hanrahan

(b) Are you suggesting that the Inpatient/Outpatient Advice Note was in essence the equivalent of a discharge letter?
I am not suggesting this, however, a copy of the Advice Note is usually sent to the GP.

(10) In your answer to question 15 of WS292/1 you have said that although Adverse Incident Reporting was introduced in 2000, it was not at that time embedded in practice at the date of Lucy's death.

Arising out of that answer please address the following matters:

(a) How are you aware that it took two years from 2000 to "roll out" adverse incident reporting across the organisation?
Adverse incident reporting was introduced into the Royal Hospitals, including RBHSC, sometime in 2000, however, I am uncertain if this was in place at the time of Lucy's death. With its introduction, incident books would have been in place in the wards and could have been completed if an adverse incident occurred. This was a new policy that created a cultural change and would have taken time to have become fully embedded in practice. It is likely that this may have taken up to two years to have evolved.

(b) During those two years, what steps were clinicians expected to take if they became aware of an adverse incident? Comment specifically on what was done in the case of Lucy?
The expectation would have been that an incident form would have been completed if an adverse incident occurred.

As the cause of Lucy's death was unexplained the Coroner was informed.

(c) What was the function of adverse incident reporting?
Incident and near miss reporting could be used as a means of identifying the risks to which patients, staff and members of the public may be exposed.

This provided

- staff an opportunity to participate in and effect changes in practice and procedures

- information to allow effective evaluation and monitoring of patient care and procedures
- formal documentation to assist in the management of complaints, claims and investigations by statutory bodies

(See attached Trust Policy - Adverse Incident Reporting May 2000)

(d) **If an adverse incident occurred after the system of reporting was embedded, explain the process by which such an incident was reported, who was responsible for reporting it and what steps could be taken after an incident was reported?**

When an adverse incident occurred, a record of what happened was completed. All staff were responsible for reporting adverse incidents. Each incident required a review of what happened, why it occurred, and steps taken to resolve the incident to prevent recurrence. (See attached document - 'Procedure for Adverse Incident Reporting Mar2000')

(e) **What were the criteria which determined whether an incident would be regarded as 'adverse' so that it would have to be reported?**

An adverse event was defined as any unexpected or untoward event that has a detrimental effect on an individual patient, member of staff or public. This included near miss reporting.

(f) **Applying this criteria, would you have expected Lucy's death to have been reported in accordance with the adverse incident reporting arrangements, had they been embedded at the time?**

In April 2000 Lucy's death was unexplained. However, I do not think an unexplained death such as hers would necessarily have triggered an incident form to have been completed.

Today, an incident form would be completed for all unexplained deaths.

(11) Arising out of your answers to question 17 of WS-292/1, can you clarify who would have been responsible for presenting the circumstances surrounding the death of Lucy Crawford to the mortality section of the RBHSC Audit meeting on the 10 August 2000?

I believe it would have been Dr Hanrahan.

(12) Do you recognise the document at Ref: 061-005-012? If so, please explain what it refers to.

I do not recognise this document.

THIS STATEMENT IS TRUE TO THE BEST OF MY KNOWLEDGE AND BELIEF

Signed: [signature] **Dated:** 23 January 2013

Pediatr Nephrol (2005) 20:1687–1700
DOI 10.1007/s00467-005-1933-6

REVIEW

Michael L. Moritz · J. Carlos Ayus

Preventing neurological complications from dysnatremias in children

Received: 30 November 2004 / Revised: 28 February 2005 / Accepted: 2 March 2005 / Published online: 4 August 2005

Abstract Dysnatremias are among the most common electrolyte abnormalities encountered in hospitalized patients. In most cases, a dysnatremia results from improper fluid management. Dysnatremias can occasionally result in death or permanent neurological damage, a tragic complication that is usually preventable. In this manuscript, we discuss the epidemiology, pathogenesis and prevention and treatment of dysnatremias in children. We report on over 50 patients who have suffered death or neurological injury from hospital-acquired hyponatremia. The main factor contributing to hyponatremic encephalopathy in children is the routine use of hypotonic fluids in patients who have an impaired ability to excrete free-water, due to such causes as the postoperative state, volume depletion and pulmonary and central nervous system diseases. The appropriate use of 0.9% sodium chloride in parenteral fluids would likely prevent most cases of hospital-acquired hyponatremic encephalopathy. We report on 15 prospective studies in over 500 surgical patients that demonstrate that normal saline effectively prevents postoperative hyponatremia, and hypotonic fluids consistently result in a fall in serum sodium. Hyponatremic encephalopathy is a medical emergency that should be treated with hypertonic saline, and should never be managed with fluid restriction alone. Hospital-acquired hypernatremia occurs in patients who have restricted access to fluids in combination with ongoing free-water losses. Hypernatremia could largely be prevented by providing adequate free-water to patients who have ongoing free-water losses or when mild hypernatremia (Na>145 mE/l) develops. A group at high-risk for neurological damage from hypernatremia in the outpatient setting is that of the breastfed infant. Breastfed infants must be monitored closely for insufficient lactation and receive lactation support. Judicious use of infant formula supplementation may be called for until problems with lactation can be corrected.

Keywords Hypernatremia · Hyponatremia · Cerebral edema · Myelinolysis · Fluid therapy

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Introduction

Dysnatremias are a common electrolyte abnormality in children in both the inpatient and outpatient settings. A serious complication of dysnatremias is brain injury. Brain injury is an especially tragic complication because in most cases it is a result of improper fluid management or inappropriate therapy. While there are numerous causes of dysnatremias in children, there are a few settings where the neurological sequelae are most common, and therefore could be prevented. Our goals are to point out the dangers of dysnatremias [1], outline the most important measures that can be instituted for prevention of dysnatremias [2] and discuss how to recognize and treat symptomatic dysnatremias [3].

Prevention and treatment of hyponatremic encephalopathy

Pathogenesis of hyponatremia

Hyponatremia, defined as a serum sodium <135 mEq/l, is a common disorder that occurs in both the inpatient and outpatient settings. The body's primary defense against developing hyponatremia is the kidney's ability to generate a dilute urine and excrete free-water. Rarely is excess ingestion of free-water alone the cause of hypona-

Table 1 Disorders in impaired renal water excretion

1. Effective circulating volume depletion
   a. Gastrointestinal losses: vomiting, diarrhea
   b. Skin losses: cystic fibrosis
   c. Renal losses: salt wasting nephropathy, diuretics, cerebral salt wa sting, hypoaldosteronism
   d. Edemetous states: heart failure, cirrhosis, nephrosis, hypoalbuminemia
   e. Decreased peripheral vascular resistance: sepsis, hypothyroid
2. Thiazide diuretics
3. Renal failure
   a. Acute
   b. Chronic
4. Non-hypovolemic states of ADH excess
   a. Central nervous system disturbances: meningitis, encephalitis, brain tumors, head injury
   b. Pulmonary disease: pneumonia, asthma, bronchiolitis
   c. Cancer
   d. Medications: cytoxan, vincristine, morphine, SSRIs, carbamazepine
   e. Nausea, emesis, pain, stress
   f. Postoperative state
   g. Cortisol deficiency

tremia, as an adult with normal renal function can typically excrete over 15 l of free-water per day. It is also rare to develop hyponatremia from excess urinary sodium losses in the absence of free-water ingestion. In order for hyponatremia to develop it typically requires a relative excess of free-water in conjunction with an underlying condition that impairs the kidney's ability to excrete free-water (Table 1). Renal water handling is primarily under the control of argenine vasopressin (AVP), which is produced in the hypothalamus and released from the posterior pituitary. AVP release impairs water diuresis by increasing the permeability to water in the collecting tubule. There are osmotic, hemodynamic and non-hemodynamic stimuli for AVP release. In most cases of hyponatremia there is a stimulus for vasopressin production that results in impaired free-water excretion. The body will attempt to preserve the extracellular volume at the expense of the serum sodium; therefore, a hemodynamic stimulus for AVP production will override any inhibitory hypoosmolar effect of hyponatremia [1]. There are numerous stimuli for AVP production (Table 1) that occur in hospitalized patients that can make virtually any hospitalized patient at risk for hyponatremia.

Epidemiology of hyponatremic encephalopathy

Moderate hyponatremia, defined as a serum sodium <130 mEq/l, occurs in over 1% of hospitalized children [2]. A major consequence of hyponatremia is the influx of water into the intracellular space resulting in cellular swelling, which can lead to cerebral edema and encephalopathy. Hyponatremic encephalopathy is a serious complication of hyponatremia that can result in death or permanent neurological injury. The true incidence of hyponatremic encephalopathy in hospitalized children is unknown as large prospective studies have not been done. A critical review of retrospective studies in children reveals that encephalopathy is a common complication of hyponatremia in both the inpatient and outpatient setting.

Over 50% of children with a serum sodium <125 mEq/l will develop hyponatremic encephalopathy (Table 2). Hospital-acquired hyponatremic encephalopathy is most often seen in association with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) or in the postoperative period [3, 4, 5]. SIADH is caused by elevated ADH secretion in the absence of an osmotic or hypovolemic stimulus [6]. SIADH can occur because of a variety of illnesses, but most often occurs because of central nervous system (CNS) disorders, pulmonary disorders, malignancies and medications. Hyponatremia from SIADH is particularly dangerous in children with CNS injury such as encephalitis, as mild hyponatremia (sodium <135 mEq/l) has been associated with neurological deterioration and herniation [7, 8]. A common contributing factor in hospitalized children with SIADH who develop hyponatremic encephalopathy is the administration of hypotonic intravenous fluids.

Postoperative hyponatremia is a serious problem in children; the majority of deaths resulting from hyponatremic encephalopathy have been reported in healthy children following routine surgical procedures [3, 4, 9]. Postoperative hyponatremia is caused by a combination of nonosmotic stumuli for ADH release, such as subclinical volume depletion, pain, nausea, stress, narcotics edema-forming conditions and the administration of hypotonic fluids. It is estimated that the mortality directly attributable to hyponatremic encephalopathy in children with postoperative hyponatremia (sodium <129 mEq/l) is 8% [3]. The most important factors resulting in postoperative hyponatremic encephalopathy are the failure to recognize the compromised ability of the patient to maintain free-water and the administration of hypotonic fluids.

Hyponatremic encephalopathy is also a concern in the outpatient setting [10, 11, 12]. It is primarily attributable to oral water intoxication in infants. Overall, 10% of children less than 2 years of age presenting to the emergency department with seizures are found to have hyponatremic encephalopathy (sodium <126 mEq/l) [10]. Of

Table 2 Incidence of hyponatremic encephalopathy in hospitalized children

Author	Reference no.	Inclusion criteria serum Na (mEq/l)	Incidence of hyponatremic encephalopathy (%)
Wattad et al. 1992	[2]	<125	53
Sarnaik et al. 1991	[5]	<125	60
Halberthal et al. 2001	[4]	<130 in 48 h	78

those children with no other recognized cause of seizures, the incidence of hyponatremic encephalopathy is 56% for children less than 2 years of age and 70% for children less than 6 months of age. Over 50% of patients with febrile seizures have hyponatremia, with the degree of hyponatremia being predictive of a repeat seizure during the same febrile period [13].

Prevention of hospital acquired-hyponatremic encephalopathy (avoid hypotonic maintenance parenteral fluids)

There is substantial evidence demonstrating that the routine administration of hypotonic fluids, as initially proposed by Holliday and Segar almost 50 years ago [14], can result in fatal hyponatremic encephalopathy [3, 4, 7, 8, 15, 16]. Holliday and Segar's initial recommendations primarily addressed the water needs for children in parenteral fluid therapy. The maintenance need for electrolytes was discussed in only one paragraph, where they surmised that the electrolyte composition of intravenous fluids should approximate that of human and cow milk. Holliday and Segar's paper was published in 1957 [14], the same year that Schwartz et al. described the first report of SIADH [17]. Since that time it has become apparent that there are numerous non-osmotic stimuli for ADH production in hospitalized children (Table 1), making the routine use of hypotonic fluids an unphysiologic and potentially dangerous therapy. In a recent report we pointed out the dangers of the routine use of hypotonic saline in maintenance parenteral fluids [9], as it has resulted in over 50 cases of death or neurological injury in children (Table 3). Other investigators, including Holliday, have since concurred that the administration of hypotonic parenteral fluids can result in dangerous hyponatremia [15, 16, 18, 19, 20, 21, 22]. Hanna et al. reported the incidence of hyponatremia to be 33% in infants transferred to the ICU with bronchiolitis, with 4% suffering hyponatremic encephalopathy. Hoorn et al. reported the incidence of acute hospital-acquired hyponatremia to be 10% in children presenting to the emergency department with a normal serum sodium. Five percent of these children went on to develop neurological sequelae. Hypotonic fluids were the main contributing factor for developing hyponatremia in both studies. In Table 3 we report on 3 additional children in western Pennsylvania who have suffered death or permanent neurological injury from hospital-acquired hyponatremia related to the administration of hypotonic fluids. A 3-week-old child was treated in a fashion that was recently recommended by Holliday [22], with a bolus of 0.9% NaCl followed by maintenance hypotonic fluids, while the other 2 received excessive hypotonic fluids as bolus therapy.

We have argued that administering isotonic saline in maintenance parental fluids is the most physiologic approach to preventing hospital-acquired hyponatremia [9]. Children requiring parenteral fluids should be considered to be at risk for developing hyponatremia, as the majority will have a hemodynamic or non-hemodynamic stimulus for ADH production (Table 1), resulting in impaired free-water excretion. The administration of hypotonic fluids to a patient with impaired free-water excretion resulting from ADH excess will predictably result in hyponatremia. Prospective studies in over 500 postoperative children and adults have demonstrated that isotonic saline effectively prevents the development of hyponatremia and that hypotonic fluids consistently result in hyponatremia (Table 4). There is no rationale for administering hypotonic fluids unless there is a free-water deficit, hypernatremia or ongoing free-water losses, from such causes as diarrhea or a renal concentrating defect (Table 5). In fluid overload states such as nephrosis, cirrhosis, congestive heart failure or glomerulonephritis, both sodium and fluid restriction are of paramount importance to prevent hyponatremia and fluid overload. Even in fluid overload states, an argument could be made to use 0.9% sodium chloride at a greatly restricted volume, as excess free-water could contribute to hyponatremia.

Some have advocated fluid restriction as the preferred therapy to prevent hospital-acquired hyponatremia [21, 23]. While this approach may be effective, it is unphysiologic and potentially dangerous as it could perpetuate a state of subclinical volume depletion [24]. Most children who are admitted to the hospital in need of parenteral fluid, such as with pulmonary infections, central nervous system infection or gastrointestinal disease, have some degree of volume depletion (Table 5). In many cases this will be subclinical and difficult to assess on physical examination [25]. Fluid restriction would perpetuate such a state of volume depletion, which could be harmful. The administration of maintenance isotonic saline would both serve as an excellent volume expander and eliminate unnecessary free-water administration.

Concerns have been raised that the administration of isotonic saline in maintenance parenteral fluids could result in additional complications not seen with hypotonic fluids, such as hypernatremia, acidosis or fluid overload [26]. Isotonic saline should not result in hypernatremia unless there is a renal concentrating defect, significant extrarenal renal free-water losses or prolonged fluid restriction (Table 5). In general, the kidney is able to generate free-water by excreting hypertonic urine, therefore providing sufficient free-water to replace insensible losses. It is also a misconception that the high chloride concentration in isotonic saline could result in acidosis. The pH of 0.9% sodium chloride in 5% dextrose in water is the same as that of 5% dextrose in water, pH 4. The acidosis reported with isotonic saline is a dilutional phenomenon resulting from rapid expansion of the extracellular volume [27]. This would not be expected with maintenance fluids. Isotonic saline should also not cause fluid overload, unless there is an impaired ability to excrete sodium, such as in an edematous state or acute glomerulonephritis (Table 5). In this situation fluid restriction would be required.

Excessive fluid administration is a risk factor for developing hyponatremia [15]. Many of the neurological

Table 3 Neurological injury due to hospital-acquired hyponatremia in children receiving hypotonic fluids. *D_5* 5% dextrose; *ND* not disclosed

Author	Age (years)	Setting	Intravenous fluid	Sodium value (mEq/l)	Complication
Duke [99]	0.15	Meningitis	0.18% NaCl	137 to 131	Cerebral edema, dilated pupil
Jenkins [19]	ND	ND	Hypotonic	<130	2 deaths
Jackson [100]	1.5	Influenza	D_5 water	120	Death, cerebral edema
	3	Meningitis	D_5 water	128	Death, cerebral edema
Keating [12]	3	Dehydration	D_5 water	133 to 114	Death, cerebral edema
	2	Hip surgery	Hypotonic	112	Death, cerebral edema
Gregorio [101]	4	Gastroenteritis	D_5 0.45% NaCl	136 to 118	Respiratory arrest, seizure, cerebral demyelination
Hoorn [15]	ND	ND	Hypotonic	142–128	Death, cerebral edema, cardiac arrest
Arieff [3]	3.5	Tonsillitis	Hypotonic	139 to 114	Quadriplegia
	5	Tonsillectomy		141 to 123	Death
	4	Tonsillectomy		139 to 115	Death
	15	Tonsillectomy		141 to 101	Death
	3.5	Tonsillectomy		138 to 121	Death
	12	Fracture setting		137 to 120	Mental retardation
	4	Fracture setting		139 to 118	Death
	3	Tonsillectomy		137 to 113	Death
	1.5	VP shunt		137 to 114	Vegetative
	9	Fracture setting		137 to 120	Vegetative
	15	Fracture setting		138 to 102	Vegetative
	4	Tonsillectomy		138 to 107	Death
	2	Orchiopexy		138 to 116	Death
	6	Nasal packing		138 to 119	Death
	12	Appendectomy		137 to 123	Death
	12	Pneumonia		134 to 116	Vegetative
Halberthal [4]	ND	ND	Hypotonic	<130	5 deaths, 1 neurological damage
Playfor [20]	1	Gastroenteritis	D_4 0.18% NaCl	137 to 120	Death, respiratory arrest, cerebral edema
Armour [102]	4	Renal transplant	Hypotonic	139 to 119	Death, respiratory arrest, cerebral edema
Eldredge [103]	5	Cerebral palsy, slit ventricles, heal cord repair	D_5 0.225% NaCl	127	Death, cardio-respiratory arrest
	8	Slit ventricles, spinal surgery	D_5 0.45% NaCl	129	Insertion of subdural bolt with eventual recovery
Paut [104]	ND	Postoperative	Hypotonic	118	Death
McRae [105]	10	Tonsillectomy	Hypotonic	115	Death, pulmonary edema, cerebral edema
	6	Tonsillectomy	D_5 0.2% NaCl	122	Death, respiratory arrest, cerebral edema
Hughes [106]	3	Spinal surgery	D_4 0.18% NaCl	118	Death, respiratory arrest, cerebral edema
Cowley [107]	ND	Spinal surgery	Hypotonic	118	Death, respiratory arrest, cerebral edema
McJunkin [7]	<15	LaCrosse encephalitis	D_5 0.45% NaCl	138 to 134	13 with neurological deterioration: 3 cerbral herniation, 6 status epilepticus, 1 coma
Moritz	0.06	Dehydration	D_5 0.225% NaCl	141 to 119	Cardio-respiratory arrest, cerebral edema, neurological devastation
	5	Tympanoplasty	Hypotonic	123	Cardiac arrest, cerebral edema, neurological devastation
	0.9	Gastroenteritis	D_5 0.3% NaCl	136 to 126	Death, cardio-respiratory arrest, cerebral edema

complications from hospital-acquired hyponatremia resulted from fluid administration well in excess of that recommended by Holliday and Segar (Table 3) [14]. Hyponatremia could develop even from the excess administration of isotonic saline if there is impaired urine dilution with a fixed urine osmolality of $\geq$ 500 mOsm/kg/H_2O. This is of particular concern in the neurosurgical patient, who is at risk for cerebral salt wasting. It has been reported in postoperative neurosurgical patients that isotonic saline may not be sufficient prophylaxis against hyponatremia (Table 4) [28]. The administration of parenteral fluids should be considered an invasive procedure requiring close monitoring.

Clinical manifestation of hyponatremic encephalopathy

The symptoms of hyponatremic encephalopathy are quite variable among individuals with the only consistent symptoms being headache, nausea, vomiting, emesis and weakness [29]. As cerebral edema worsens, patients then develop behavioral changes and impaired response to verbal and tactile stimuli. Advanced symptoms are signs of cerebral herniation and include seizures, respiratory arrest, neurogenic pulmonary edema, dilated pupils and decorticate posturing. Arrhythmias have also been reported [30]. Not all patients have the usual progression in symptoms, and advanced symptoms can present suddenly.

Table 4 Relationship between postoperative fluid composition and change in serum sodium. 0.9% NaCl=[Na] 154 mEq/l. *RL* Ringer's lactate [Na] 131 mEq/l. *Hartmann's 131* Hartmann' solution [Na] 131 mEq/l. *Plasmalyte 148* [Na] 148 mEq/l. *NA* not available

Age group	Authors	Surgical procedure	*n*	Fluid composition	Preop. Na mEq/l	Postop. Na mEq/l
Adult	Steele 1997 [108]	Gynecological	22	RL intraop., 0.9% NaCl postop.	140±0.5	136±0.5
Adult	Bomberger 1986 [109]	Aortic	102	RL	138±0.7	137.9±0.7
			80	0.45% NaCl	138±0.5	133.5±1.1
Adult	Scheingraber 1997 [27]	Gynecological	12	0.9% NaCl	140±1.8	141.9±2
			12	RL	140±1.8	137.8±1.4
Adult	Tindall 1981 [110]	Vagotomy	6	0.9% NaCl	140±0.86	139.4±0.78
			6	D_5W	140±0.86	131.8±0.7
Adult	Stillstrom 1987 [111]	Cholecystectomy	9	RL	141±0.8	138±0.7
			9	0.45% NaCl	140±0.7	137±6.7
			9	D_5W	138±0.6	134±1.1
Adult	McFarlane 1994 [112]	Hepatobiliary	15	0.9% NaCl	141±3.1	142±1.3
			15	Plasmalyte 148	139±3.4	139.6±1.8
Adult	Wilkes 2001 [113]	Elective (general)	24	0.9% NaCl	141±3.1	142±1.3
			23	Hartmann's 131	137.8±2.7	137±2.7
Adult	Waters 2001 [114]	Aortic	33	0.9% NaCl	141±3	143±4
			33	RL	142±3	139±3
Adult	Takil 2002 [115]	Spinal	15	0.9% NaCl	140±2	143±3
			15	RL	142±3	136±4
Adult	Boldt 2002 [116]	Abdominal (cancer)	21	0.9% NaCl	134±3	135±4
			21	RL	136±2	133±3
Pediatric	Burrows 1983 [117]	Spinal	4	RL	138±2.7	135±1.9
			20	0.45 or 0.22% NaCl	138±1.7	131±2.8
Pediatric	Brazel 1996 [118]	Spinal	5	Hartmann's 131	141±2.8	138.1±1.9
			7	0.3 or 0.18% NaCl	139.5±1.9	129.5±3.7
Pediatric	Judd 1990 [119]	Tonsillectomy	6	0.9% NaCl	140*	141.2±1.2
Pediatric	Levine 1999 [28]	Cranial vault	10	0.9% NaCl	NA	132.3±2.45
Pediatric	Cowley 1988 [107]	Spinal	8	0.45% NaCl	140.6±1.1	132.7±1.6

* Standard deviation not available

Risk factors for developing hyponatremic encephalopathy

Age

Children under 16 years of age are at increased risk for developing hyponatremic encephalopathy due to their relatively larger brain to intracranial volume ratio as compared with adults [3, 31]. A child's brain reaches adult size by 6 years of age, whereas the skull does not reach adult size until 16 years of age [32, 33]. Consequently, children have less room available in their rigid skulls for brain expansion and are likely to develop brain herniation from hyponatremia at higher serum sodium concentrations than adults. The average serum sodium in children with hyponatremic encephalopathy is 120 mEq/l [5, 34], while that in adults is 111 mEq/l [5, 34, 35, 36]. Animal data also suggest that prepubertal children may have impaired ability to regulate brain cell volume due to diminished cellular sodium extrusion related to lower testosterone levels [31]. Children will have a high morbidity from symptomatic hyponatremia unless appropriate therapy is instituted early [3, 4, 7, 8, 9].

Hypoxia

Hypoxia is a major risk factor for the development of hyponatremic encephalopathy. The occurrence of a hypoxic event such as respiratory insufficiency is a major factor militating against survival without permanent brain damage in patients with hyponatremia [37]. The combination of systemic hypoxia and hyponatremia is more deleterious than is either factor alone because hypoxia impairs the ability of the brain to adapt to hyponatremia, leading to a vicious cycle of worsening hyponatremic encephalopathy [38]: hyponatremia in turn leads to a decrement of both cerebral blood flow and arterial oxygen content [39]. Patients with symptomatic hyponatremia can develop hypoxia by one of at least two different mechanisms: neurogenic pulmonary edema or hypercapnic respiratory failure [39]. Respiratory failure can be of very sudden onset in patients with symptomatic hyponatremia [37, 40]. Prompt recognition of neurogenic pulmonary edema and treatment with hypertonic saline are imperative, as failure to treat is almost always fatal [40]. The majority of neurological morbidity seen in patients with hyponatremia has occurred in patients who have had a respiratory arrest as a feature of hyponatremic encephalopathy [3, 35, 36, 37, 41]. Recent data have shown that

Table 5 Adjusting maintenance parenteral fluids for disease states

Isotonic saline (0.9% sodium chloride)	Fluid restriction	Hypotonic fluids
Effective circulating volume depletion ● Dehydration ● Salt wasting nephropathy ○ Bartter syndrome ○ Adrenal insufficiency ● Decreased peripheral vascular resistance ○ Sepsis ○ Hypothyroid **Non-hypovolemic states of ADH excess** ● Central nervous system disturbances ○ Meningitis ○ Encephalitis ○ Brain tumors ○ Head injury ● Pulmonary disease ○ Pneumonia ○ Asthma ○ Bronchiolitis ● Cancer ● Medications ○ Cytoxan ○ Vincristine ○ Narcotics ○ Carbamazepine ○ SSRIs ● Nausea, emesis, pain, stress ● Postoperative state ● Glucocorticoid deficiency	**Edematous states** ● Congestive heart failure ● Nephrosis ● Cirrhosis ● Hypoalbuminemia **Renal insufficiency** ● Acute glomerulonephritis ● Acute tubular necrosis ● End stage renal disease	**Free-water deficit** ● Hypernatremia **Renal concentrating defect** ● Congenital nephrogenic diabetes insibidus ● Sickle cell disease ● Obstructive uropathy ● Reflux nephropathy ● Renal dysplasia ● Nephronophthisis ● Tubulo-interstitial nephritis **Extra-renal free-water losses** ● Burns ● Premature neonates ● Fever ● Infectious diarrhea

hypoxia is the strongest predictor of mortality in patients with symptomatic hyponatremia [42].

Therapy of hyponatremic encephalopathy

In general, correction with hypertonic saline is unnecessary and potentially harmful if there are no neurological manifestations of hyponatremia. Symptomatic hyponatremia, on the other hand, is a medical emergency. Once signs of encephalopathy are identified prompt treatment is required in a monitored setting, even before imaging studies are performed. The airway should be secured; endotrachial intubation and mechanical ventilation may be necessary. Symptomatic hyponatremia should never be treated with fluid restriction alone. If symptomatic hyponatremia is recognized and treated promptly, prior to developing a hypoxic event, the neurological outcome is good [5, 36, 41, 43].

Patients with symptomatic hyponatremia should be treated with hypertonic saline (3%, 513 mEq/l) using an infusion pump. The rate of infusion should raise the plasma sodium by about 1 mEq/l per hour until either (1) the patient is alert and seizure free, (2) the plasma sodium has increased by 20 mEq/l or (3) a serum sodium of about 125–130 mEq/l has been achieved, whichever occurs first [5, 41, 43, 44, 45, 46, 47, 48, 49]. If the patient is actively seizing or with impending respiratory arrest the serum sodium can be raised by as much as 4–8 mEq/l in the first hour or until the seizure activity ceases [48]. Prospective studies have demonstrated that the optimal rate of correction of symptomatic hyponatremia is approximately 15–20 mEq in 48 h, as patients with correction of hyponatremia in this range have a much lower mortality and an improved neurological outcome compare to those with a correction of less than 10 mEq in 48 h [36, 41]. Assuming that total body water comprises 50% of total body weight, 1 ml/kg of three percent sodium chloride will raise the plasma sodium by about 1 mEq/l. In some cases furosemide can also be used to prevent pulmonary congestion and to increase the rate of serum sodium correction.

Risk factors for developing cerebral demyelination

Cerebral demyelination is a rare complication that has been associated with symptomatic hyponatremia [50]. Animal data have demonstrated that correction of hyponatremia by >25 mEq/l in 24 h is associated with cerebral demyelination [51, 52]. This has resulted in a mistaken belief that a rapid rate of correction is likely to result in cerebral demyelination [53]. In fact, studies have shown that the rate of correction has little to do with the development of cerebral demyelinating lesions, and that lesions seen in hyponatremic patients are more closely associated with other comorbid factors or the magnitude of correc-

Table 6 Risk factors for developing cerebral demyelination in hyponatremic patients

Risk factor
1. Development of hypernatremia
2. Increase in serum sodium exceeding 25 mmol/l in 48 h
3. Hypoxemia
4. Severe liver disease
5. Alcoholism
6. Cancer
7. Severe burns
8. Malnutrition
9. Hypokalemia
10. Diabetes
11. Renal failure

tion in serum sodium (Table Table 6) [41, 52, 54, 55, 56]. In one prospective study it was observed that hyponatremic patients who develop demyelinating lesions had either (1) been made hypernatremic inadvertently, (2) had their plasma sodium levels corrected by greater then 25 mmol/l in 48 h, (3) suffered a hypoxic event or (4) had severe liver disease [41]. Some data have suggested that azotemia may decrease the risk of developing cerebral demyelination [57].

When symptomatic cerebral demyelination does follow the correction of hyponatremia, it typically follows a biphasic pattern. There is initially clinical improvement of the hyponatremic encephalopathy associated with correction of the serum sodium, which is followed by neurological deterioration 2 to 7 days later [37, 58]. Cerebral demyelination can be both pontine and extrapontine. Classic features of pontine demyelination include mutism, dysarthria, spastic quadriplegia, pseudobulbar palsy, a pseudocoma with a "locked-in stare" and ataxia [59]. The clinical features of extrapontine lesions are more varied, including behavior changes and movement disorders. Radiographic features of cerebral demyelination typically lag behind the clinical symptomatology [60]. Cerebral demyelination is best diagnosed on MRI approximately 14 days following correction [61]. The classic radiographic findings on MRI are symmetrical lesions that are hypointense on T1-weighted images and hyperintense on T2-weighted images [62]. Some data suggest that cerebral demyelination can be detected earlier on MRI with diffusion-weighted imaging [60].

The outcome of cerebral demyelination in not as severe as was previously believed [63]. Cerebral demyelination has been found to be an incidental finding on neuroimaging and at autopsy in patients with chronic illnesses [64]. In most reported cases of cerebral demyelination attributed to dysnatremias, long-term follow-up has demonstrated improvement in neurological symptoms and regression of radiographic findings [58, 63]. The primary cause of brain damage in patients with hyponatremia is not cerebral demyelination, but cerebral edema and herniation [35, 36, 65]. Most brain damage occurs in untreated patients and is not a consequence of therapy; therefore, patients with symptomatic hyponatremia need prompt therapy.

Patients with hyponatremia due to water intoxication, diarrheal dehydration, thiazide diuretics or dDAVP are at high risk for overcorrection of hyponatremia and require extreme care and monitoring. In these illnesses, once volume depletion is corrected or when the offending medication is discontinued, there will be a reversal of the urine osmolality from concentrated to dilute, resulting in a free-water diuresis with a potentially rapid overcorrection of hyponatremia if saline-containing fluids are administered. This will not typically occur in SIADH, as this is a saline-resistant hyponatremia. To prevent an overcorrection of hyponatremia, hypotonic fluids and possibly even dDAVP may have to be given. It has also been demonstrated that where there is an overcorrection of hyponatremia, a therapeutic re-lowering can ameliorate the symptoms of cerebral demyelination [66]. Children with symptomatic hyponatremia should have close neurological follow up for the first few months as neurological sequelae can be subtle and a delayed phenomenon.

Case illustrations (beware of formulas)

It is tempting to rely on formulas to aid in correcting the serum sodium in dysnatremias. Unfortunately, these equations either assume that the body is a closed system [67] or require the assistance of a programmable calculator [68]. Equations that assume the body is a closed system and do not account for renal water handling are physiologically incorrect and can result in either an overcorrection or an under-correction in serum sodium. There are two groups of patients in which closed system equations that do not take into account urinary losses will result in a significant miscalculation. The first group is patients who will have a natriuresis associated with volume expansion. Examples would be SIADH, postoperative states and cerebral salt wasting. In this situation, closed-system equations will underestimate the change in serum sodium. The second group is patients who will have a reverse urine osmolality or free-water diuresis following volume expansion with saline. Examples would be patients with psychogenic polydypsia, discontinuation of dDAVP, water intoxication (primarily in infants) and diarrheal dehydration. These patients require special care, as saline administration can result in a brisk free-water diuresis and, consequently, overcorrection of hyponatremia, which leads to brain damage. It must be emphasized that any formula that does not take into account the urinary response will be inaccurate and should only be used as a rough guide to aid in therapy. Below are illustrative cases of hyponatremic encephalopathy.

Case 1: SIADH

A 10-kg 1-year-old child is admitted to the hospital for severe bronchiolitis with hypoxia and tachypnea. The child is placed on parenteral fluids with 0.225% sodium chloride in 5% dextrose in water at a rate of 40 ml/h.

Twenty-four hours following admission the child suffers a generalized tonic-clonic seizure. Biochemistries reveal serum sodium 122 mEq/l, potassium 4 mEq/l, blood urea nitrogen 2 mg/dl, creatinine 0.3 mg/dl, osmolality 238 mOsm/kg H_20, urine osmolality 400 mOsm/kg H_20 and urine sodium plus potassium concentration 90 mEq/l.

This child has developed hyponatremic encephalopathy due to the administration of hypotonic fluid in the setting of SIADH associated with pulmonary disease. An acute elevation in serum sodium is required as the child is actively seizing. Assuming that total body water is 50% of body weight, 1 ml/kg of 3% sodium chloride will increase the serum sodium by 1 mEq/l in a closed system. Over 1 h, 5 ml/kg (50 ml) of 3% sodium chloride is administered to increase the serum sodium by 5 mEq/l. Following the infusion the serum sodium is 126 mEq/l, slightly lower than predicted due to urinary sodium losses, and seizures have abated. The patient is then fluid restricted with 20 ml/h of 0.9% sodium chloride in 10% dextrose in water and slowly corrects over the next 48 h.

Case 2: cerebral salt wasting

A 10-kg 1-year-old child is admitted for surgical removal of an astrocytoma. Postoperatively, this child is placed on 0.9% sodium chloride in 5% dextrose in water at a rate of 40 ml/h as prophylaxis against hyponatremia. Twenty-four hours following surgery, the child's level of alertness has decreased, and is having dry heaves. The child is in negative fluid balance by 400 ml with a 0.5 kg weight loss and is tachycardic. Serum biochemistries reveal serum sodium 123 mEq/l, potassium 4 mEq, blood urea nitrogen 10 mEq/l, creatinine 0.3 mg/dl, osmolality 240 mOsm/kg H_20, urine osmolality 600 mOsm/kg H_20 and urine sodium plus potassium concentration 250 mEq/l.

Despite prophylaxis with normal saline, this child developed severe hyponatremia from a hypertonic urine from cerebral salt wasting. The child is symptomatic, but is not actively seizing and without respiratory compromise; therefore, a rate of correction of 1 mEq/l/h would be a safe initial rate of correction until neurological symptoms improve. The child is given two 200 ml boluses of 0.9% sodium chloride to correct the volume deficit. Continuous parenteral fluids consist of 30 ml/h of 3% sodium chloride (513 mEq/l) and 30 ml/h of 0.9% sodium chloride in 10% dextrose in water. This would result in an average sodium concentration for both fluids combined of 333 mEq/l. Assuming ongoing urinary losses of 60 ml/h, the serum sodium would correct by about 1 mEq/h, far less than the 3 mEq/h predicted by a closed-system equation. The rate of infusion of saline and 3% sodium chloride would be further adjusted to match urine output and control the rate of correction of serum sodium.

Case 3: thiazide diuretic

A 3-kg 5-month-old infant, born pre-term, is evaluated in the emergency department for lethargy and irritability. The child is on hydrochlorothiazide for bronchopulmonary dysplasia and is fed Neocate infant formula. Lab work is obtained and the child is bolused with 20 ml/kg of 0.9% sodium chloride. Biochemistries reveal serum sodium 105 mEq/l, potassium 3.2 mEq/l, total CO2 30 mEq/l, blood urea nitrogen 8 mg/dl, creatinine 0.2 mg/dl and osmolality 205 mOsm/kg H_20. Urine biochemistries are subsequently obtained, which reveal urine sodium less than 10 mEq/l, potassium 15 mEq/l and urine osmolality 100 mOsm/kg H_20. Repeat serum chemistries reveal serum sodium of 111 mEq/l, and the child is more alert.

Infant formula has a low electrolyte concentration and can result in profound hyponatremia when infants are on a thiazide diuretic, which causes urinary electrolyte losses in excess of intake. The child is mildly symptomatic because this is a chronic hyponatremia developing over weeks. Following volume expansion with 0.9% sodium chloride, the child is experiencing a free-water diuresis and may develop a rapid and extreme correction if 0.9 or 3% sodium chloride is administered. The safest approach would be to administer 0.225% sodium chloride with 30 mEq/l potassium chloride at a rate of 12 ml/h and discontinue the diuretic. As soon as the child is more alert, parenteral fluid should be discontinued and oral feeds resumed. The correction in serum sodium should be limited to no more than 25 mEq/48 h. If the rate of correction is too rapid the fluid sodium composition may need to be changed to 0.115% sodium chloride or therapeutic relowering with the addition of dDAVP may be necessary.

Case 4: dDAVP administration

A 50-kg, 16-year-old female with a history of cleft lip and palate is to undergo maxillofacial surgery. Preoperative evaluation reveals Von Willebrand's disease. Perioperatively, she is administered dDAVP and postoperatively 0.45% sodium chloride in 5% dextrose at a rate of 90 ml/h and dDAVP. She begins to complain of a severe headache, followed by nausea, which does not respond to antiemetics. The intravenous fluid rate is then increased to 140 ml/h. She then develops confusion and combativeness, followed by obtundation and urinary incontinence. A CAT scan reveals cerebral edema. Serum biochemistries are then obtained that reveal sodium 118 mEq/l, potassium 4 mEq/l, blood urea nitrogen 4 mg/dl, creatinine 0.7 mg/dl, osmolality 233 mOsm/kg H_20, urine osmolality 500 mOsm/kg H_20 and urine sodium plus potassium 200 mEq/l.

This adolescent has hyponatremia from the exogenous administration of dDAVP in conjunction with hypotonic fluids. She is symptomatic with cerebral edema and could have an impending respiratory arrest. Over 1 h, 8 ml/kg (400 ml) of 3% sodium chloride are administered, with an

anticipated rise of no more than 8 mEq/l as she is excreting a hypertonic urine. Following the infusion of hypertonic saline her serum sodium is 123 mEq/l, and her symptoms have much improved. The dDAVP is continued, as withdrawal would result in excessive correction from a free-water diuresis. To complete a slow correction, 0.9% sodium chloride in 10% dextrose in water is administered at 40 ml/h.

Prevention of hypernatremia (morbidity and mortality)

Pathogenesis

Hypernatremia is defined as a serum sodium greater than 145 mEq/l. The body has two defenses to protect against developing hypernatremia: the ability to produce a concentrated urine and a powerful thirst mechanism. ADH release occurs when the plasma osmolality exceeds 275–280 mosmol/kg/H_2O and results in a maximally concentrated urine when the plasma osmolality exceeds 290–295 mosmol/kg/H_2O. Thirst is the body's second line of defense, but provides the ultimate protection against hypernatremia. If the thirst mechanism is intact and there is unrestricted access to free-water, it is rare for someone to develop sustained hypernatremia from either excess sodium ingestion or a renal concentrating defect.

Epidemiology of hypernatremia

Hypernatremia is primarily a hospital-acquired condition occurring in children of all ages who have restricted access to fluids. Moderate hypernatremia, serum sodium greater than 150 mEq/l, occurs in over 1% of hospitalized patients [69]. The majority of children with hypernatremia are debilitated by an acute or chronic illness, have neurological impairment, are critically ill or are born premature [69]. Hypernatremia in the intensive care setting is a particularly common problem as patients are usually either intubated or moribund, and frequently are fluid restricted, receive large amounts of sodium as blood products and/or have renal concentrating defects from diuretics or renal dysfunction [69]. The majority of hypernatremia results from the failure to administer sufficient free-water to patients who are unable to care for themselves and have restricted access to fluids [69].

A group at high risk for developing hypernatremia in the outpatient setting is that of the breastfed infant [70]. Breastfeeding-associated hypernatremia is on the rise [71]. Over 15% of mother-infant diads have difficulty establishing successful lactation during the 1st week post partum [72]. This is of particular concern for the primaparous infant. Reasons for lactation failure are multifactorial, including physiological factors that require 3–5 days for optimal breast milk production and mechanical factors resulting in a poor latch or insufficient time on the breast to stimulate optimal milk production [70]. Hypernatremic dehydration results from a combination of insufficient lactation and increased breast milk sodium concentration [73]. Hypernatremic dehydration can be difficult to diagnose as hypernatremic infants will have a better preserved extracellular volume [74]. Diarrheal dehydration is also an important cause of hypernatremia in the outpatient setting, but is much less common than previously reported, presumably due to the advent of low solute infant formulas and the increased use and availability of oral rehydration solutions.

Morbidity and mortality

Anatomical changes and brain adaptation

Hypernatremia results in an efflux of fluid from the intracellular space to the extracellular space to maintain osmotic equilibrium. This leads to transient cerebral dehydration with cell shrinkage. Brain cell volume can decrease by as much as 10–15% acutely, but then quickly adapts [44]. Within 1 h the brain can significantly increase its intracellular content of sodium and potassium, amino acids and unmeasured organic substances called idiogenic osmoles. Within 1 week the brain regains approximately 98% of its water content. If severe hypernatremia develops acutely, the brain may not be able to increase its intracellular solute sufficiently to preserve its volume, and the resulting cellular shrinkage can cause structural changes. Cerebral dehydration from hypernatremia can result in a physical separation of the brain from the meninges, leading to a rupture of the delicate bridging veins and intracranial or intracerebral hemorrhages [75, 76] and venous sinus thrombosis leading to infarction [77]. Acute hypernatremia has also been shown to cause cerebral demyelinating lesions in both animals and humans [44, 78, 79, 80]. Patients with hepatic encephalopathy are at the highest risk for developing demyelinating lesions [81].

Clinical manifestations and mortality

Children with hypernatremia are usually agitated and irritable, but can progress to lethargy, listlessness and coma [82]. On neurological examination they frequently have increased tone, nuchal rigidity and brisk reflexes. Myoclonus, asterixis and chorea can be present; tonic-clonic and absence seizures have been described. Hyperglycemia is a particularly common consequence of hypernatremia in children. Severe hypernatremia can also result in rhabdomyolysis [83]. While earlier reports showed that hypocalcemia was associated with hypernatremia, this has not been found in more recent literature [69].

Hypernatremia is associated with a mortality rate of 15% in children; this rate is estimated to be 15 times higher than the age-matched mortality in hospitalized children without hypernatremia [69]. The high mortality is unexplained. Most of the deaths are not directly related

to central nervous system pathology and appear to be independent of the severity of hypernatremia. Recent studies have noted that patients who develop hypernatremia following hospitalization and patients with a delay in treatment have the highest mortality [69, 84, 85]. Approximately 40% of the deaths in children with hypernatremia occurred while patients were still hypernatremic [69].

A subset of patients that have a particularly high morbidity and mortality are infants with hypernatremic dehydration [86] and patients with end-stage liver disease [81, 87]. Most of the current deaths or neurological damage directly attributable to hypernatremia have resulted from vascular thrombosis and intracranial hemorrhages in infants with hypernatremic dehydration in general [88], and breastfeeding-associated hypernatremia in particular [89]. Patients with end-stage liver disease are particularly susceptible to additional brain injury from hypernatremia and at high risk for developing cerebral demyelination [50, 78].

Prevention of hypernatremia

Pediatricians face new challenges in preventing hypernatremia in children. Hypernatremia is primarily a hospital-acquired condition that affects children with restricted access to fluids in combination with ongoing free-water losses via the urine or gastrointestinal tract. Large amounts of sodium-containing fluids such as blood products or sodium bicarbonate administration can also be contributing factors. Mild hypernatremia (serum Na >145 mEq/l) is the first sign that inadequate free-water is being administered to maintain body water homeostasis and that fluid therapy must be adjusted. Increased free-water will need to be administered by either increasing the volume of fluid administration and/or decreasing the sodium content in perenteral fluids. This will largely depend on the volume and composition of ongoing losses. Mild hypernatremia should not be considered a benign occurrence, and should be a signal to the physician to reassess fluid therapy. All patients who have restricted access to enteral fluids should have fluid balance and serum biochemistries monitored daily.

In order to prevent hypernatremia in the breast fed infant, it is imperative that nursing mothers be provided adequate lactation support and that the American Academy of Pediatrics guidelines be followed, including a weight check within 3 to 5 days of age [90]. Breastfed infants with greater than 7% weight loss or jaundice should be evaluated for hypernatremic dehydration, and aggressive lactation support should be provided. Infant formula should be used judiciously to support the infant until problems with lactation are corrected.

Treatment of hypernatremia

The cornerstone of the management of hypernatremia is providing adequate free-water to correct the serum sodium. Hypernatremia is frequently accompanied by volume depletion; therefore fluid resuscitation with normal saline or colloid should be instituted prior to correcting the free-water deficit. Following initial volume expansion, the composition of parenteral fluid therapy largely depends on the etiology of the hypernatremia. Patients with sodium overload or a renal concentrating defect will require a more hypotonic fluid than patients with volume depletion and intact renal concentrating ability. Oral hydration should be instituted as soon as it can be safely tolerated. Plasma electrolytes should be checked every 2 h until the patient is neurologically stable.

A simple way of estimating the minimum amount of fluid necessary to correct the serum sodium is by the following equation, which assumes the total body water to be 50% of body weight:

$$\text{Free} - \text{water deficit (ml)} = 4\ \text{ml} \times \text{lean body weight (kg)} \times [\text{Desired change in serum Na mEq/L}] \quad (1)$$

Larger amounts of fluid will be required depending on the fluid composition. To correct a 3-l free-water deficit, approximately 4 l of 0.225% sodium chloride in water or 6 l of 0.45% sodium chloride in water would be required, as they contain approximately 75 and 50% free-water, respectively. The calculated deficit does not account for insensible losses or ongoing urinary or gastrointestinal losses. Maintenance fluids, which include replacement of urine volume with hypotonic fluids, are given in addition to the deficit replacement.

The rate of correction of hypernatremia is largely dependent on the severity of the hypernatremia and the etiology. Because of the brain's relative inability to extrude unmeasured organic substances called idiogenic osmoles, rapid correction of hypernatremia can lead to cerebral edema [44]. Surprisingly, there are few reports of death or serious neurological morbidity in humans resulting from rapid correction of hypernatremia. In the case of mass accidental salt poisoning, there are reports of infants with serum sodium greater than 200 mEq/l who were corrected by as much as 120 mEq in 24 h without adverse neurological sequelae [91]. While there are no definitive studies that document the optimal rate of correction that can be undertaken without developing cerebral edema, empirical data have shown that unless symptoms of hypernatremic encephalopathy are present, a rate of correction not exceeding 1 mEq/h or 15 mEq/24 h is reasonable [92, 93, 94]. In severe hypernatremia (>170 mEq/l), serum sodium should not be corrected to below 150 mEq/l in the first 48–72 h [93]. Seizures occurring during the correction of hypernatremia are not uncommon in children, and may be a sign of cerebral edema [95, 96, 97]. They can usually be managed by slowing the rate of correction or by giving hypertonic saline to increase the serum sodium a few milliequiva-

lents. Seizures are usually self-limited and not a sign of long-term neurological sequelae [92, 93]. Patients with acute hypernatremia, corrected by the oral route, can tolerate a more rapid rate of correction with a much lower incidence of seizures [95, 98]. The type of therapy is largely dependent on the etiology of the hypernatremia and should be tailored to the pathophysiologic events of each patient.

Case illustrations

Case 1: gastroenteritis

A 7-kg, 6-month-old child with vomiting and diarrhea for 3 days presents to the emergency department and appears 10% dehydrated. Biochemistries reveal serum sodium 156 mEq/l, potassium 5.6 mEq/l, total carbon dioxide 12 mEq/l, blood urea nitrogen 40 mg/dl and creatinine 0.8 mg/dl. Urine biochemistries reveal sodium <5 mEq/l, potassium 20 mEq/l and osmolality 800 mOsm/kg/H_2O.

This child has an estimated volume deficit of approximately 700 ml with a composition of approximately 0.9% NaCl (154 mEq/l). In order to correct the serum sodium by 10 mEq/l in 24 h, a minimum of 280 ml of electrolyte free-water (4 ml×7 kg×10 mEq/l=280 ml) would have to be administered. The child should initially be bolused with 50 ml/kg (350 ml) of normal saline. This would leave the remaining deficit of 350 ml of isotonic fluid to be corrected over 24 h. Maintenance fluids of 700 ml for the next 24 h in addition to 350 ml of deficit therapy would result in a total volume of 1,050 ml or 44 ml/h; 0.45% NaCl in 5% dextrose in water would provide 575 ml of free-water and 575 ml of isotonic fluid. This would be adequate therapy to correct both the volume deficit and free-water deficit and to provide for urinary losses.

Case 2: nephrogenic diabetes insipidus

A 20-kg, 5-year-old child with nephrogenic diabetes insipidus has contracted a stomach flu and has not been able to keep down fluids for the past 12 h. He presents to the emergency department markedly dehydrated with sunken eyes, doughy skin and documented 2-kg weight loss. Serum biochemistries reveal serum sodium 172 mEq/l, potassium 4.5 mEq/l, blood urea nitrogen 20 mg/dl and creatinine 0.6 mg/dl. Urine biochemistries reveal sodium 25 mEq/l, potassium 15 mEq/l and osmolality 100 mOsm/kg/H_2O. On further history his mother reports that the child usually drinks between 4 and 5 l of fluids a day.

This child's fluid deficit is primarily free-water. To correct the serum sodium back to normal value of 140 mEq/l would require approximately 2.5 l of free-water (4 ml×20 kg×30 mEq/l). Unfortunately, bolus therapy with free-water will result in too rapid a fall in serum sodium. The child will initially have to be bolused with 40 ml/kg of 0.9 NaCl in order to restore the extracellular volume. Further fluid therapy would require maintenance fluids, which for him are about 4,000 ml/day plus free-water deficit to lower the serum sodium by 10 mEq/24 h, which is 800 ml (4 ml×20 kg×10 mEq/l) to give total 24 h volume of 4,800 ml or 200 ml/h. In order to lower the sodium the composition of fluid will need to be more hypotonic than his urine; 0.115% NaCl (Na 19 mEq/l) in 2.5% dextrose in water with 10 mEq of KCl per liter would be appropriate to start with. A higher dextrose concentration could result in hyperglycemia given the high rate of fluid administration. Biochemistries would have to be monitored hourly initially as response to therapy can be unpredictable based on the urinary response. As soon as the child can keep down oral fluids, parenteral fluids should be tapered off.

References

1. Dunn FL, Brennan TJ, Nelson AE, Robertson GL (1973) The role of blood osmolality and volume in regulating vasopressin secretion in the rat. J Clin Invest 52:3212–3219
2. Wattad A, Chiang ML, Hill LL (1992) Hyponatremia in hospitalized children. Clin Pediatr (Phila) 31:153–157
3. Arieff AI, Ayus JC, Fraser CL (1992) Hyponatraemia and death or permanent brain damage in healthy children. BMJ 304:1218–1222
4. Halberthal M, Halperin ML, Bohn D (2001) Lesson of the week: acute hyponatraemia in children admitted to hospital: retrospective analysis of factors contributing to its development and resolution. BMJ 322:780–782
5. Sarnaik AP, Meert K, Hackbarth R, Fleischmann L (1991) Management of hyponatremic seizures in children with hypertonic saline: a safe and effective strategy. Crit Care Med 19:758–762
6. Bartter FC, Schwartz WB (1967) The syndrome of inappropriate secretion of antidiuretic hormone. Am J Med 42:790–806
7. McJunkin JE, de los Reyes EC, Irazuzta JE, Caceres MJ, Khan RR, Minnich LL, et al (2001) La Crosse encephalitis in children. N Engl J Med 344:801–807
8. Moritz ML, Ayus JC (2001) La Crosse encephalitis in children. N Engl J Med 345:148–149
9. Moritz ML, Ayus JC (2003) Prevention of hospital-acquired hyponatremia: a case for using isotonic saline. Pediatrics 111:227–230
10. Farrar HC, Chande VT, Fitzpatrick DF, Shema SJ (1995) Hyponatremia as the cause of seizures in infants: a retrospective analysis of incidence, severity, and clinical predictors. Ann Emerg Med 26:42–48
11. David R, Ellis D, Gartner JC (1981) Water intoxication in normal infants: role of antidiuretic hormone in pathogenesis. Pediatrics 68:349–353
12. Keating JP, Schears GJ, Dodge PR (1991) Oral water intoxication in infants. An American epidemic. Am J Dis Child 145:985–990
13. Hugen CA, Oudesluys-Murphy AM, Hop WC (1995) Serum sodium levels and probability of recurrent febrile convulsions. Eur J Pediatr 154:403–405
14. Holliday MA, Segar WE (1957) The maintenance need for water in parenteral fluid therapy. Pediatrics 19:823–832
15. Hoorn EJ, Geary D, Robb M, Halperin ML, Bohn D (2004) Acute hyponatremia related to intravenous fluid administration in hospitalized children: an observational study. Pediatrics 113:1279–1284
16. Hanna S, Tibby SM, Durward A, Murdoch IA (2003) Incidence of hyponatraemia and hyponatraemic seizures in severe

respiratory syncytial virus bronchiolitis. Acta Paediatr 92:430–434
17. Schwartz WB, Bennet W, Curelop S, Bartter FC (1957) A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. Am J Med 23:529–542
18. Duke T, Molyneux EM (2003) Intravenous fluids for seriously ill children: time to reconsider. Lancet 362:1320–1323
19. Jenkins J, Taylor B (2004) Prevention of hyponatraemia. Arch Dis Child 89:93
20. Playfor S (2003) Fatal iatrogenic hyponatraemia. Arch Dis Child 88:646–647
21. Kaneko K, Shimojima T, Kaneko KI (2004) Risk of exacerbation of hyponatremia with standard maintenance fluid regimens. Pediatr Nephrol
22. Holliday MA, Friedman AL, Segar WE, Chesney R, Finberg L (2004) Acute hospital-induced hyponatremia in children: A physiologic approach. J Pediatr 145:7
23. Hatherill M (2004) Rubbing salt in the wound. Arch Dis Child 89:414–418
24. Moritz ML, Ayus C (2004) Hospital-acquired hyponatremia is associated with excessive administration of intravenous maintenance fluid: in reply. Pediatrics 114:9
25. Steiner MJ, DeWalt DA, Byerley JS (2004) Is this child dehydrated? JAMA 291:2746–2754
26. Holliday MA, Segar WE, Friedman A (2003) Reducing errors in fluid therapy. Pediatrics 111:424–425
27. Scheingraber S, Rehm M, Sehmisch C, Finsterer U (1999) Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 90:1265–1270
28. Levine JP, Stelnicki E, Weiner HL, Bradley JP, McCarthy JG (2001) Hyponatremia in the postoperative craniofacial pediatric patient population: a connection to cerebral salt wasting syndrome and management of the disorder. Plast Reconstr Surg 108:6
29. Moritz ML, Ayus JC (2004) Dysnatremias in the critical care setting. Contrib Nephrol 144:132–157
30. Mouallem M, Friedman E, Shemesh Y, Mayan H, Pauzner R, Farfel Z (1991) Cardiac conduction defects associated with hyponatremia. Clin Cardiol 14:165–168
31. Arieff AI, Kozniewska E, Roberts TP, Vexler ZS, Ayus JC, Kucharczyk J (1995) Age, gender, and vasopressin affect survival and brain adaptation in rats with metabolic encephalopathy. Am J Physiol 268:R1143–1152
32. Sgouros S, Goldin JH, Hockley AD, Wake MJ, Natarajan K (1999) Intracranial volume change in childhood. J Neurosurg 91:610–616
33. Xenos C, Sgouros S, Natarajan K (2002) Ventricular volume change in childhood. J Neurosurg 97:584–590
34. Bruce RC, Kliegman RM (1997) Hyponatremic seizures secondary to oral water intoxication in infancy: association with commercial bottled drinking water. Pediatrics 100:E4
35. Ayus JC, Wheeler JM, Arieff AI (1992) Postoperative hyponatremic encephalopathy in menstruant women. Ann Intern Med 117:891–897
36. Ayus JC, Arieff AI (1999) Chronic hyponatremic encephalopathy in postmenopausal women: association of therapies with morbidity and mortality. JAMA 281:2299–2304
37. Arieff AI (1986) Hyponatremia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in healthy women. N Engl J Med 314:1529–1535
38. Vexler ZS, Ayus JC, Roberts TP, Fraser CL, Kucharczyk J, Arieff AI (1994) Hypoxic and ischemic hypoxia exacerbate brain injury associated with metabolic encephalopathy in laboratory animals. J Clin Invest 93:256–264
39. Ayus JC, Arieff AI (1995) Pulmonary complications of hyponatremic encephalopathy. Noncardiogenic pulmonary edema and hypercapnic respiratory failure. Chest 107:517–521
40. Ayus JC, Arieff AI (2000) Noncardiogenic pulmonary edema in marathon runners. Ann Intern Med 133:1011
41. Ayus JC, Krothapalli RK, Arieff AI (1987) Treatment of symptomatic hyponatremia and its relation to brain damage. A prospective study. N Engl J Med 317:1190–1195
42. Nzerue C, Baffoe-Bonnie H, Dail C (2003) Predicters of mortality with severe hyponatremia. J Natl Med Assoc 95 (5):335–343
43. Hantman D, Rossier B, Zohlman R, Schrier R (1973) Rapid correction of hyponatremia in the syndrome of inappropriate secretion of antidiuretic hormone. An alternative treatment to hypertonic saline. Ann Intern Med 78:870–875
44. Ayus JC, Armstrong DL, Arieff AI (1996) Effects of hypernatraemia in the central nervous system and its therapy in rats and rabbits. J Physiol 492:243–255
45. Ayus JC, Arieff AI (1993) Pathogenesis and prevention of hyponatremic encephalopathy. Endocrinol Metab Clin North Am 22:425–446
46. Lauriat SM, Berl T (1997) The hyponatremic patient: practical focus on therapy. J Am Soc Nephrol 8:1599–1607
47. Verbalis JG (1998) Adaptation to acute and chronic hyponatremia: implications for symptomatology, diagnosis, and therapy. Semin Nephrol 18:3–19
48. Worthley LI, Thomas PD (1986) Treatment of hyponatraemic seizures with intravenous 29.2% saline. Br Med J (Clin Res Ed) 292:168–170
49. Fraser CL, Arieff AI (1997) Epidemiology, pathophysiology, and management of hyponatremic encephalopathy. Am J Med 102:67–77
50. Norenberg MD, Leslie KO, Robertson AS (1982) Association between rise in serum sodium and central pontine myelinolysis. Ann Neurol 11:128–135
51. Kleinschmidt-DeMasters BK, Norenberg MD (1981) Rapid correction of hyponatremia causes demyelination: relation to central pontine myelinolysis. Science 211:1068–1070
52. Ayus JC, Krothapalli RK, Armstrong DL. Rapid correction of severe hyponatremia in the rat: histopathological changes in the brain. Am J Physiol 248:F711–719
53. Sterns RH (1994) Treating hyponatremia: why haste makes waste. South Med J 87:1283–1287
54. Ayus JC, Krothapalli RK, Armstrong DL, Norton HJ (1989) Symptomatic hyponatremia in rats: effect of treatment on mortality and brain lesions. Am J Physiol 257:F18–22
55. Tien R, Arieff AI, Kucharczyk W, Wasik A, Kucharczyk J (1992) Hyponatremic encephalopathy: is central pontine myelinolysis a component? Am J Med 92:513–522
56. Cadman TE, Rorke LB (1969) Central pontine myelinolysis in childhood and adolescence. Arch Dis Child 44:342–350
57. Soupart A, Penninckx R, Stenuit A, Decaux G (2000) Azotemia (48 h) decreases the risk of brain damage in rats after correction of chronic hyponatremia. Brain Res 852:167–172
58. Ho VB, Fitz CR, Yoder CC, Geyer CA (1993) Resolving MR features in osmotic myelinolysis (central pontine and extrapontine myelinolysis). AJNR Am J Neuroradiol 14:163–167
59. Wright DG, Laureno R, Victor M (1979) Pontine and extrapontine myelinolysis. Brain 102:361–385
60. Ruzek KA, Campeau NG, Miller GM (2004) Early diagnosis of central pontine myelinolysis with diffusion-weighted imaging. AJNR Am J Neuroradiol 25:210–213
61. Kumar SR, Mone AP, Gray LC, Troost BT (2000) Central pontine myelinolysis: delayed changes on neuroimaging. J Neuroimaging 10:169–172
62. Chua GC, Sitoh YY, Lim CC, Chua HC, Ng PY (2002) MRI findings in osmotic myelinolysis. Clin Radiol 57:800–806
63. Menger H, Jorg J (1999) Outcome of central pontine and extrapontine myelinolysis (n =44). J Neurol 246:700–705
64. Newell KL, Kleinschmidt-DeMasters BK (1996) Central pontine myelinolysis at autopsy; a 12-year retrospective analysis. J Neurol Sci 142:134–139
65. Ellis SJ (1995) Severe hyponatraemia: complications and treatment. QJM 88:905–909
66. Soupart A, Ngassa M, Decaux G (1999) Therapeutic relowering of the serum sodium in a patient after excessive correction of hyponatremia. Clin Nephrol 51:383–386

67. Adrogue HJ, Madias NE (1997) Aiding fluid prescription for the dysnatremias. Intensive Care Med 23:309–316
68. Nguyen MK, Kurtz I (2003) A new quantitative approach to the treatment of the dysnatremias. Clin Exp Nephrol 7:2
69. Moritz ML, Ayus JC (1999) The changing pattern of hypernatremia in hospitalized children. Pediatrics 104:435–439
70. Manganaro R, Mami C, Marrone T, Marseglia L, Gemelli M (2001) Incidence of dehydration and hypernatremia in exclusively breast-fed infants. J Pediatr 139:673–675
71. Laing IA, Wong CM (2002) Hypernatraemia in the first few days: is the incidence rising? Arch Dis Child Fetal Neonatal Ed 87:F158–162
72. Dewey KG, Nommsen-Rivers LA, Heinig MJ, Cohen RJ (2003) Risk factors for suboptimal infant breastfeeding behavior, delayed onset of lactation, and excess neonatal weight loss. Pediatrics 112:607–619
73. Anand SK, Sandborg C, Robinson RG, Lieberman E (1980) Neonatal hypernatremia associated with elevated sodium concentration of breast milk. J Pediatr 96:66–68
74. Moritz ML, Ayus JC (2002) Disorders of water metabolism in children: hyponatremia and hypernatremia. Pediatr Rev 23:371–380
75. Finberg L, Luttrell C, Redd H (1959) Pathogenesis of lesions in the nervous system in hypernatremic states. II. Experimental studies of gross anatomic changes and alterations of chemical composition of the tissues. Pediatrics 23:46–53
76. Luttrell CN, Finberg L (1959) Hemorrhagic encephalopathy induced by hypernatremia. I. Clinical, laboratory, and pathological observations. AMA Arch Neurol Psychiatry 81:424–432
77. Grant PJ, Tate GM, Hughes JR, Davies JA, Prentice CR (1985) Does hypernatraemia promote thrombosis? Thromb Res 40:393–399
78. Clark WR (1992) Diffuse demyelinating lesions of the brain after the rapid development of hypernatremia. West J Med 157:571–573
79. Brown WD, Caruso JM (1999) Extrapontine myelinolysis with involvement of the hippocampus in three children with severe hypernatremia. J Child Neurol 14:428–433
80. Soupart A, Penninckx R, Namias B, Stenuit A, Perier O, Decaux G (1996) Brain myelinolysis following hypernatremia in rats. J Neuropathol Exp Neurol 55:106–113
81. Fraser CL, Arieff AI (1985) Hepatic encephalopathy. N Engl J Med 313:865–873
82. Finberg L (1959) Pathogenesis of lesions in the nervous system in hypernatremic states. I. Clinical observations of infants. Pediatrics 23:40–45
83. Abramovici MI, Singhal PC, Trachtman H (1992) Hypernatremia and rhabdomyolysis. J Med 23:17–28
84. Moritz ML (1996) Hypernatremia in hospitalized patients. Ann Intern Med 125:860
85. Mandal AK, Saklayen MG, Hillman NM, Markert RJ (1997) Predictive factors for high mortality in hypernatremic patients. Am J Emerg Med 15:130–132
86. Morris-Jones PH, Houston IB, Evans RC (1967) Prognosis of the neurological complications of acute hypernatraemia. Lancet 2:9
87. Warren SE, Mitas JA 2nd, Swerdlin AH (1980) Hypernatremia in hepatic failure. JAMA 243:1257–1260
88. Mocharla R, Schexnayder SM, Glasier CM (1997) Fatal cerebral edema and intracranial hemorrhage associated with hypernatremic dehydration. Pediatr Radiol 27:785–787
89. Kaplan JA, Siegler RW, Schmunk GA (1998) Fatal hypernatremic dehydration in exclusively breast-fed newborn infants due to maternal lactation failure. Am J Forensic Med Pathol 19:19–22
90. Gartner LM, Morton J, Lawrence RA, Naylor AJ, O'Hare D, Schanler RJ, et al (2005) Breastfeeding and the use of human milk. Pediatrics 115:2
91. Finberg L, Kiley J, Luttrell CN (1963) Mass accidental salt poisoning in infancy. A study of a hospital disaster. JAMA 184:90
92. Banister A, Matin-Siddiqi SA, Hatcher GW (1975) Treatment of hypernatraemic dehydration in infancy. Arch Dis Child 50:179–186
93. Rosenfeld W, deRomana GL, Kleinman R, Finberg L (1977) Improving the clinical management of hypernatremic dehydration. Observations from a study of 67 infants with this disorder. Clin Pediatr (Phila) 16:411–417
94. Pizarro D, Posada G, Levine MM (1984) Hypernatremic diarrheal dehydration treated with slow (12-h) oral rehydration therapy: a preliminary report. J Pediatr 104:316–319
95. Hogan GR, Pickering LK, Dodge PR, Shepard JB, Master S (1985) Incidence of seizures that follow rehydration of hypernatremic rabbits with intravenous glucose or fructose solutions. Exp Neurol 87:249–259
96. Hogan GR, Dodge PR, Gill SR, Pickering LK, Master S (1984) The incidence of seizures after rehydration of hypernatremic rabbits with intravenous or ad libitum oral fluids. Pediatr Res 18:340–345
97. Hogan GR, Dodge PR, Gill SR, Master S, Sotos JF (1969) Pathogenesis of seizures occurring during restoration of plasma tonicity to normal in animals previously chronically hypernatremic. Pediatrics 43:54–64
98. Pizarro D, Posada G, Villavicencio N, Mohs E, Levine MM (1983) Oral rehydration in hypernatremic and hyponatremic diarrheal dehydration. Am J Dis Child 137:730–734
99. Duke T (2004) Intravenous fluids for seriously ill children. Lancet 363:242
100. Jackson J, Bolte RG(2000) Risks of intravenous administration of hypotonic fluids for pediatric patients in ED and prehospital settings: let's remove the handle from the pump. Am J Emerg Med 18:269–270
101. Gregorio L, Sutton CL, Lee DA (1997) Central pontine myelinolysis in a previously healthy 4-year-old child with acute rotavirus gastroenteritis. Pediatrics 99:738–743
102. Armour A (1997) Dilutional hyponatraemia: a cause of massive fatal intraoperative cerebral oedema in a child undergoing renal transplantation. J Clin Pathol 50:444–446
103. Eldredge EA, Rockoff MA, Medlock MD, Scott RM, Millis MB (1997) Postoperative cerebral edema occurring in children with slit ventricles. Pediatrics 99:625–630
104. Paut O, Remond C, Lagier P, Fortier G, Camboulives J (2000) [Severe hyponatremic encephalopathy after pediatric surgery: report of seven cases and recommendations for management and prevention]. Ann Fr Anesth Reanim 19:467–473
105. McRae RG, Weissburg AJ, Chang KW (1994) Iatrogenic hyponatremia: a cause of death following pediatric tonsillectomy. Int J Pediatr Otorhinolaryngol 30:227–232
106. Hughes PD, McNicol D, Mutton PM, Flynn GJ, Tuck R, Yorke P (1998) Postoperative hyponatraemic encephalopathy: water intoxication. Aust N Z J Surg 68:165–168
107. Cowley DM, Pabari M, Sinton TJ, Johnson S, Carroll G, Ryan WE (1988) Pathogenesis of postoperative hyponatraemia following correction of scoliosis in children. Aust N Z J Surg 58
108. Steele A, Gowrishankar M, Abrahamson S, Mazer CD, Feldman RD, Halperin ML (1997) Postoperative hyponatremia despite near-isotonic saline infusion: a phenomenon of desalination. Ann Intern Med 126:20–25
109. Bomberger RA, McGregor B, DePalma RG (1986) Optimal fluid management after aortic reconstruction: a prospective study of two crystalloid solutions. J Vasc Surg 4:164–167
110. Tindall SF, Clark RG (1981) The influence of high and low sodium intakes on post-operative antidiuresis. Br J Surg 68:639–644
111. Stillstrom A, Persson E, Vinnars E (1987) Postoperative water and electrolyte changes in skeletal muscle: a clinical study with three different intravenous infusions. Acta Anaesthesiol Scand 31:4
112. McFarlane C, Lee A (1994) A comparison of Plasmalyte 148 and 0.9% saline for intra-operative fluid replacement. Anaesthesia 49:779–781
113. Wilkes NJ, Woolf R, Mutch M, Mallett SV, Peachey T, Stephens R, et al (2001) The effects of balanced versus saline-

based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. Anesth Analg 93:811–816
114. Waters JH, Gottlieb A, Schoenwald P, Popovich MJ, Sprung J, Nelson DR (2001) Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. Anesth Analg 93:817–822
115. Takil A, Eti Z, Irmak P, Yilmaz Gogus F (2002) Early postoperative respiratory acidosis after large intravascular volume infusion of lactated Ringer's solution during major spine surgery. Anesth Analg 95:table of contents
116. Boldt J, Haisch G, Suttner S, Kumle B, Schellhase F (2002) Are lactated Ringer's solution and normal saline solution equal with regard to coagulation? Anesth Analg 94:378–384
117. Burrows FA, Shutack JG, Crone RK (1983) Inappropriate secretion of antidiuretic hormone in a postsurgical pediatric population. Crit Care Med 11:527–531
118. Brazel PW, McPhee IB (1996) Inappropriate secretion of antidiuretic hormone in postoperative scoliosis patients: the role of fluid management. Spine 21:724–727
119. Judd BA, Haycock GB, Dalton RN, Chantler C (1990) Antidiuretic hormone following surgery in children. Acta Paediatr Scand 79:461–466

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REFERENCES

1. Grubb BP, Wolfe D. Head-upright tilt table testing: current concepts. *Cardiology*. 1992;9:85–87
2. Kosinski D, Grubb BP, Temesy-Armos P. Pathophysiological aspects of neurocardiogenic syncope: current concepts and new perspectives. *Pacing Clin Electrophysiol*. 1995;18:716–723
3. Benditt DG, Remole S, Bailin S, et al. Tilt table testing for evaluation of neurally-mediated (cardioneurogenic) syncope: rationale and proposed protocols. *Pacing Clin Electrophysiol*. 1991;14:1528–1537
4. Fish FA, Strasburger JF, Benson DW. Reproducibility of a symptomatic response to upright tilt in young patients with unexplained syncope. *Am J Cardiol*. 1992;70:605–609
5. Grubb BP, Temesy-Armos P, Moore J, et al. Head-upright tilt-table testing in evaluation and management of the malignant vasovagal syndrome. *Am J Cardiol*. 1992;69:904–908
6. Grubb BP, Temesy-Armos P, Hahn H, et al. Utility of upright tilt-table testing in the evaluation and management of syncope of unknown origin. *Am J Med*. 1991;90:6–10
7. Grubb BP, Gerard G, Roush K, et al. Cerebral vasoconstriction during head-upright tilt-induced vasovagal syncope: a paradoxic and unexpected response. *Circulation*. 1991;84:1157–1164
8. Grubb BP, Temesy-Armos P, Moore J, et al. The use of head-upright tilt table testing in the evaluation and management of syncope in children and adolescents. *Pacing Clin Electrophysiol*. 1992;15:742–748
9. Grubb BP, Wolfe D, Temesy-Armos P, et al. Reproducibility of head upright tilt table test results in patients with syncope. *Pacing Clin Electrophysiol*. 1992;15:1477–1481
10. Grubb BP, Kosinski D, Samoil D, et al. Postpartum syncope. *Pacing Clin Electrophysiol*. 1995;18:1028–1031
11. Hackel A, Linzer M, Anderson N, et al. Cardiovascular and catecholamine responses to head-up tilt in the diagnosis of recurrent unexplained syncope in elderly patients. *J Am Geriatr Soc*. 1991;39:663–669
12. Lerman-Sagie T, Rechavia E, Strasberg B, et al. Head-up tilt for the evaluation of syncope of unknown origin in children. *J Pediatr*. 1991; 118:676–679
13. Milstein S, Reyes WJ, Benditt D. Upright body tilt for evaluation of patients with recurrent, unexplained syncope. *Pacing Clin Electrophysiol*. 1989;12:117–124
14. Pongiglione G, Fish FA, Strasburger JF, et al. Heart rate and blood pressure response to upright tilt in young patients with unexplained syncope. *J Am Coll Cardiol*. 1990;16:165–170
15. Ross BA, Hughes S, Anderson E, et al. Abnormal responses to orthostatic testing in children and adolescents with recurrent unexplained syncope. *Am Heart J*. 1991;122:748–754
16. Samoil D, Grubb BP, Kip K, et al. Head-upright tilt table testing in children with unexplained syncope. *Pediatrics*. 1993;92:426–430
17. Sheldon R, Killam S. Methodology of isoproterenol-tilt table testing in patients with syncope. *J Am Coll Cardiol*. 1992;19:773–779
18. Sra JS, Murthy V, Natale A, et al. Circulatory and catecholamine changes during head-up tilt testing in neurocardiogenic (vasovagal) syncope. *Am J Cardiol*. 1994;73:33–37
19. Thilenius OG, Quinones JA, Husayni TS, et al. Tilt test for diagnosis of unexplained syncope in pediatric patients. *Pediatrics*. 1991;87:334–338
20. Wiley TM, O'Donoghue S, Platia EV. Neurocardiogenic syncope-evaluation and management. *Cardiovasc Res*. 1993;(October):12–25
21. Benditt DJ, Chair. ACC expert consensus document: tilt table testing for assessing syncope. *J Am Coll Cardiol*. 1996;283:263–275
22. Grubb BP, Kosinski DJ, Boehm KE, et al. The postural orthostatic tachycardia syndrome: a neurocardiogenic variant identified during head up tilt table testing. *PACE*. In press
23. Sarrel PM. Ovarian hormones and the circulation. *Maturitas*. 1990;590: 287–298
24. Rosano GMC, Sarrel PM. Ovarian hormones and the cardiovascular system: recent findings. *Cardiologia*. 1994;39:275–279
25. Herrington DM, Graden GA, Williams JK, et al. Endothelial-dependent coronary vasomotor responsiveness in postmenopausal women with and without estrogen replacement therapy. *Am J Cardiol*. 1994;73: 951–952
26. Holst J, Backstrom T, Hammarback S, et al. Progestogen addition during oestrogen replacement therapy—effects on vasomotor symptoms and mood. *Maturitas*. 1989;11:13–20
27. Omar HA, Ramirex R, Gibson M. Properties of a progesterone-induced relaxation in human placental arteries and veins. *J Clin Endocrinol Metab*. 1995;80:370–373
28. von Schoultz B. Vasomotor symptoms and estrogen-progestogen therapy. *Acta Obstet Gynecol Scand Suppl*. 1985;132:15–18
29. Kaplan BJ, Whitsett SF, Robinson JW. Menstrual cycle phase is a potential confound in psychophysiology research. *Psychophysiology*. 1990;27:445–450
30. Hastrup JL, Light KC. Sex differences in cardiovascular stress responses modulation as a function of menstrual cycle phases. *J Psychosom Res*. 1984;28:475–483

Postoperative Cerebral Edema Occurring in Children With Slit Ventricles

ABBREVIATIONS. SV, slit ventricles; CT, computed tomographic (scan); MRI, magnetic resonance imaging; SVS, slit ventricle syndrome; ICP, intracranial pressure; CSF, cerebrospinal fluid; ICU, intensive care unit; ADH, antidiuretic hormone.

Slit ventricles (SV) are collapsed or abnormally small ventricles apparent on computed tomographic (CT) or magnetic resonance imaging (MRI) scans after insertion of a ventricular shunt in a patient with hydrocephalus. Although many patients with SV are asymptomatic, slit ventricle syndrome (SVS) is said to exist when SV are accompanied by intermittent episodes of severe headaches, cyclic nausea and/or vomiting, and slow refill of the shunt's pumping device after compression.[1,2] These episodes are believed to reflect sudden, periodic increases in intracranial pressure (ICP), possibly related to underlying decreased intracranial compliance.[2,3]

This report describes two children with known SV who developed symptomatic cerebral edema after uncomplicated orthopedic surgery. One had a fatal outcome. Hyponatremia occurring in the postoperative period was the likely precipitating factor. Recommendations for recognizing, treating, and potentially preventing this catastrophic complication are discussed.

CASE STUDIES

Case 1

A 5-year-old, 12.5-kg girl, who was a former 29-week premature infant with spastic diplegia and cerebral palsy, underwent elective heel-cord lengthening. Her medical history was significant for insertion of a ventriculoperitoneal shunt at 6 weeks of age for hydrocephalus after Listeria meningitis and an intraventricular hemorrhage. Routine CT scans throughout early childhood revealed SV, but the patient was in remarkably good health except for intermittent headaches often accompanied by vomiting.

At the time of surgery, the patient was asymptomatic. A mask induction with oxygen, nitrous oxide, and halothane was performed, and anesthesia was maintained with oxygen, nitrous oxide, isoflurane, pancuronium, and fentanyl. Anesthesia lasted 3 hours and was uneventful. Before awakening, a caudal block of 10 mL of .25% bupivacaine was administered. The estimated blood

Received for publication Nov 15, 1995; accepted Aug 20, 1996.
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loss was 50 mL and the patient received 350 mL of lactated Ringer's solution. She awakened, her trachea was extubated, and she was transferred to the recovery room, where she was soon alert and conversing with the nurses and her mother. Postoperative intravenous fluids administered were 5% glucose in .225% saline at 45 mL/h. After 1 hour, the patient was transferred to the orthopedic ward in stable condition.

Approximately 3 hours later, the patient began to complain of a headache and leg pain. She was treated with acetaminophen (125 mg) orally and morphine (1.5 mg) intravenously. She then slept, but awoke several hours later vomiting and still complaining of a headache. A neurology consultant found no focal findings and recommended ketorolac for pain. Throughout the night, her headache persisted and she had multiple episodes of emesis. She received 2 doses of ketorolac (15 mg intravenously at 9:20 PM and again at 1:45 AM), 2 doses of morphine (1.5 mg intravenously at 6:00 PM and again at 5:00 AM), 1 dose of oral ibuprofen (100 mg at 3:00 PM), 1 additional dose of oral acetaminophen (125 mg at 10:00 PM), and 1 dose of oral diazepam (2 mg at 3:45 AM). At 6:50 AM, the patient was noted to be crying but soon went back to sleep. At 8:00 AM (22 hours postoperatively), she was found apneic, cyanotic, unresponsive, and pulseless. She was treated immediately with tracheal intubation; mechanical hyperventilation; chest compressions; placement of a femoral intravenous catheter; administration of epinephrine (2 doses), calcium, and lidocaine; and electrical defibrillation. Only normal saline was administered during the resuscitation. After 12 minutes of resuscitation, she regained a spontaneous heart rate and blood pressure. Initial arterial blood obtained after several minutes of resuscitation revealed a hematocrit of 30%, pH 7.04, Pco_2 26 mm Hg, Po_2 331 mm Hg, sodium 123 mEq/L, potassium 4.1 mEq/L, chloride 93 mEq/L, and glucose 565 mg/dL. All electrolyte values were measured directly on a Kodak Ektachem (Kodak Co, Rochester, NY) machine. The high serum glucose was believed to be attributable to the patient's arrest and her physiological response to resuscitative measures.

An emergency tap of the shunt reservoir followed by a ventricular tap with a spinal needle through the ventricular catheter each produced only a few drops of slightly bloody cerebrospinal fluid (CSF). A CT scan performed shortly thereafter revealed SV (as in previous scans), but now also demonstrated blurring of the gray-white junction and effacement of the basilar cisterns, both consistent with cerebral edema (Figs 1 and 2). The patient was transferred to the intensive care unit (ICU), where her neurologic examination revealed no brain or brainstem function. Initial serum laboratory values obtained upon arrival in the ICU revealed a sodium of 127 mEq/L, potassium 3.7 mEq/L, and osmolality of 277 mOsm/kg. Corresponding urine electrolytes revealed a sodium of 86 mEq/L, potassium 29 mEq/L, and urine osmolality of 475 mOsm/kg. Serum and urine osmolalities were not calculated, but measured directly on an osmometer. A labile blood pressure was controlled with a dopamine infusion, and when diabetes insipidus developed several hours after admission to the ICU, a pitressin infusion was initiated. An electroencephalogram was performed and was isoelectric. Forty-eight hours after her arrest, the patient was declared brain-dead.

Postmortem findings were notable for global neuronal ischemia, leptomeningeal fibrosis, subependymal gliosis, and extensive infarction of the anterior pituitary. The presence of transtentorial or cerebellar herniation could not be assessed due to damage to the basal surface of the brain during autopsy removal.

Case 2

An 8-year-old, 20-kg girl with myelodysplasia and a ventriculoperitoneal shunt underwent surgical correction of scoliosis. Her medical history was significant for closure of a lumbar myelomeningocele and shunt placement shortly after birth. At age 3, she had a shunt malfunction complicated by respiratory arrest, but made a complete recovery after placement of new bilateral ventricular catheters. Subsequent CT scans were notable for small, SV. At age 5, she underwent hip surgery and was extremely lethargic for 2 days postoperatively. At that time, the lethargy was attributed to an adverse reaction to codeine. However, in retrospect, her postoperative serum sodium was 129 mEq/L and she appeared edematous. This was treated by decreasing the rate of her intravenous infusion, and she returned to her baseline neurologic status within 24 hours. At age 6, scoliosis was diagnosed and treated with spinal braces. When the scoliosis progressed, surgical repair was scheduled.

The patient's preoperative examination was notable for a heart rate of 125 bpm, blood pressure of 110/60 mm Hg, and flaccid lower extremities with no sensation below the L1 dermatomal level. Anesthesia for the scoliosis repair consisted of thiopental, pancuronium, fentanyl, oxygen, nitrous oxide, and isoflurane, and was uneventful. Surgery was performed via a posterior approach with Harrington rods and Luque wire instrumentation from T10 to the sacrum. The operation lasted 7 hours and the estimated blood loss was 3 L. Replacement therapy consisted of 3 units of whole blood, 375 mL of cell saver blood, 250 mL of .9% normal saline, and 1250 mL of lactated Ringer's solution. The patient's trachea was extubated upon awakening and she was transferred to the ICU for routine overnight observation. Postoperative fluids were administered as 5% glucose in .45% normal saline at 60 mL/h.

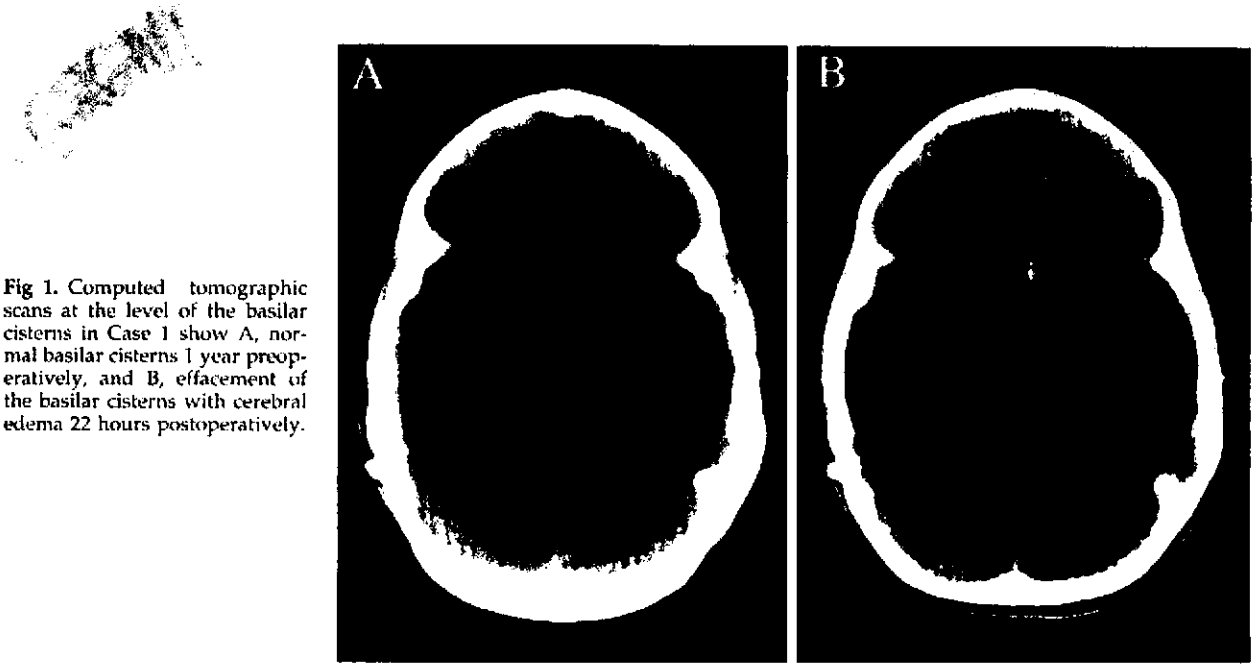

Fig 1. Computed tomographic scans at the level of the basilar cisterns in Case 1 show A, normal basilar cisterns 1 year preoperatively, and B, effacement of the basilar cisterns with cerebral edema 22 hours postoperatively.

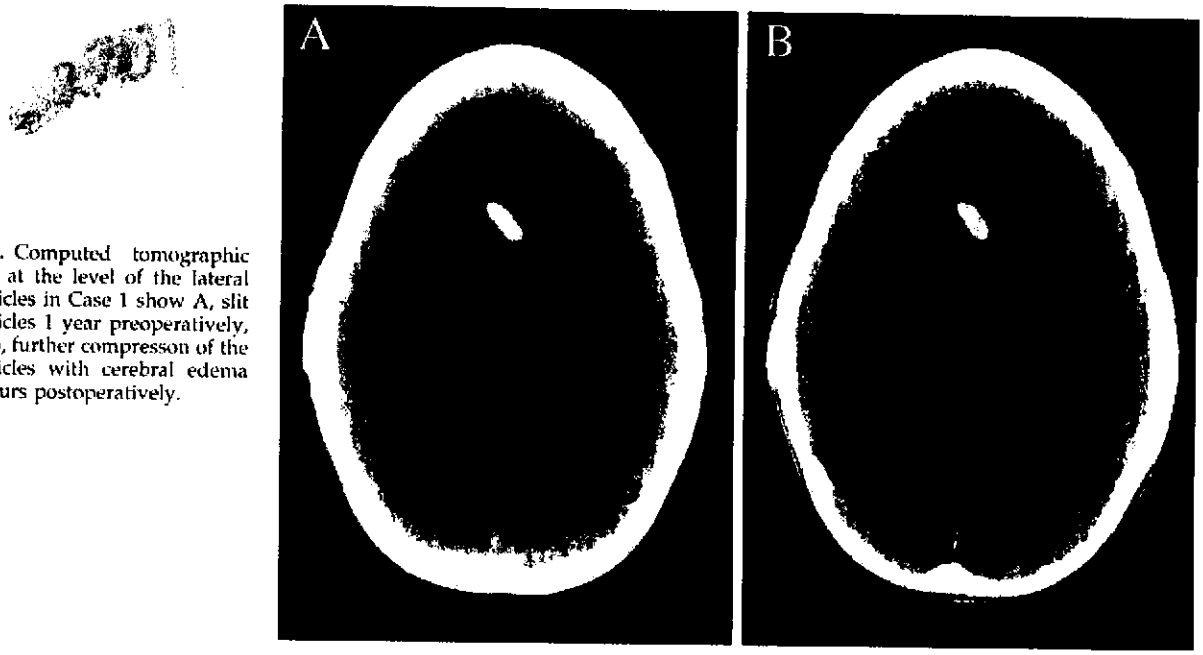

Fig 2. Computed tomographic scans at the level of the lateral ventricles in Case 1 show A, slit ventricles 1 year preoperatively, and B, further compresson of the ventricles with cerebral edema 22 hours postoperatively.

After initially appearing awake, the patient gradually became more lethargic. By 12 hours postoperatively, she was unresponsive to verbal commands. Her heart rate was in the 60s and her systolic blood pressure had increased to 150 mm Hg. Her pupils were equal and responsive to light. While receiving oxygen by face mask, an arterial blood gas revealed pH 7.40, Pco_2 37 mm Hg, and Po_2 223 mm Hg. Her ventricular reservoir was tapped to rule out a shunt malfunction. This revealed clear colorless CSF, an opening pressure of 140 mm H_2O, and good respiratory variations. The shunt appeared to be functioning appropriately, although the opening pressure was higher than expected because she had a Hakim valve which, at the time of placement, had initially opened at 110 mm H_2O. In view of the patient's medical history and previous CT scans, the neurosurgeons felt that the clinical picture was consistent with SVS and increased ICP, rather than a shunt malfunction. The head of the bed was elevated, and mannitol (0.5 gm/kg) and furosemide (1 mg/kg) were administered intravenously. Within an hour, the patient's heart rate and blood pressure decreased to her baseline level. The patient became alert and was able to follow simple commands. A CT scan later that day revealed SV, unchanged from previous CT scans, and generalized cerebral edema.

Soon thereafter, the patient became more lethargic and ultimately unresponsive. She again exhibited bradycardia and hypertension, and then developed decerebrate posturing. Blood drawn at this time was notable for a serum sodium of 129 mEq/L, potassium 3.5 mEq/L, chloride 95 mEq/L, osmolality 252 mOsm/kg, and glucose 166 mg/dL. Osmolality was not calculated, but was measured directly with an osmometer. Electrolyte values were measured directly with a Kodak Ektachem (Kodak Co, Rochester, NY) machine. The patient was treated with thiopental, fentanyl, pancuronium, tracheal intubation, and mechanical hyperventilation. All fluids were changed to normal saline at minimal infusion rates, and additional doses of mannitol and furosemide were administered. Repeat arterial blood gases while receiving 100% oxygen revealed pH 7.44, Pco_2 35 mm Hg, Po_2 521 mm Hg, sodium 131 mEq/L, potassium 3.5 mE/L, chloride 95 mE/L,and glucose 112 mg/dL. Measured serum osmolality had increased to 263 mOsm/kg. Samples of urine were sent for electrolyte and osmolality analysis but were difficult to interpret due to prior mannitol and furosemide administration. Approximately 1 hour later, a subdural bolt was inserted over the right frontal area. At the time of insertion, the brain could be seen retracting away from the dura and the first ICP reading was −2 mm Hg with appropriate respiratory and cardiac variations. These low values were thought to reflect a response to the previous therapeutic measures designed to reduce ICP. Throughout the night, the ICP remained <5 mm Hg. By the next morning the patient was awake and oriented. Her trachea was extubated, the ICP bolt was removed, and laboratory studies revealed a serum sodium of 141 mEq/L, potassium 3.9 mEq/L, chloride 99 mEq/L, and osmolality of 287 mOsm/kg. The patient's neurologic function at discharge 1 week later was unchanged from her preoperative state. Several years later, the patient died suddenly for unknown reasons shortly after arriving in her local emergency room. No autopsy was performed.

DISCUSSION

This report describes two children with SV who developed severe neurologic deterioration after uneventful orthopedic procedures. Hyponatremia leading to cerebral edema in the postoperative period was a precipitating factor. It appears that patients with SV, and SVS in particular, have decreased intracranial compliance.[2-4] Any cause of increased ICP (cerebral edema secondary to hyponatremia, closed head injury, increased cerebral blood flow, masses, etc) is likely to be poorly tolerated in patients with SV when compared with otherwise normal individuals,[3] and may possibly lead to increased morbidity and/or mortality.[4]

The etiologies of SV and SVS are uncertain. SV have been noted radiographically in 5% to 53% of all shunted patients, but clinical symptoms occur much less commonly.[1-3,5-8] When shunts are inserted before 1 year of age, the risk of developing SV increases.[6]

The development of SV after shunt placement is generally attributed to chronic overdrainage of CSF.[2,7,9] In addition, an extremely compliant cerebral parenchyma, as seen in neonates and young children, may be more prone to ventricular collapse. The immature brain is known to contain a smaller population of glial cells, incompletely myelinated axons, and a high water content, all of which may increase the brain's compliance.[10] Thus, with a very compliant brain and little pressure to keep the ventricles open after shunt insertion, ventricular collapse may occur.[4]

The compliance of the growing infant brain with a

shunt in place may then start to significantly decrease as myelination occurs and chronic scar formation begins to develop around narrowed ventricles.[6,11,12] Periventricular scar formation has been shown to occur in experimental studies of dogs with artificially-induced hydrocephalus, and has also been noted in the autopsy reports of patients treated with hydrocephalus.[13,14] The lack of pathways for drainage of interstitial fluid into the CSF attributable to scar tissue (subependymal and ependymal gliosis), in addition to the subnormal ventricular volume for CSF, both appear to significantly decrease the CSF buffering capability.[10,11,13] Thus, the hydrocephalic brain with a shunt in place, especially when inserted at a young age, may have small, scarred, slit-like ventricles with limited drainage capability and very little compliance. As a result, intracranial hypertension may easily develop.[3,4,10-14]

Why some patients with SV develop symptoms of SVS while others do not is poorly understood. Many possible mechanisms have been suggested.[1,2,6,14,15] Prevention of SV has also been limited. No single prophylactic intervention has proven effective in all cases. Higher pressure valves, antisiphon devices, and siphon control devices all have been inserted in shunt systems to permit drainage of CSF while avoiding overdrainage, especially when patients assume the upright position.[1,2,7] New programmable valves may permit gradual adjustment of shunt pressure and may reduce the incidence of SV. Treatment of SV, once it develops, has also been controversial, in part related to the complexity and possible multiple etiologies of SVS.[2,6,7,9,15,16] Various methods of CSF venting, such as placement of a lumbar-peritoneal shunt or third ventriculostomy, have been attempted. Cranial decompression to increase intracranial volume has also been utilized in patients with recurring and disabling symptoms.[2,9,16] Because it appears that the final common pathway leading to SVS is related to acute increases in ICP with decreased intracranial compliance, acute symptomatic episodes are often treated with mannitol, furosemide, and fluid restriction. Nevertheless, whenever new neurologic symptoms develop in a patient with a ventricular shunt in place, it is always necessary to first rule out any type of shunt malfunction before considering the diagnosis of SVS, as was done in both of these cases where shunt and ventricular taps were performed.

Hyponatremia and/or hypoosmolality can produce cerebral edema and intracranial hypertension, particularly in children.[17] Although postoperative hyponatremia does occur (1% to 4% incidence in adults, .34% incidence in pediatric patients), symptomatic postoperative hyponatremia is rare.[17-19] Patients with SV, however, may become symptomatic earlier and at levels of hyponatremia that may otherwise be well-tolerated by normal individuals. Postoperative serum sodiums of 125–130 mEq/L are usually only associated with mild lethargy, nausea, and/or vomiting, and can easily be attributed to recovery from anesthesia or the effects of analgesic medications used to treat postoperative pain. In most cases of hyponatremia, however, severe symptoms are not likely to appear unless the serum sodium level decreases below 120 mEq/L.[20,21] Symptoms of severe hyponatremia may include respiratory depression, impaired responses to stimuli, lethargy, decorticate and decerebrate posturing, and seizure activity.[18] In both of the cases described here, the patients may have become symptomatic initially at serum sodium levels >130 mEq/L, although sodium levels were not analyzed until both patients became unresponsive. Even then, sodium levels were >120 mEq/L. The rate of decline of the serum sodium levels may have also influenced the degree of symptomatology in each of these patients.

Hyponatremia and hypoosmolality are particularly liable to develop in the postoperative period because 1) secretion of antidiuretic hormone (ADH), induced by multiple factors including stress, pain, surgery, administration of anesthetic and analgesic medications, and mechanical ventilation, causes free water retention, and 2) extrarenal fluid losses are often replaced (sometimes too rapidly) with hypotonic fluids.[17-19,21-25] The effects of ADH secretion can clearly be seen in Case 1 when comparing the urine and serum electrolytes and osmolalities.

The majority of symptoms of hyponatremia are attributable to hyponatremic encephalopathy.[22,26] This encephalopathy is caused by cerebral edema, which develops as the brain cells acutely absorb and retain water in response to a low serum osmolality and hyponatremia. In addition, perioperative cerebral edema may be exacerbated due to the direct effects of ADH on the brain. Rat studies have shown that ADH has direct effects on brain cells via vasopressin V1 receptors, whether or not hyponatremia is present.[18,22,27] Under the direct influence of ADH, water is able to enter into brain cells while the efflux of sodium is impaired. Thus, the synergistic presence of both ADH secretion (direct and indirect effects) and hyponatremia, as may occur during the perioperative period, may allow brain swelling to easily develop. Hypoxia, indirectly caused by hyponatremic encephalopathy, may also worsen cerebral edema in a potentially fatal fashion.[18,22,27]

The occurrence of postoperative hyponatremia may be influenced by the choice of intravenous fluids administered and their rate of administration, in addition to the factors discussed above.[18,19,21-25,28,29] Hyponatremic solutions (ie, 5% dextrose in .225% normal saline, sodium 38.5 mEq/L) are generally not administered intraoperatively but are frequently given in the postoperative period. The glucose is rapidly metabolized, resulting in administration of free water. Lactated Ringer's solution is a balanced salt solution that is more commonly used intraoperatively. However, it is slightly hyponatremic (sodium 130 mEq/L) and hypotonic (osm = 273 mOsm/kg) when compared with normal serum (sodium 140 mEq/L, osm = 285–290 mOsm/kg). When administered in generous amounts, lactated Ringer's solution may contribute to a decrease in serum sodium and osmolality. Normal saline (0.9%, sodium 154 mEq/L, osm = 308 mOsm/kg) is somewhat hypernatremic and hypertonic compared with serum, and might therefore be a better choice when large

amounts of intravenous fluids are to be administered, especially if brain swelling is of concern. The rate of administration of intravenous fluids is also important in the development of hyponatremia.[21,29] Rapid hydration of a patient in the operating room or postoperatively with hypotonic intravenous fluids can drop the serum sodium and osmolality acutely, allowing little time for the brain to compensate for the decrease in osmolality. As a result, cerebral edema may develop acutely, causing potentially disastrous results, especially in a patient with little intracranial compliance.[21,29]

Although reductions in postoperative serum sodiums are similar in men and women, menstruant women and young children more often become symptomatic, encephalopathic, and suffer a higher incidence of morbidity and mortality.[17,18,22,26] Recent studies have shown several mechanisms at the cellular and molecular levels that may help explain why hyponatremic encephalopathy develops more commonly in menstruant females. These may involve the direct and indirect effects of estrogen and other sex hormones and their biological influences on the brain's adaptation to hyponatremia and ADH secretion.[17,18,22,27,30] Young children and infants, on the other hand, have several physiological and mechanical factors such as a higher percentage of brain water content, a higher intracellular sodium concentration in brain cells, less CSF volume than adults, and a higher ratio of brain content to intracranial capacity, all of which may help explain why children have a relatively decreased intracranial compliance compared with adults, and thus why children become encephalopathic more often.[17,18,19,22,30]

In summary, we report two children who developed marked neurologic deterioration in the postoperative period that appeared to be a result of intracranial hypertension caused by hyponatremia. Preexisting SV prevented normal CSF compensatory responses. Symptoms of neurologic deterioration were attributed to recovery from anesthesia and surgery and to the effects of analgesic medications.

All physicians caring for patients with ventriculoperitoneal or ventriculoatrial shunts should be aware of those patients who have SV, because intracranial compliance can be markedly reduced. If hyponatremia should develop, patients with SV (children in particular, as illustrated in these cases) may be at great risk for developing symptoms of intracranial hypertension. Careful cardiorespiratory monitoring and close observation should always be instituted promptly whenever symptoms develop in patients with SV, because potentially life-threatening complications can develop suddenly. Mild increases in ICP that may be tolerated by patients with normal neuroanatomy can result in severe symptoms in patients with SV. Unexpected lethargy, headache, nausea, and/or vomiting occurring in any patient with SV should prompt immediate concern. Evaluation of serum and urine electrolytes and osmolality should be performed, particularly in the postoperative period, as well as neurosurgical evaluation to exclude shunt malfunction. Administration of hyponatremic intravenous fluids and/or rapid fluid hydration should be performed with caution in the perioperative period to patients with SV. In addition, free water administration may need to be limited until the ability to produce dilute urine is established. As a result, normal saline solutions may be safer to use intraoperatively and postoperatively in these patients. Further studies are necessary to determine whether this can prevent the development of postoperative hyponatremia and symptomatic cerebral edema in these circumstances.

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ACKNOWLEDGMENTS

The authors thank Patrick Barnes, MD for review of the CT scans and John Kosartes, MA for his help in the production of this manuscript.

REFERENCES

1. Hahn Y. Use of the distal double-slit valve system in children with hydrocephalus. *Childs Nerv Syst.* 1994;10:99–103
2. Pudenz R, Foltz E. Hydrocephalus: overdrainage by ventricular shunts. A review and recommendations. *Surg Neurol.* 1991;35:200–212
3. Obana W, Raskin N, Cogen P, Szymanski J, Edwards M. Antimigraine treatment for slit ventricle syndrome. *Neurosurgery.* 1990;27:760–763
4. Oi S, Matsumoto S. Infantile hydrocephalus and the slit ventricle syndrome in early infancy. *Childs Nerv Syst.* 1987;3:145–150
5. Serlo W, Saukkonen A, Heikkinen E, von Wendt L. The incidence and management of the slit ventricle syndrome. *Acta Neurochir (Wien).* 1989; 99:113–116
6. Wisoff J, Epstein F. Diagnosis and treatment of slit ventricle syndrome. In: Scott RM, ed. *Concepts in Neurosurgery, III.* Baltimore, MD: Williams & Wilkins; 1990:79–85
7. Benzel E, Reeves J, Kesterson L, Hadden T. Slit ventricle syndrome in children: clinical presentation and treatment. *Acta Neurochir (Wien).* 1992;117:7–14
8. Kiekens R, Mortier W, Pothmann R, Bock W, Seibert H. The slit-ventricle syndrome after shunting in hydrocephalic children. *Neuropediatrics.* 1982;13:190–194
9. Holness R, Hoffman H, Hendrick E. Subtemporal decompression for the slit-ventricle syndrome after shunting in hydrocephalic children. *Childs Brain.* 1979;5:137–144
10. Cardoso E, Del Bigio M, Schroeder G. Age-dependent changes of cerebral ventricular size. *Acta Neurochir (Wien).* 1989;97:40–46
11. Dahlerup B, Gjerris F, Harmsen A, Sorensen P. Severe headache as the only symptom of long-standing shunt dysfunction in hydrocephalic children with normal or slit ventricles revealed by computed tomography. *Childs Nerv Syst.* 1985;1:49–52
12. Saukkonen A, Serlo W, von Wendt L. Electroencephalographic findings and epilepsy in the slit ventricle syndrome of shunt-treated hydrocephalic children. *Childs Nerv Syst.* 1988;4:344–347
13. Oi S, Matsumoto S. Morphological findings of postshunt slit-ventricle in experimental canine hydrocephalus. *Childs Nerv Syst.* 1986;2:179–184
14. Engel M, Carmel P, Chutorian A. Increased intraventricular pressure without ventriculomegaly in children with shunts: 'normal volume' hydrocephalus. *Neurosurgery.* 1979;5:549–552

15. McLaurin R, Olivi A. Slit-ventricle syndrome: review of 15 cases. *Pediatr Neurosci.* 1987;13:118–124
16. Reddy K, Fewer H, West M, Hill N. Slit ventricle syndrome with aqueduct stenosis: third ventriculostomy as definitive treatment. *Neurosurgery.* 1988;23:756–759
17. Arieff A, Ayus J, Fraser C. Hyponatraemia and death or permanent brain damage in healthy children. *Br Med J.* 1992;304:1218–1222
18. Ayus J, Arieff A. Pathogenesis and prevention of hyponatremic encephalopathy. *Endocrinol Metab Clin North Am.* 1993;22:425–446
19. Chung H, Kluge R, Schrier R, Anderson R. Postoperative hyponatremia: a prospective study. *Arch Intern Med.* 1986;146:333–336
20. Ayus J, Krothapalli R, Arieff A. Treatment of symptomatic hyponatremia and its relation to brain damage. *N Engl J Med.* 1987;5: 1190–1195
21. Berry P, Belsha C. Hyponatremia. *Pediatr Clin North Am.* 1990;37: 351–363
22. Arieff A, Ayus J. Pathogenesis of hyponatremic encephalopathy. *Chest.* 1993;103:607–610
23. Judd B, Haycock G, Dalton R, Chantler C. Antidiuretic hormone following surgery in children. *Acta Paediatr.* 1990;79:461–466
24. Burrows F, Shutack J, Crone R. Inappropriate secretion of antidiuretic hormone in a postsurgical pediatric population. *Crit Care Med.* 1983;11: 527–531
25. Judd B, Haycock G, Dalton N, Chantler C. Hyponatraemia in premature babies and following surgery in older children. *Acta Paediatr.* 1987;76: 385–393
26. Ayus J, Wheeler J, Arieff A. Postoperative hyponatremic encephalopathy in menstruant women. *Ann Intern Med.* 1992;117:891–897
27. Faraci F, Mayhan W, Heistad D. Effect of vasopressin on production of cerebrospinal fluid: possible role of vasopressin (V1)-receptors. *Am J Physiol.* 1990;258:R94–R98
28. Kovacs L, Lichardus B, Bireák J, et al. Normovolaemic hyponatraemia in hospitalized children. *Cesk Pediatr.* 1987;42:326–327
29. Berl T. Treating hyponatremia: damned if we do and damned if we don't. *Kidney Int.* 1990;37:1006–1018
30. Trachtman H. Cell volume regulation: a review of cerebral adaptive mechanisms and implications for clinical treatment of osmolal disturbances. Part I. *Pediatr Nephrol.* 1991;5:743–750

Treatment of Hypereosinophilic Syndrome in a Child Using Cyclosporine: Implication for a Primary T-cell Abnormality

ABBREVIATIONS. HES, hypereosinophilic syndrome; Ig, immunoglobulin; IL, interleukin.

Hypereosinophilic syndrome (HES) is a systemic disease of unknown cause characterized by peripheral eosinophilia and eosinophilic infiltration of tissues, resulting in severe organ dysfunction. We report the first pediatric case of HES with primarily skin involvement that responded favorably to the immunosuppressive drug cyclosporine.

CASE REPORT

A 7-year-old white girl was referred for persistent eosinophilia, hyperimmunoglobulinemia E, and a chronic severely debilitating cutaneous eruption associated with extreme pruritus. At 18 months of age, she had raised macularpapular, erythematous, and erosive lesions on her upper extremities, which gradually spread to her entire trunk, back, and lower extremities. Her scalp, forehead, cheeks, and chin were also affected, but her neck was completely unaffected. Some of the affected areas began to turn bluish and were firm and indurated. The erosive lesions were extremely pruritic and had become secondarily infected with staphylococcal and streptococcal bacteria. She also had molluscum contagiosum and *Trichophyton rubrum* onychomycosis.

Her birth history was unremarkable. Birth weight was 3200 g. Developmental milestones were within normal limits. There were no pets in the household. There was no history of travel before the onset of the rash. She had never had chickenpox or any serious systemic illness. The patient did have mild reactive airways disease treated with inhaled steroids on an as-needed basis. She was an only child, and there was a positive family history of eczema. The patient's father worked for the railroads, and her mother was a housewife. Both parents were healthy.

At the initial physical examination, she seemed well nourished and well hydrated. She was in moderate distress because of the pruritus associated with the rash. Lymph nodes were palpable. Oropharyngeal examination showed evidence of mild oral thrush with cheilitis and tonsillar tissue present. Her chest, cardiovascular, and abdominal examinations were unremarkable. Her musculoskeletal and central nervous system examination showed nothing abnormal. Examination of the skin showed multiple erythematous, macularpapular, ulcerated, and erosive lesions on her face, trunk, and lower extremities (Fig 1). There were also large, indurated, bluish plaques on the right upper arm, left forearm, and left thigh. Scattered on her chin and shoulders and over her right scapulae were soft, flesh-color, pedunculated papules consistent with molluscum contagiosum infection. She also had dyskeratosis and onychomycosis of the toenails.

Admission laboratory studies showed significant eosinophilia (9×10^9 cells/L or 56%) and hyperimmunoglobulinemia (2200 μg/L). Urinalysis revealed 1+ glucose and no ketones or protein. Stool analyses for ova and parasites were negative.

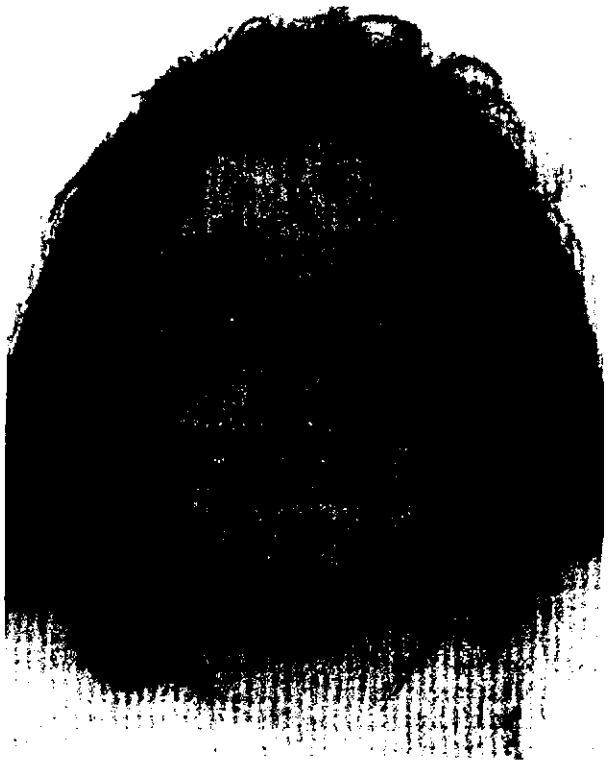

Fig 1. The skin condition before treatment with cyclosporine consisted of multiple papillary, erythematous, ulcerated, and erosive lesions on the face, trunk, and lower extremities.

Received for publication May 23, 1996; accepted Aug 13, 1996.
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Pediatr Nephrol (2010) 25:1225–1238
DOI 10.1007/s00467-009-1323-6

EDUCATIONAL REVIEW

New aspects in the pathogenesis, prevention, and treatment of hyponatremic encephalopathy in children

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Received: 24 June 2009 / Revised: 17 August 2009 / Accepted: 27 August 2009 / Published online: 6 November 2009

Abstract Hyponatremia is the most common electrolyte abnormality encountered in children. In the past decade, new advances have been made in understanding the pathogenesis of hyponatremic encephalopathy and in its prevention and treatment. Recent data have determined that hyponatremia is a more serious condition than previously believed. It is a major comorbidity factor for a variety of illnesses, and subtle neurological findings are common. It has now become apparent that the majority of hospital-acquired hyponatremia in children is iatrogenic and due in large part to the administration of hypotonic fluids to patients with elevated arginine vasopressin levels. Recent prospective studies have demonstrated that administration of 0.9% sodium chloride in maintenance fluids can prevent the development of hyponatremia. Risk factors, such as hypoxia and central nervous system (CNS) involvement, have been identified for the development of hyponatremic encephalopathy, which can lead to neurologic injury at mildly hyponatremic values. It has also become apparent that both children and adult patients are dying from symptomatic hyponatremia due to inadequate therapy. We have proposed the use of intermittent intravenous bolus therapy with 3% sodium chloride, 2 cc/kg with a maximum of 100 cc, to rapidly reverse CNS symptoms and at the same time avoid the possibility of overcorrection of hyponatremia. In this review, we discuss how to recognize patients at risk for inadvertent overcorrection of hyponatremia and what measures should taken to prevent this, including the judicious use of 1-desamino-8d-arginine vasopressin (dDAVP).

Keywords Hyponatremia · Encephalopathy · Cerebral edema · Pulmonary edema · Fluid therapy · Saline · Sodium chloride · Myelinolysis · Arginine vasopressin

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Introduction

Hyponatremia is one of the most common electrolyte abnormalities encountered in children, with mild hyponatremia, serum sodium (SNa) <135 mEq/L, occurring in ~25% of hospitalized children and moderate hyponatremia, SNa <130 mEq/L, in ~1% (Table 1). Recent data in both children and adults have demonstrated that hyponatremia is a far more serious condition than previously believed. The most serious complication of hyponatremia is hyponatremic encephalopathy. Hyponatremic encephalopathy is a topic that has been mired in controversy. The main disputes have centered on (1) the most appropriate fluid management strategies to prevent hyponatremic encephalopathy, (2) the optimal therapy for symptomatic hyponatremia, and (3) the risks of developing cerebral demyelination from the correction of hyponatremia. In this review, we discuss new aspects in the pathogenesis of

Table 1 Incidence of hyponatremia in hospitalized children

Author	Inclusion criteria serum sodium (mEq/L)	Incidence (%)
Hasegawa et al. 2009 [121]	<135 on admission	17
Don et al. 2008 [122]	<135 on admission with community-acquired pneumonia	45
Hoorn et al. et al. 2004 [123]	<135 in emergency department patients with serum sodium checked	22
Arnon et al. 2008 [124]	Hospitalized patients on intravenous fluids	
	<135	24
	<130	5
Wattad et al. 1992 [125]	<130 in hospitalized patients	1.4

hyponatremic encephalopathy with an emphasis on strategies for prevention and treatment.

Why does hyponatremia develop?

Under normal circumstances, the human body can maintain plasma sodium levels within the normal range (135–145 mEq/L), even with wide fluctuations in fluid intake. The body's primary defense against developing hyponatremia is the kidney's ability to generate a dilute urine and excrete free water. Rarely is excess ingestion of free water alone the cause of hyponatremia, as an adult with normal renal function can typically excrete >15 L of free water per day [1]. It is also rare to develop hyponatremia from excess urinary sodium loss in the absence of free-water ingestion. In order for hyponatremia to develop, there must typically be a relative excess of free water in conjunction with an underlying condition that impairs the kidney's ability to excrete free water (see Table 2). Excretion of free water will be impaired when there is either (1) a marked reduction in glomerular filtration rate, (2) renal hypoperfusion, or (3) arginine vasopressin (AVP) excess. Most cases of hyponatremia are the result of increased AVP production.

Renal water handling is primarily under the control of AVP, which is produced in the hypothalamus and released from the posterior pituitary. The action of AVP is mediated via the vasopressin V2 receptor. AVP binding of V2 receptors results in the insertion of aquaporin 2 (AQP2) water channels on the apical surface of the principal cells of the cortical collecting duct, which markedly increases water permeability and impairs water excretion [2]. There are osmotic, hemodynamic, and nonhemodynamic stimuli for AVP release. The body will attempt to preserve extracellular volume at the expense of SNa. Therefore, a hemodynamic stimulus for AVP production will override any inhibitory hypo-osmolar effect of hyponatremia [3]. There are numerous hemodynamic and non-hemodynamic stimuli for AVP production (Table 1) that occur in hospitalized patients and that can put virtually any hospitalized patient at risk for hyponatremia. In order for hyponatremia to develop in the presence of AVP excess, there must be an additional source of free-water intake, either intravenous or oral. Even isotonic fluid administration could in theory result in hyponatremia in the presence of AVP excess, as the kidney can generate free water by excreting a hypertonic urine, i.e. a urine sodium plus potassium concentration greater than that of the plasma [4].

- Hyponatremia typically results from the combination of AVP excess plus free water intake.

Is asymptomatic hyponatremia a benign condition?

Increased attention has been focused on the possible deleterious consequences of asymptomatic hyponatremia. Most of this data comes from adult studies, but pediatric data are starting to appear. Recent data have revealed that hyponatremia is an independent predictor of mortality in

Table 2 Disorders in impaired renal water excretion

1. Effective circulating volume depletion
   a) Gastrointestinal losses: vomiting, diarrhea
   b) Skin losses: cystic fibrosis
   c) Renal losses: salt-wasting nephropathy, diuretics, cerebral salt wasting, hypoaldosteronism
   d) Edematous states: heart failure, cirrhosis, nephrosis, hypoalbuminemia
   e) Decreased peripheral vascular resistance: sepsis, hypothyroidism
2. Thiazide diuretics
3. Renal failure
   a) Acute
   b) Chronic
4. Non-hypovolemic states of antidiuretic hormone (ADH) excess
   a) Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
   b) Nausea, emesis, pain, stress
   c) Post-operative state
   d) Cortisol deficiency
5. Nephrogenic syndrome of inappropriate antidiuresis (NSIAD)

adult patients with a variety of diseases, in particular, patients with pneumonia, congestive heart failure, and end-stage liver disease [5–7]. It has recently been demonstrated that mild chronic hyponatremia (mean SNa 128 mEq/L) in adults can result in subtle neurological impairment affecting both gait and attention, similar to that of moderate alcohol intake [8]. This appears to explain why hyponatremia has come to be associated with falls and bone fractures in the elderly [8–10].

There are data to suggest that hyponatremia has deleterious consequences in the preterm neonate, though data are lacking in older children. Preterm neonates with hyponatremia show impaired growth and development compared with those who have been salt supplemented [11, 12] and have increased sodium intake as adolescents [13]. Hyponatremia is also a significant risk factor for sensorineural hearing loss [14], cerebral palsy [15], and intracranial hemorrhage [16]. Hyponatremia has been shown to be a risk factor for increased mortality in neonates who suffered perinatal birth asphyxia [17].

- Asymptomatic hyponatremia in adults is associated with attention and gait abnormalities, falls and fractures, and increased mortality in patients with pneumonia, heart failure and liver disease.
- Asymptomatic hyponatremia in preterm neonates is associated with poor growth and development, sensorineural hearing loss, and increased sodium intake in later life.

What are the clinical features of hyponatremic encephalopathy?

Hyponatremic encephalopathy is a medical emergency that can be lethal. The pathogenesis and epidemiology of hyponatremic encephalopathy have been reviewed in detail by us elsewhere [18–20]. The primary symptoms of hyponatremia are those of cerebral edema (see Table 3). Hypoosmolality results in intracellular or cytotoxic cerebral edema caused by the influx of water into the intracellular space down a concentration gradient, resulting in parenchymal brain swelling. Cerebral edema results in increased intracranial pressure that can lead to brain ischemia, herniation, and death. The brain's primary mechanism in adapting to hyponatremia is the intracellular extrusion of electrolytes and organic osmolytes. Some of these organic osmolytes are excitatory amino acids, such as glutamate and aspartate, that can produce seizures in the absence of detectable cerebral edema [21].

Hyponatremic encephalopathy can be difficult to recognize, as the presenting symptoms are variable and can be nonspecific (see Table 3). The only universal presenting features of hyponatremic encephalopathy are headache, nausea, vomiting, and lethargy. These symptoms can easily be overlooked, as they occur in a variety of conditions. There must be a high index of suspicion for diagnosing hyponatremic encephalopathy, as the progression from mild to advanced symptoms can be abrupt and does not follow a consistent progression. A cranial computed tomography (CT) scan cannot consistently be used to rule out hyponatremic encephalopathy, as it is not sensitive enough to detect mild cerebral edema that could be detected by diffusion-weighted magnetic resonance imaging (MRI) [22, 23].

Table 3 Clinical symptoms of hyponatremic encephalopathy

1. Early
a. Headache
b. Nausea and vomiting
c. Lethargy
d. Weakness
e. Confusion
f. Altered consciousness
g. Agitation
h. Gait disturbances
2. Advanced
a. Seizures
b. Coma
c. Apnea
d. Pulmonary edema
e. Decorticate posturing
f. Dilated pupils
g. Anisocoria
h. Papilledema
i. Cardiac arrhythmias
j. Myocardial ischemia
k. Central diabetes insipidus

A common yet underrecognized feature of hyponatremic encephalopathy is noncardiogenic pulmonary edema, also referred to as Ayus-Arieff syndrome [24, 25]. Cerebral edema leads to increased intracranial pressure, which can result in pulmonary edema via two mechanisms: (1) centrally mediated increase in pulmonary vascular permeability to proteins, leading to increased alveolar and interstitial fluid [26], and (2) increased sympathetic neuronal activity with catecholamine release, resulting in pulmonary vasoconstriction with increased capillary hydrostatic pressure and capillary wall injury (Fig. 1) [27, 28]. This has primarily been reported in patients with postoperative hyponatremic encephalopathy and exercise-associated hyponatremia [29, 30]. It is important to recognize this syndrome, as it is rapidly reversible with hypertonic saline and is almost universally fatal if left untreated.

- The most consistent clinical features of hyponatremic encephalopathy are headache, nausea, and vomiting.

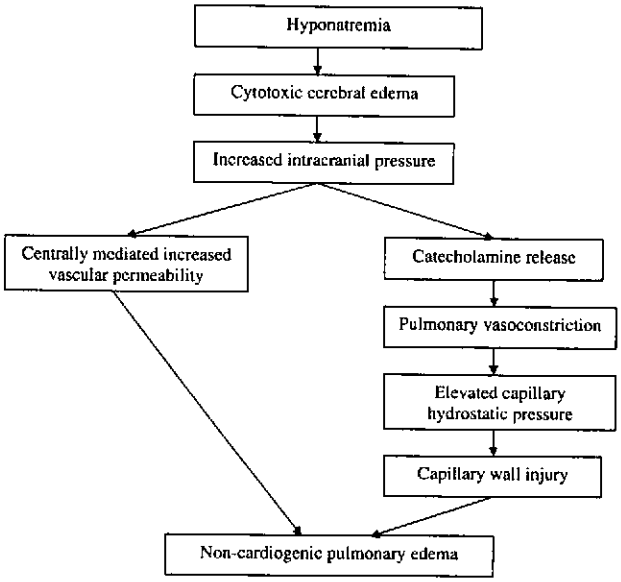


Fig. 1 Mechanism of noncardiogenic pulmonary edema in hyponatremic encephalopathy

- Noncardiogenic pulmonary edema is an underrecognized feature of hyponatremic encephalopathy.
- Hyponatremic encephalopathy can occur in the absence of CT evidence of cerebral edema.

What are the risks factors for developing hyponatremic encephalopathy?

Here we describe the major risk factors for hyponatremic encephalopathy development (Table 4).

Children

It is important to realize that children are at significantly higher risk than are adults for developing hyponatremic encephalopathy. The average SNa in children with hyponatremic encephalopathy is 120 mEq/L [31, 32], whereas that in adults is 111 mEq/L [9, 31–33]. More than 50% of children with an SNa <125 mEq/L will develop hyponatremic encephalopathy [20]. The reason for this is that children have a relatively larger brain to intracranial volume ratio compared with adults [34, 35]. A child's brain reaches adult size by 6 years of age, whereas the skull does not reach adult size until 16 years of age [36, 37]. As a result, children have less room available in their rigid skulls for brain expansion and are likely to develop brain herniation from hyponatremia at higher SNa concentrations than adults. The fontanelles in infants appear to offer little protection, as the incidence of hyponatremic encephalopathy in infants is quite high [38].

Factors that impair brain-cell-volume regulation and decrease cerebral perfusion: female sex steroids, elevated AVP, and hypoxia

There are various factors that can impair the normal brain regulatory volume decrease and place patients at increased risk for the development of hyponatremic encephalopathy, independent of the degree of hyponatremia or the rate of fall in SNa. The primary factors are female sex steroids, elevated AVP levels, and hypoxia. Women in their reproductive years are at high risk for developing hyponatremic encephalopathy [33]. The reason for this appears to be that estrogens impair brain-cell-volume regulation by reducing the sodium/potassium/adenosine triphosphatase (Na+/K+/ATPase) pump activity, thereby inhibiting sodium extrusion from brain astrocytes. Androgens, on the other hand, appear to enhance Na+/K+/ATPase pump activity and confer a protective role in men [18]. Another reason that women are more susceptible to hyponatremic encephalopathy is that the vasoconstrictive effects of AVP are more pronounced in the female brain than in that of the male brain. AVP excess leads to cerebral vasoconstriction with

Table 4 Risk factors for developing hyponatremic encephalopathy

1) Impaired brain cell volume regulation and decreased cerebral perfusion
   a) Elevated AVP levels
   b) Female sex steroids
   c) Hypoxia
2) Decreased cranial capacity
   a) Children <16 years
   b) Space-occupying brain lesion
      i) Tumor
      ii) Hematoma/hemorrhage
   c) Hydrocephalus
      i) Chiari malformation
      ii) Dandy Walker
3) Central nervous system disorders (cytotoxic and vasogenic cerebral edema)
   a) Infections
      i) Meningitis/encephalitis
   b) Encephalopathy
      i) Metabolic
         (1) Diabetic ketoacidosis
         (2) Hyperammonemia
         (3) Bilirubin
      ii) Hepatic
      iii) Ischemic
      iv) Toxic
   c) Cerebritis
   d) Brain injury and neurosurgery
   e) Seizure disorders

corresponding decreased oxygen delivery [18]. AVP is known to increase brain-water content in the absence of hyponatremia and to impair brain regulatory volume mechanisms [39–41]. Postoperative patients are at particularly high risk for developing hyponatremic encephalopathy, and this may be explained in part by the high AVP levels associated with surgery [33]. Hypoxemia is a major risk factor for developing hyponatremic encephalopathy. The occurrence of a hypoxic event such as respiratory insufficiency is a major factor militating against survival without permanent brain damage in patients with hyponatremia [42]. The combination of systemic hypoxemia and hyponatremia is more deleterious than is either factor alone because hypoxemia impairs the ability of the brain to adapt to hyponatremia, leading to a vicious cycle of worsening hyponatremic encephalopathy [43]. Studies of hyponatremic animals have revealed that hypoxia impairs brain-cell-volume regulation, decreases cerebral perfusion, and increases the probability of developing neuronal lesions [44].

Underlying CNS disease

Hyponatremia is poorly tolerated in patients with central nervous system (CNS) disorders [45]. Even a small fall in SNa can aggravate cerebral edema and increase intracranial pressure (ICP) [46–48]. CNS pathology can lead to increased ICP from space-occupying brain lesions, hydrocephalus, or cerebral edema. Cerebra edema can occur via two mechanisms: vasogenic and cytotoxic. Vasogenic edema is the accumulation of fluid in the extracellular brain parenchyma from a disruption in the blood–brain barrier, such as is seen with a brain tumor, abscess, or meningitis. Cytotoxic cerebral edema is the accumulation of fluid in the intracellular space, which is seen with hypoxic brain injury, metabolic encephalopathy, and hyponatremia [49]. These mechanisms are not mutually exclusive. A patient with a CNS disorder will already be at risk for increased ICP and have impaired brain-cell-volume regulation. The additional water movement into the brain from even mild hyponatremia can be lethal.

It has been demonstrated that in children with a variety of neurologic diseases that hyponatremia is associated with prolonged hospital stay and poor neurologic outcome [50]. Similar findings have been reported in adults with traumatic brain injury [51]. In a study of children with Lacrosse encephalitis, mild hyponatremia was strongly associated with neurological deterioration [46]. SNa of patients with neurological deterioration was only 2 mmol/L less than in those without (131.9 vs. 133.8 mmol), and a fall in SNa of only 4 mmol/L resulted in neurological deterioration. In a study in children with pneumococcal meningitis, the mortality was 100% for those who presented with SNa <130 mEq/L [52]. Hyponatremia has been reported to lead to progressive cerebral edema in children with maple-syrup-urine disease during episodes of acute metabolic intoxication [53]. Mild hyponatremia, SNa <135 mEq/L, also appears to play a role in the development of cerebral edema in patients with diabetic ketoacidosis (DKA). It has been demonstrated on MRI that patients with DKA have evidence of vasogenic cerebral edema [54]. The development of worsening cerebral edema in DKA has been associated with a fall in serum osmolality during therapy and a slower rise in serum osmolality compared with controls [55, 56]. No degree of hyponatremia should be considered safe in a patient with CNS disease.

- Major risk factors for developing hyponatremic encephalopathy are: (a) age <16 years, (b) hypoxemia, and (c) CNS disease.

Can hospital-acquired hyponatremia be prevented?

The majority of the morbidity and mortality from hyponatremic encephalopathy has occurred in hospitalized patients receiving hypotonic intravenous fluids, in particular, postoperative patients. In 2003 [57], we proposed that 0.9% sodium chloride (NaCl: Na 154 mEq/L) be administered to prevent hospital-acquired hyponatremia in patients at risk for AVP excess (see Table 5) and that the routine practice of administration of hypotonic and near-isotonic intravenous fluids (Na ≤ 130 mEq/L) be abandoned [45, 57, 58]. We recommended that hypotonic fluids be restricted in their use in patients with either hypernatremia (Na > 145 mEq/L) or ongoing urinary or extrarenal free-water losses. This concept, which challenged the traditional view of fluid therapy in children, was received with skepticism [59]. The main criticism of this approach was that 0.9% NaCl could result in either hypernatremia or fluid overload. Subsequent

Table 5 Primary indications for using 0.9% NaCl in parenteral fluids for the prevention of hospital-acquired hyponatremia

1. Central nervous system disorders
2. Peri-operative state
a. Ear, nose, and throat (ENT) and orthopedic in particular
3. Volume depletion
4. Hypotension
5. Pulmonary disease
a. Pneumonia and bronchiolitis in particular
6. Hydration for chemotherapy
a. Cytoxan in particular

studies have confirmed that hypotonic fluids produce hyponatremia and that the administration of 0.9% NaCl does not result in either hypernatremia or fluid overload.

In 2005, we presented data of >50 reports, from 1992–2004, of death or neurologic dysfunction from hyponatremic encephalopathy associated with the administration of hypotonic fluids in children. To the best of our knowledge, there have been nine additional reports of hyponatremic encephalopathy related to hypotonic fluids, with three deaths (Table 6) [58, 60–66]. It is estimated that there are >600 deaths per year from postoperative hyponatremic encephalopathy in children in the USA and one death per year in France [34, 65]. In Australia, it is estimated that about 10% of medical emergencies in the hospital involve hospital-acquired hyponatremia [67]. Despite the well-documented dangers of using hypotonic fluids, multiple recent studies in the USA and UK have revealed that between 80–100% of postoperative children are still being administered hypotonic fluids (0.18–0.45% NaCl) [58, 68–70]. In September 2007, the National Patient Safety Agency in the UK issued a warning about the use of hypotonic fluids in postoperative children and children with mild illness and recommended that 0.18% NaCl be removed from patient care areas [71].

Since our initial recommendations were made in 2003, there have been at least 11 studies in >1,000 children confirming our hypothesis that (a) hypotonic fluids, including Ringer's Lactate (Na 130 mEq/L), produce hyponatremia and that (b) isotonic fluids prevent the development of hyponatremia (Table 7). The most convincing evidence that 0.9% NaCl is effective in preventing hospital-acquired hyponatremia has come from two recent prospective randomized studies comparing isotonic to hypotonic fluids. Yung and Keely conducted a prospective randomized controlled trial in 50 pediatric patients receiving either 0.9% NaCl or 0.18% saline at either standard maintenance or 2/3 maintenance rate [72]. Thirty-six (72%) were postsurgical. The 0.9% NaCl group had a fall in SNa of 0.2 mEq/L at 2/3 maintenance and 1.5 mEq/L at full maintenance, whereas the 0.18% NaCl group had a fall in SNa of 3 mEq/L at 2/3 maintenance and 4.9 mEq/L at full maintenance. They concluded that fluid type, not rate, was associated with a fall in SNa. Montanana et al. similarly conducted a prospective randomized controlled trial of 122 postoperative pediatric patients admitted to the intensive care unit who received either an isotonic fluid (Na + K= 155 mEq/L) or hypotonic fluids (Na < 100 mEq/L) [73]. The incidence of hyponatremia (Na < 135) at 24 h was 20.6% in the hypotonic fluid group compared with 5.1% in the isotonic group. Both studies failed to document any complications from isotonic fluids, such as hypertension or hypernatremia.

Based on all the available data, 0.9% NaCl should be the fluid of choice in maintenance parenteral fluids, especially in the postoperative setting and in children with CNS or pulmonary disease. It must be emphasized that 0.9% NaCl is not appropriate for all clinical circumstances. Normal saline could result in hypernatremia if given to children with conditions causing ongoing urinary or extrarenal free-water losses, such as diabetes insipidus or profuse water diarrhea. Also, 0.9% NaCl may not always be able to prevent hyponatremia, in particular, in cases of CNS injury where there is cerebral salt wasting or Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) where the urine osmolality is >500 mOsm/kg. Patients receiving parenteral fluids should have close monitoring with daily weights, frequent vitals, strict intake and output measurement, and daily chemistries, especially during the first 72 h of therapy.

Table 6 Hospital-acquired hyponatremic encephalopathy in children receiving hypotonic fluids (2005–2009)

Authors	Age (years)	Setting	Intravenous fluid	Sodium value (mEq/L)	Symptoms	Treatment	Outcome
Duke et al. 2005 [61]	19	ALL, dDAVP	0.18% NaCl	138 to 124	Seizures	3% NaCl	Survived
	2	Medulloblastoma	0.18% NaCl	143 to 119	Seizures & hypoxia	3% NaCl	Survived
	6	ALL	0.45% NaCl	136 to 125	Seizures & respiratory depression	3% NaCl	Survived
Ashraf and Albert 2006 [64]	0.1	Bronchiolitis	0.22% NaCl	142–107	Lethargy	3% NaCl	Survived
Osier et al. 2006 [62]	8	Burkitt's lymphoma	0.45% NaCl	138 to 96	Seizures	Fluid restriction	Survived
Agut Fuster et al. 2006 [60]	3.5	Adenoidectomy	D_5 Water	116	Seizures, comatose	3% NaCl	Survived
Donaldson et al. 2007 [63]	5.5	Adrenal suppression	0.45% NaCl	125 to 123	Seizures, coma, respiratory arrest, cardiogenic shock	None	Death
Auroy et al. 2008 [65]	4	Dental extraction	D_5 Water & 0.35% NaCl	120	Coma, respiratory distress, heart failure	None	Death
Cansick et al. 2009 [126]	11	Renal transplant	0.45 NaCl	140–121	Seizures, cerebral herniation	Lorazepam	Death

ALL acute lymphoblastic leukemia, dDAVP 1-desamino-8d-arginine vasopressin, *NaCl* sodium chloride, *D_5 water* 5% dextrose in water

Table 7 Relationship between intravenous fluid composition and development of hyponatremia (2003–2009)

Authors	Study design	Number	Outcome
Hoorn et al. 2004 [123]	Retrospective. Incidence of acute (48 h) hospital-acquired hyponatremia (SNa < 136 mEq/L) in children presenting to the ED with a normal SNa	432	40 patients (10%) developed acute hyponatremia with a fall in SNa from 139±3 to 133±2 mEq/L in 19±10 h. All received hypotonic fluids
Neville et al. 2005 [127]	Prospective. Change in SNa at 4 h in normonatremic children with gastroenteritis receiving 0.45% NaCl	25	Fall in SNa from 138±1.6 to 135±2 mEq/L
Mehta et al. 2005 [128]	Prospective. Change in SNa at 24 h in jaundiced neonates receiving 0.18% NaCl	37	Fall in SNa from 141±5 to 134±4 mEq/L
Neville et al. 2006 [129]	Prospective randomized trial. Change in SNa at 4 h in normonatremic children with gastroenteritis receiving either 0.45% NaCl or 0.9% NaCl	65	Fall in SNa in the 0.45% NaCl group from 137±7 to 135±1.8 mEq/L SNa unchanged in 0.9% NaCl group, 137±2.2 to 138±2.9 mEq/L
Dearlove et al. 2006 [130]	Retrospective. Incidence of hyponatremia in children following appendectomy; 87% received 0.45% NaCl	51	32% incidence of hyponatremia (127–133 mEq/L)
Stewart and McGrath 2007 [131]	Prospective. Change in SNa in children following appendectomy treated with 0.45% NaCl or 0.9% NaCl	30	Fall in SNa in the 0.45% NaCl group by 1.2 mEq/L/day Increase in SNa in the 0.9% NaCl group by 1.7 mEq/L/day
Coulthard et al. 2007 [132]	Retrospective. Change in SNa in children following spinal surgery treated with 0.3% NaCl at 2/3 maintenance or full maintenance with Hartmann's solution (Na=131 mEq/L)	59	Fall in SNa in 0.3% NaCl group from 140.7±2.4 to 135.5±2.5 Fall in SNa in Hartmans's group from 140.1±2.5 to 137.6±2.8
Yung and Keely 2009 [72]	Prospective randomized trial. Change in SNa at 12–24 h in children admitted to the ICU randomized to either 0.18% NaCl or 0.9% NaCl at 2/3 or full maintenance rate	50	Fall in SNa in 0.18% NaCl group by 3 mEq/L and 4.9 mEq/L, respectively Increase in SNa in the 0.9% NaCl group by 0.2 and 1.5 mEq/L, respectively
Armon et al. 2008 [124]	Cross-sectional survey. Incidence of hyponatremia (SNa < 135 mEq/L) in children receiving hypotonic fluids one day; 77% received hypotonic fluids	86	24% incidence of hyponatremia
Au et al. 2008 [58]	Retrospective. Incidence of moderate hyponatremia (SNa < 130 mEq/L) within 24 h in postoperative children admitted to the ICU receiving hypotonic fluids (Na < 130 mEq/L) or near isotonic fluids (Na ≥ 130 mEq/L)	145	12.9% incidence of moderate hyponatremia in the hypotonic group 3.4% incidence in moderate hyponatremia in the near isotonic group
Montonana et al. 2008 [73]	Prospective randomized. Incidence of hyponatremia (SNa < 135 mEq/L) within 24 h in postoperative children admitted to the ICU receiving either hypotonic fluids (Na < 100 mEq/L) or isotonic fluid (Na + K=155 mEq/L)	122	20.6% incidence of hyponatremia in the hypotonic group 5.1% incidence of hyponatremia in the isotonic group
Singhi and Jayashre 2009 [133]	Prospective observational. Incidence of hyponatremia (SNa <130) in children admitted to the ICU receiving 0.18% NaCl	38	31% incidence of hyponatremia

SNa serum sodium, *ED* emergency department, *NaCl* sodium chloride, *Na* sodium, *ICU* intensive care unit

- Randomized controlled trials have confirmed that 0.9% NaCl is effective in preventing the development of hospital-acquired hyponatremia.

What is the optimal therapy for treating hyponatremic encephalopathy?

Hyponatremic encephalopathy is a medical emergency that requires early recognition and treatment. The definitive therapy for treating hyponatremic encephalopathy is administration of hypertonic saline (3% NaCl, 513 mEq/L). The majority of morbidity associated with hyponatremic encephalopathy has resulted from insufficient therapy rather than overcorrection [9, 74–77]. As can be seen from Table 6, all recent deaths in children have resulted from failure to recognize and treat hyponatremic encephalopathy appropriately. Even in patients who had a good outcome, many had a significant delay in instituting therapy. This is consistent with recent data in adults with hyponatremic encephalopathy that reveal that there is an average delay of 11 h in instituting therapy with 3% NaCl because of either absence of severe neurological symptoms or failure to increase the SNa with other therapies [78].

Fluid restriction alone has no role in the management of symptomatic hyponatremia; 0.9% NaCl is also inappropriate for treating hyponatremic encephalopathy due to non-hemodynamic states of AVP excess, such as SIADH, postoperative hyponatremia, and exercise-associated hyponatremia, as it is not sufficiently hypertonic to induce the necessary reduction in cerebral edema central to the management of this condition [27]. In the presence of elevated AVP levels, there will be an impaired ability to excrete free water with the urine osmolality exceeding that of the plasma. This is a saline-resistant state in which the urinary electrolyte level can be hypertonic to that of the plasma. There is a new class of drug called V2-receptor antagonists (V2RA), or Vaptans, which cannot be recommended for the treatment of hyponatremic encephalopathy at this time [27]. V2RAs block the binding of AVP to its V2 receptor located in the renal collecting duct [79]. These drugs are primarily indicated for treating euvolemic hyponatremia from SIADH and hypervolemic hyponatremia in congestive heart failure. There are no data to suggest that V2-receptor antagonists will cause either a sufficiently rapid or sufficiently consistent increase in SNa for it to be used in the treatment of symptomatic hyponatremia. Current data indicate that V2-receptor antagonists do not exert an effect for 1–2 h, which would make it an inappropriate agent for symptomatic hyponatremia [79]. The only consistent way of acutely increasing plasma Na is to administer 3% NaCl, which has a sodium concentration that exceeds the kidney's ability to generate free water. There may be a role for V2-receptor antagonists in conjunction with 3% NaCl for treating hyponatremic encephalopathy, but this needs to be further evaluated.

- 3% NaCl is the most effective therapy for treating hyponatremic encephalopathy.
- V2-receptor antagonists should not be used as the sole treatment of hyponatremic encephalopathy.

Hypertonic saline (3% NaCl, 513 mEq/L) bolus therapy for treating hyponatremic encephalopathy

We introduced a new approach to using 3% NaCl for treating hyponatremic encephalopathy in order to (a) facilitate early and aggressive therapy and (b) prevent inadvertent overcorrection of hyponatremia (see Table 8). In 2005, we recommended using a 100-cc bolus of 3% NaCl to treat exercise-associated hyponatremic encephalopathy [80]. This approach has since been adopted by the Second International Exercise-Associated Hyponatremia Consensus Development Conference [81]. We have since recommended that any patient with suspected hyponatremic encephalopathy, with either mild or advanced symptoms, should receive a 2-cc/kg bolus of 3% NaCl with a maximum of 100 cc [27, 45]. Our approach has now been recommended by other experts to treat adults with hyponatremic encephalopathy [82, 83]. A single bolus would result in at most a 2-mEq/L acute rise in SNa, which would quickly reduce brain edema. The bolus could be repeated one or two times if symptoms persist. This approach can also serve as a diagnostic maneuver, as a patient who does not show some clinical improvement after two to three boluses of 3% NaCl most likely is not suffering from hyponatremic encephalopathy. The advantage of this approach over a continuous infusion of 3% NaCl is that there is a controlled and immediate rise in SNa and also little or no risk of inadvertent overcorrection from a 3% NaCl infusion

Table 8 Treatment of symptomatic hyponatremia

1. 2 cc/kg bolus of 3% NaCl over 10 min. Maximum 100 cc
2. Repeat bolus 1–2 times as needed until symptoms improve. Goal: 5–6 mEql/L increase in serum sodium (SNa) in first 1–2 h
3. Recheck SNa following second bolus or Q 2 h
4. Hyponatremic encephalopathy is unlikely if no clinical improvement following an acute rise in serum sodium of 5–6 mEq/L
5. Stop further therapy with 3% NaCl boluses when patient is either:
   a. Symptom free: awake, alert, responding to commands, resolution of headache and nausea
   b. Acute rise in sodium of 10 mEq/L in if first 5 h
6. Correction in first 48 h should:
   a. Not exceed 15–20 mEq/L
   b. Avoid normo- or hypernatremia

running too long. No harm could come from using this approach in a patient with suspected hyponatremic encephalopathy, even if the patient proves not to have hyponatremic encephalopathy. It is our opinion that treatment of suspected symptomatic hyponatremic encephalopathy should begin with a 3% NaCl bolus. This should precede radiologic investigations because (a) neurologic deterioration could occur if there is a delay in therapy and (b) a CT scan cannot always rule out hyponatremic encephalopathy. This maneuver will stabilize the patient until further diagnostic studies can be done and serve as a bridge to instituting other therapies, such as V2-receptor antagonists.

Recommended safe limits for the correction of hyponatremia vary among experts depending on the setting of hyponatremia, including from 6 to 8 mEq/L in 24 h [82], 10 mEq/L in 24 h [84], 15 mEq/24 h [85] or 20 mEq/L in 48 h [45], as do recommendations for using hypertonic saline. Our recommendation to use bolus therapy is a unifying approach that would stay well within all recommended limits of correction and can be used safely in any setting, from mildly symptomatic to severe encephalopathy and in acute or chronic hyponatremia. Our approach does not rely on formulas or complicated calculations, and it can be administered safely and quickly in the emergency department or at the bedside prior to transfer to a monitored setting.

- A 2 cc/kg bolus of 3% NaCl, maximum 100 cc, should be administered promptly over 10 min if there are signs of hyponatremic encephalopathy.
- A 3% NaCl bolus can be repeated one or two times as needed until symptoms improve.
- The goal of correction should be 5–6 mEql/L in the first 1–2 h.

Who is at risk for developing cerebral demyelination?

A significant barrier to the use of hypertonic saline has been the perceived risk of developing cerebral demyelination from overcorrection of hyponatremia. Cerebral demyelination is a rare condition that has been reported in patients with chronic hyponatremia (>48 h) who have additional risk factors such as liver disease or alcoholism, severe malnutrition, hypoxia, or correction in SNa of >25 mEq/L in the first 24–48 h of therapy [74]. In these high-risk patients (see Table 9), it is not clear that cerebral demyelination is completely preventable, as there have been multiple reports of cerebral demyelination occurring with both careful correction or in the absence of hyponatremia [86–96]. Cerebral demyelination has not been reported in children with acute hospital-acquired hyponatremia, nor have neurological complications been associated with the use of 3% NaCl to treat children with acute hyponatremic encephalopathy [97–100].

Table 9 Risk factors for developing cerebral demyelination in hyponatremic patients

1. Severe chronic hyponatremia: Na ≤115 mEq/L
2. Development of hypernatremia
3. Increase in serum sodium exceeding 25 mmol/L in 48 hours
4. Hypoxemia
5. Severe liver disease
6. Thiazide diuretics
7. Alcoholism
8. Cancer
9. Severe Burns
10. Malnutrition
11. Hypokalemia
12. Diabetes
13. Renal failure

When cerebral demyelination does occur, it can be either symptomatic or asymptomatic [20]. The classical presentation typically follows a biphasic pattern, with initial clinical improvement of hyponatremic encephalopathy associated with correction of SNa, followed by a neurological deterioration 2–7 days following correction [42, 101]. Typical neurological features are mutism, dysarthria, spastic quadriplegia, pseudobulbar palsy, ataxia, and pseudobulbar palsy with "locked-in stare" [102]. Cerebral demyelination is best diagnosed by MRI 14 days following correction of hyponatremia, and the lesions can be both pontine and extrapontine [103].

- Patients at highest risk for developing cerebral demyelination have chronic hyponatremia and either (a) liver disease, (b) malnutrition, (c) hypoxia, or (d) an increase in SNa of >25 mEq/l.
- Patients with acute hyponatremia are not at significant risk for developing cerebral demyelination.

What are the dangers of overcorrection of hyponatremia?

There are limits to the brain's ability to maintain cell volume and cellular integrity when faced with extreme elevations in osmolality. Animal studies have revealed that extreme elevations in SNa are injurious to the brain, producing cellular necrosis, myelinolysis, disruption of the blood–brain barrier, and increase in cerebral blood flow [104–110]. For chronically hyponatremic animals, the threshold for brain injury appears to be an acute elevation in SNa of 25 mEq/L within 24 h [106, 107, 111, 112].

Chronically hyponatremic rats can be corrected with hypertonic saline by as much as 20 mEq/L in 1 h without developing brain pathology [111]. Acutely hyponatremic and normonatremic animals have a significant mortality when SNa is increased by >25 mEq/L but a much lower incidence of brain injury when compared with chronically hyponatremic animals [104–106, 113, 114]. Clinical observations in chronically hyponatremic humans also suggest that increases in SNa of >25 mEq/L in 48 h can result in neurologic impairment [9, 74]. Based on these animal studies and clinical observations, increases in SNa of a magnitude >25 mEq/L in a 48-h period should be avoided.

- Acute elevations in SNa exceeding 25 mEq/L in 48 h can produce brain injury.

Can inadvertent overcorrection of hyponatremia be prevented?

Preventing an extreme rise in SNa (>25 mEq/L in 48 h) can be difficult, particularly in the severely hyponatremic patient (SNa ≤ 115 mEq/L). The overall rate of correction of hyponatremia is primarily a determinant of the renal response to fluid therapy, more so than the composition of fluids administered. Under most circumstances, hyponatremia develops due to a state of high AVP production. Once the stimulus for AVP production abates, there will be brisk urinary excretion of free water and hyponatremia will correct rapidly. The main conditions in which correction by fluid therapy will induce a brisk free-water diuresis are (a) thiazide-induced hyponatremia, (b) water intoxication, (c) gastroenteritis, (d) adrenal insufficiency following replacement therapy, and (e) 1-desamino-8d-arginine vasopressin (dDAVP)-induced hyponatremia following dDAVP withdrawal. Even in patients who are not typically at high risk for overcorrection, such as those with SIADH and postoperative hyponatremia, when the stimuli for AVP production abates, a free-water diuresis will ensue. It is important to recognize that equations for predicting the correction of hyponatremia will not apply in these patients, as most of these equations are closed-system equations that due not take into account the renal response to fluid therapy [19, 78]. In general, if the SNa is >115 mEq/L, then even if there is a brisk free-water diuresis, the absolute rise in SNa will not likely exceed 25 mEq/L, and the risk of brain injury is small.

We recommend that the following measures be taken to prevent overcorrection of hyponatremia: (1) Patients with an SNa <115 mEq/L should be monitored to see whether a water diuresis ensues, as evidenced by an increase in SNa of >1 mEq/L per hour accompanied by a urine flow rate of >1 ml/kg per hour. In general, a urine tonicity (urine Na + K) <80 mEq/L or urine osmolality less than that of the plasma is consistent with a significant free-water diuresis during the correction phase of hyponatremia. (2) Hydration with either 3% NaCl or 0.9% NaCl should be limited to the minimal amount necessary to correct the SNa to a safe level or correct volume depletion. (3) Sodium-containing intravenous fluid should be restricted once a free-water diuresis commences, and oral intake should be encouraged. (4) Parenteral fluids, when needed, should be hypotonic, Na concentration <80 mEq/L, if there is a free-water diuresis. On the rare occasion that a pediatric patient with severe hyponatremia fails these above measures, the administration of dDAVP could be considered. DDAVP administration was first suggested to prevent the overcorrection of hyponatremia in 1993 [115] and has subsequently been used successfully in adult patients [116, 117]. DDAVP has also been used successfully to therapeutically re-lower the SNa in an adult patient with overcorrection of chronic hyponatremia. dDAVP should be used with caution and in consultation with someone familiar with this therapy, as it can result in inadvertent hyponatremia. If used, hypotonic fluid administration should be avoided following the administration of dDAVP, and isotonic saline should be administered at a restricted rate when needed. An inadvertent lowering of the SNa following dDAVP administration can be corrected with a bolus of 3% NaCl.

Management of dDAVP-induced hyponatremia

Hyponatremia caused by dDAVP is particularly difficult to manage. Hyponatremic encephalopathy from dDAVP-induced hyponatremia has been reported in children taking this medication for the treatment of enuresis, central diabetes insipidus (CDI), and as part of perioperative management of Von Willebrand's disease [118, 119]. A common and dangerous way to manage dDAVP-induced hyponatremia is by stopping dDAVP and administering 0.9% NaCl. This can result in an overcorrection of hyponatremia, as withdrawal of dDAVP will result in a free-water diuresis, and in combination with 0.9% NaCl or 3% NaCl, hypernatremia could develop, especially in the case of CDI, where there will not be endogenous AVP production in response to hyperosmolality [120]. This is particularly likely to occur when the SNa is <115 mEq/L. We have previously reported on cases of brain injury from overcorrection of hyponatremia following dDAVP withdrawal [120]. The safer approach is to continue the dDAVP to allow controlled correction in SNa. Then, 3% NaCl boluses can be administered as needed to correct the SNa. Fluid restriction should then be instituted, with isotonic fluids used in parenteral fluids if needed. Once the SNa has been corrected to mildly hyponatremic values, dDAVP could be discontinued.

- dDAVP should not be discontinued in the management of dDAVP-induced hyponatremia.

Questions

(Answers appear following the reference list)

1. What is the main risk factor for developing hyponatremia?
   a. AVP excess
   b. Intravenous fluid therapy
   c. Prematurity
   d. Prolonged hospitalization
   e. Mechanical ventilation
2. Which of the following is NOT a feature of hyponatremic encephalopathy?
   a. Headache
   b. Noncardiogenic pulmonary edema
   c. Hyperpyrexia
   d. Seizures
   e. Orthopedic injuries
3. Why are children at increased risk for developing hyponatremic encephalopathy?
   a. Increased expression of aquaporin 4
   b. Increased sensitivity of AVP
   c. Increased basal metabolic rate
   d. Increased brain- to skull-size ratio
   e. Increased brain idiogenic osmole production
4. What is the most effective therapy of hyponatremic encephalopathy?
   a. Vasopressin 2 antagonists
   b. Mannitol
   c. 0.9% NaCl plus Lasix
   d. Craniotomy
   e. 3% NaCl
5. Which of the following is NOT a risk factor for developing cerebral demyelination?
   a. Liver disease
   b. Acute hyponatremic encephalopathy
   c. Hypoxia
   d. Correction in SNa of >25 mEq/L in 48 h
   e. Thiazide diuretics

Note added in proof

Following the submission of this manuscript, Neville et al. [134] reported on a prospective randomized trial of 124 postoperative children who received either 0.9% NaCl or 0.45% NaCl at either 100% or 50% of standard maintenance. The incidence of hyponatremia (Na < 135) within the first 24 hours of surgery was 30% in the 0.45% NaCl group compared to 10% in the 0.9% NaCl (p=0.02), with 15% of patients in the 0.45% NaCl group having a fall in SNa of ≥5 mEq/L compared to none in the 0.9% NaCl. Fluid restriction at 50% maintenance did not decrease the incidence of hyponatremia, but resulted in a 23% incidence of dehydration. Administration of 0.9% NaCl did not result in clinically significant hypernatremia.

References

1. Barlow ED, De Wardener HE (1959) Compulsive water drinking. Q J Med 28:235–258
2. Oksche A, Rosenthal W (1998) The molecular basis of nephrogenic diabetes insipidus. J Mol Med 76:326–337
3. Dunn FL, Brennan TJ, Nelson AE, Robertson GL (1973) The role of blood osmolality and volume in regulating vasopressin secretion in the rat. J Clin Invest 52:3212–3219
4. Moritz ML (2008) Urine sodium composition in ambulatory healthy children: hypotonic or isotonic? Pediatr Nephrol 23:955–957
5. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN (1997) A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 336:243–250
6. Gheorghiade M, Abraham WT, Albert NM, Gattis Stough W, Greenberg BH, O'Connor CM, She L, Yancy CW, Young J, Fonarow GC (2007) Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. Eur Heart J 28:980–988
7. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, Edwards E, Therneau TM (2008) Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med 359:1018–1026
8. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G (2006) Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. Am J Med 119:e71–e78
9. Ayus JC, Arieff AI (1999) Chronic hyponatremic encephalopathy in postmenopausal women: association of therapies with morbidity and mortality. JAMA 281:2299–2304
10. Gankam Kengne F, Andres C, Sattar L, Melot C, Decaux G (2008) Mild hyponatremia and risk of fracture in the ambulatory elderly. QJM 101:583–588
11. Al-Dahhan J, Haycock GB, Nichol B, Chantler C, Stimmler L (1984) Sodium homeostasis in term and preterm neonates. III. Effect of salt supplementation. Arch Dis Child 59:945–950
12. Al-Dahhan J, Jannoun L, Haycock GB (2002) Effect of salt supplementation of newborn premature infants on neurodevelopmental outcome at 10–13 years of age. Arch Dis Child Fetal Neonatal Ed 86:F120–F123
13. Shirazki A, Weintraub Z, Reich D, Gershon E, Leshem M (2007) Lowest neonatal serum sodium predicts sodium intake in low birth weight children. Am J Physiol Regul Integr Comp Physiol 292:R1683–R1689
14. Ertl T, Hadzsiev K, Vincze O, Pytel J, Szabo I, Sulyok E (2001) Hyponatremia and sensorineural hearing loss in preterm infants. Biol Neonate 79:109–112
15. Murphy DJ, Hope PL, Johnson A (1997) Neonatal risk factors for cerebral palsy in very preterm babies: case-control study. BMJ 314:404–408

16. Li YF, Lu GJ, Han YK (2007) Risk factors for intracranial hemorrhage in very low birth weight infants. Zhongguo Dang Dai Er Ke Za Zhi 9:297–300
17. Mir NA, Faquih AM, Legnain M (1989) Perinatal risk factors in birth asphyxia: relationship of obstetric and neonatal complications to neonatal mortality in 16, 365 consecutive live births. Asia Oceania J Obstet Gynaecol 15:351–357
18. Ayus JC, Achinger SG, Arieff A (2008) Brain cell volume regulation in hyponatremia: role of sex, age, vasopressin, and hypoxia. Am J Physiol Renal Physiol 295:F619–F624
19. Moritz ML, Ayus JC (2003) The pathophysiology and treatment of hyponatraemic encephalopathy: an update. Nephrol Dial Transplant 18:2486–2491
20. Moritz ML, Ayus JC (2005) Preventing neurological complications from dysnatremias in children. Pediatr Nephrol 20:1687–1700
21. Kimelberg HK (2004) Increased release of excitatory amino acids by the actions of ATP and peroxynitrite on volume-regulated anion channels (VRACs) in astrocytes. Neurochem Int 45:511–519
22. Schoonman GG, Sandor PS, Nirkko AC, Lange T, Jaermann T, Dydak U, Kremer C, Ferrari MD, Boesiger P, Baumgartner RW (2008) Hypoxia-induced acute mountain sickness is associated with intracellular cerebral edema: a 3 T magnetic resonance imaging study. J Cereb Blood Flow Metab 28:198–206
23. Sundgren PC, Reinstrup P, Romner B, Holtas S, Maly P (2002) Value of conventional, and diffusion- and perfusion weighted MRI in the management of patients with unclear cerebral pathology, admitted to the intensive care unit. Neuroradiology 44:674–680
24. Kalantar-Zadeh K, Nguyen MK, Chang R, Kurtz I (2006) Fatal hyponatremia in a young woman after ecstasy ingestion. Nat Clin Pract Nephrol 2:283–288, quiz 289
25. Campbell GA, Rosner MH (2008) The agony of ecstasy: MDMA (3, 4-methylenedioxymethamphetamine) and the kidney. Clin J Am Soc Nephrol 3:1852–1860
26. McClellan MD, Dauber IM, Weil JV (1989) Elevated intracranial pressure increases pulmonary vascular permeability to protein. J Appl Physiol 67:1185–1191
27. Moritz ML, Ayus JC (2008) Exercise-associated hyponatremia: why are athletes still dying? Clin J Sport Med 18:379–381
28. Smith WS, Matthay MA (1997) Evidence for a hydrostatic mechanism in human neurogenic pulmonary edema. Chest 111:1326–1333
29. Ayus JC, Arieff AI (1995) Pulmonary complications of hyponatremic encephalopathy. Noncardiogenic pulmonary edema and hypercapnic respiratory failure. Chest 107:517–521
30. Ayus JC, Varon J, Arieff AI (2000) Hyponatremia, cerebral edema, and noncardiogenic pulmonary edema in marathon runners. Ann Intern Med 132:711–714
31. Sarnaik AP, Meert K, Hackbarth R, Fleischmann L (1991) Management of hyponatremic seizures in children with hypertonic saline: a safe and effective strategy. Crit Care Med 19:758–762
32. Bruce RC, Kliegman RM (1997) Hyponatremic seizures secondary to oral water intoxication in infancy: association with commercial bottled drinking water. Pediatrics 100:E4
33. Ayus JC, Wheeler JM, Arieff AI (1992) Postoperative hyponatremic encephalopathy in menstruant women. Ann Intern Med 117:891–897
34. Arieff AI, Ayus JC, Fraser CL (1992) Hyponatraemia and death or permanent brain damage in healthy children. BMJ 304:1218–1222
35. Arieff AI, Kozniewska E, Roberts TP, Vexler ZS, Ayus JC, Kucharczyk J (1995) Age, gender, and vasopressin affect survival and brain adaptation in rats with metabolic encephalopathy. Am J Physiol 268:R1143–R1152
36. Sgouros S, Goldin JH, Hockley AD, Wake MJ, Natarajan K (1999) Intracranial volume change in childhood. J Neurosurg 91:610–616
37. Xenos C, Sgouros S, Natarajan K (2002) Ventricular volume change in childhood. J Neurosurg 97:584–590
38. Farrar HC, Chande VT, Fitzpatrick DF, Shema SJ (1995) Hyponatremia as the cause of seizures in infants: a retrospective analysis of incidence, severity, and clinical predictors. Ann Emerg Med 26:42–48
39. Vajda Z, Pedersen M, Doczi T, Sulyok E, Stodkilde-Jorgensen H, Frokiaer J, Nielsen S (2001) Effects of centrally administered arginine vasopressin and atrial natriuretic peptide on the development of brain edema in hyponatremic rats. Neurosurgery 49:697–704, discussion 704–705
40. Doczi T, Laszlo FA, Szerdahelyi P, Joo F (1984) Involvement of vasopressin in brain edema formation: further evidence obtained from the Brattleboro diabetes insipidus rat with experimental subarachnoid hemorrhage. Neurosurgery 14:436–441
41. Kozniewska E, Gadamski R, Klapczynska K, Wojda R, Rafalowska J (2008) Morphological changes in the brain during experimental hyponatraemia. Do vasopressin and gender matter? Folia Neuropathol 46:271–277
42. Arieff AI (1986) Hyponatremia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in healthy women. N Engl J Med 314:1529–1535
43. Vexler ZS, Ayus JC, Roberts TP, Fraser CL, Kucharczyk J, Arieff AI (1994) Hypoxic and ischemic hypoxia exacerbate brain injury associated with metabolic encephalopathy in laboratory animals. J Clin Invest 93:256–264
44. Ayus JC, Armstrong D, Arieff AI (2006) Hyponatremia with hypoxia: effects on brain adaptation, perfusion, and histology in rodents. Kidney Int 69:1319–1325
45. Moritz ML, Carlos Ayus J (2007) Hospital-acquired hyponatremia–why are hypotonic parenteral fluids still being used? Nat Clin Pract Nephrol 3:374–382
46. McJunkin JE, de los Reyes EC, Irazuzta JE, Caceres MJ, Khan RR, Minnich LL, Fu KD, Lovett GD, Tsai T, Thompson A (2001) La Crosse encephalitis in children. N Engl J Med 344:801–807
47. Moritz ML, Ayus JC (2001) La Crosse encephalitis in children. N Engl J Med 345:148–149
48. Moritz ML, Ayus JC (2006) Case 8–2006: a woman with Crohn's disease and altered mental status. N Engl J Med 354:2833–2834
49. Papadopoulos MC, Krishna S, Verkman AS (2002) Aquaporin water channels and brain edema. Mt Sinai J Med 69:242–248
50. Al-Zahraa Omar F, Al Bunyan M (1997) Severe hyponatremia as poor prognostic factor in childhood neurologic diseases. J Neurol Sci 151:213–216
51. Moro N, Katayama Y, Igarashi T, Mori T, Kawamata T, Kojima J (2007) Hyponatremia in patients with traumatic brain injury: incidence, mechanism, and response to sodium supplementation or retention therapy with hydrocortisone. Surg Neurol 68:387–393
52. Chao YN, Chiu NC, Huang FY (2008) Clinical features and prognostic factors in childhood pneumococcal meningitis. J Microbiol Immunol Infect 41:48–53
53. Morton DH, Strauss KA, Robinson DL, Puffenberger EG, Kelley RI (2002) Diagnosis and treatment of maple syrup disease: a study of 36 patients. Pediatrics 109:999–1008
54. Glaser NS, Wootton-Gorges SL, Marcin JP, Buonocore MH, Dicarlo J, Neely EK, Barnes P, Bottomly J, Kuppermann N (2004) Mechanism of cerebral edema in children with diabetic ketoacidosis. J Pediatr 145:164–171
55. Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, Louie J, Kaufman F, Quayle K, Roback M, Malley R, Kuppermann N (2001) Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. N Engl J Med 344:264–269
56. Hoorn EJ, Carlotti AP, Costa LA, MacMahon B, Bohn G, Zietse R, Halperin ML, Bohn D (2007) Preventing a drop in effective

plasma osmolality to minimize the likelihood of cerebral edema during treatment of children with diabetic ketoacidosis. J Pediatr 150:467–473
57. Moritz ML, Ayus JC (2003) Prevention of hospital-acquired hyponatremia: a case for using isotonic saline. Pediatrics 111:227–230
58. Au AK, Ray PE, McBryde KD, Newman KD, Weinstein SL, Bell MJ (2008) Incidence of postoperative hyponatremia and complications in critically-ill children treated with hypotonic and normotonic solutions. J Pediatr 152:33–38
59. Holliday MA, Segar WE, Friedman A (2003) Reducing errors in fluid therapy. Pediatrics 111:424–425
60. Agut Fuster MA, del Campo Biosca J, Ferrer Rodriguez A, Ramos Martinez MJ, Viel Martinez JM, Agulles Fornes MJ (2006) Post-tonsillectomy hyponatremia: a posible lethal complication. Acta Otorrinolaringol Esp 57:247–250
61. Duke T, Kinney S, Waters K (2005) Hyponatraemia and seizures in oncology patients associated with hypotonic intravenous fluids. J Paediatr Child Health 41:685–686
62. Osier FH, Berkley JA, Newton CR (2006) Life-threatening hyponatraemia and neurotoxicity during chemotherapy for Burkitt's lymphoma. Trop Doct 36:177–178
63. Donaldson MD, Morrison C, Lees C, McNeill E, Howatson AG, Paton JY, McWilliam R (2007) Fatal and near-fatal encephalopathy with hyponatraemia in two siblings with fluticasone-induced adrenal suppression. Acta Paediatr 96:769–772
64. Ashraf A, Albert A (2006) Bronchiolitis with hyponatremia. Clin Pediatr (Phila) 45:101–102
65. Auroy Y, Benhamou D, Pequignot F, Jougla E, Lienhart A (2008) Hyponatraemia-related death after paediatric surgery still exists in France. Br J Anaesth 101:741
66. Moritz ML, Ayus JC (2008) 0.9% saline solution for the prevention of hospital-acquired hyponatremia: why is there still doubt? J Pediatr 153:444; author reply 444–446; discussion 446–447
67. Kinney S, Tibballs J, Johnston L, Duke T (2008) Clinical profile of hospitalized children provided with urgent assistance from a medical emergency team. Pediatrics 121:e1577–e1584
68. Way C, Dhamrait R, Wade A, Walker I (2006) Perioperative fluid therapy in children: a survey of current prescribing practice. Br J Anaesth 97:371–379
69. Snaith R, Peutrell J, Ellis D (2008) An audit of intravenous fluid prescribing and plasma electrolyte monitoring; a comparison with guidelines from the National Patient Safety Agency. Paediatr Anaesth 18:940–946
70. Davies P, Hall T, Ali T, Lakhoo K (2008) Intravenous postoperative fluid prescriptions for children: a survey of practice. BMC Surg 8:10
71. National Patient Safety Agency (2007) Reducing the risk of hyponatraemia when administering intravenous infusions to children. Available at http://www.nrls.npsa.nhs.uk/resources
72. Yung M, Keeley S (2009) Randomised controlled trial of intravenous maintenance fluids. J Paediatr Child Health 45:9–14
73. Montanana PA, Modesto i Alapont V, Ocon AP, Lopez PO, Lopez Prats JL, Toledo Parreno JD (2008) The use of isotonic fluid as maintenance therapy prevents iatrogenic hyponatremia in pediatrics: a randomized, controlled open study. Pediatr Crit Care Med 9:589–597
74. Ayus JC, Krothapalli RK, Arieff AI (1987) Treatment of symptomatic hyponatremia and its relation to brain damage. A prospective study. N Engl J Med 317:1190–1195
75. Hoorn EJ, Lindemans J, Zietse R (2006) Development of severe hyponatraemia in hospitalized patients: treatment-related risk factors and inadequate management. Nephrol Dial Transplant 21:70–76
76. Huda MS, Boyd A, Skagen K, Wile D, van Heyningen C, Watson I, Wong S, Gill G (2006) Investigation and management of severe hyponatraemia in a hospital setting. Postgrad Med J 82:216–219
77. Nzerue C, Baffoe-Bonnie H, Dail C (2002) Predicters of mortality with severe hyponatremia. J Am Soc Nephrol 13: A0728
78. Mohmand HK, Issa D, Ahmad Z, Cappuccio JD, Kouides RW, Sterns RH (2007) Hypertonic saline for hyponatremia: risk of inadvertent overcorrection. Clin J Am Soc Nephrol 2:1110–1117
79. Decaux G, Soupart A, Vassart G (2008) Non-peptide arginine-vasopressin antagonists: the vaptans. Lancet 371:1624–1632
80. Ayus JC, Arieff A, Moritz ML (2005) Hyponatremia in marathon runners. N Engl J Med 353:427–428
81. Hew-Butler T, Ayus JC, Kipps C, Maughan RJ, Mettler S, Meeuwisse WH, Page AJ, Reid SA, Rehrer NJ, Roberts WO, Rogers IR, Rosner MH, Siegel AJ, Speedy DB, Stuempfle KJ, Verbalis JG, Weschler LB, Wharam P (2008) Statement of the Second International Exercise-Associated Hyponatremia Consensus Development Conference, New Zealand, 2007. Clin J Sport Med 18:111–121
82. Sterns RH, Nigwekar SU, Hix JK (2009) The treatment of hyponatremia. Semin Nephrol 29:282–299
83. Palmer BF, Sterns RH (2009) Fluid, electrolytes and acid-base disturbances. Nephrol Self Assess Program 8:136–142
84. Decaux G, Soupart A (2003) Treatment of symptomatic hyponatremia. Am J Med Sci 326:25–30
85. Lauriat SM, Berl T (1997) The hyponatremic patient: practical focus on therapy. J Am Soc Nephrol 8:1599–1607
86. Tan H, Onbas O (2004) Central pontine myelinolysis central pontine myelinolysis manifesting with massive myoclonus. Pediatr Neurol 31:64–66
87. Hagiwara K, Okada Y, Shida N, Yamashita Y (2008) Extensive central and extrapontine myelinolysis in a case of chronic alcoholism without hyponatremia: a case report with analysis of serial MR findings. Intern Med (Tokyo, Japan) 47:431–435
88. Schuster M, Diekmann S, Klingebiel R, Volk T (2009) Central pontine myelinolysis despite slow sodium rise in a case of severe community-acquired hyponatraemia. Anaesth Intensive Care 37:117–120
89. Orakzai RH, Orakzai SH, Hasley PB (2008) Treating hyponatremia: how slow is safe? Central pontine myelinolysis despite appropriate correction of hyponatremia. Eur J Intern Med 19: e29–e31
90. Yoon B, Shim YS, Chung SW (2008) Central pontine and extrapontine myelinolysis after alcohol withdrawal. Alcohol Alcohol 43:647–649
91. Germiniani FM, Roriz M, Nabhan SK, Teive HA, Werneck LC (2002) Central pontine and extra-pontine myelinolysis in an alcoholic patient without hydro-electrolyte disturbances: case report. Arq Neuropsiquiatr 60:1030–1033
92. Nagaishi A, Yukitake M, Eriguchi M, Kuroda Y (2007) A case of alcoholic with vitamin B12 deficiency presenting central pontine and extrapontine myelinolysis on MRI. Rinsho shinkeigaku 47:173–176
93. Georgy V, Mullhi D, Jones AF (2007) Central pontine myelinolysis following 'optimal' rate of correction of hyponatraemia with a good clinical outcome. Ann Clin Biochem 44:488–490
94. Savasta S, Sepe V, Scagnelli P, Cisternino M, Libetta C, Soccio G, Marchi MA (2006) Severe hyponatremia followed by extrapontine myelinolysis. Kidney Int 69:423
95. Dellabarca C, Servilla KS, Hart B, Murata GH, Tzamaloukas AH (2005) Osmotic myelinolysis following chronic hyponatremia corrected at an overall rate consistent with current recommendations. Int Urol Nephrol 37:171–173

96. Pradhan S, Jha R, Singh MN, Gupta S, Phadke RV, Kher V (1995) Central pontine myelinolysis following 'slow' correction of hyponatremia. Clin Neurol Neurosurg 97:340–343
97. Alam NH, Yunus M, Faruque AS, Gyr N, Sattar S, Parvin S, Ahmed JU, Salam MA, Sack DA (2006) Symptomatic hyponatremia during treatment of dehydrating diarrheal disease with reduced osmolarity oral rehydration solution. JAMA 296:567–573
98. Keating JP, Schears GJ, Dodge PR (1991) Oral water intoxication in infants. An American epidemic. Am J Dis Child 145:985–990
99. Moritz ML (2007) Fluid replacement for severe hyponatremia. JAMA 297:41–42
100. Sasaki S (2004) Nephrogenic diabetes insipidus: update of genetic and clinical aspects. Nephrol Dial Transplant 19:1351–1353
101. Ho VB, Fitz CR, Yoder CC, Geyer CA (1993) Resolving MR features in osmotic myelinolysis (central pontine and extrapontine myelinolysis). AJNR Am J Neuroradiol 14:163–167
102. Wright DG, Laureno R, Victor M (1979) Pontine and extrapontine myelinolysis. Brain 102:361–385
103. Kumar SR, Mone AP, Gray LC, Troost BT (2000) Central pontine myelinolysis: delayed changes on neuroimaging. J Neuroimaging 10:169–172
104. Adler S, Verbalis JG, Williams D (1995) Effect of rapid correction of hyponatremia on the blood-brain barrier of rats. Brain Res 679:135–143
105. Ayus JC, Armstrong DL, Arieff AI (1996) Effects of hypernatraemia in the central nervous system and its therapy in rats and rabbits. J Physiol 492:243–255
106. Ayus JC, Krothapalli RK, Armstrong DL (1985) Rapid correction of severe hyponatremia in the rat: histopathological changes in the brain. Am J Physiol 248:F711–F719
107. Ayus JC, Krothapalli RK, Armstrong DL, Norton HJ (1989) Symptomatic hyponatremia in rats: effect of treatment on mortality and brain lesions. Am J Physiol 257:F18–F22
108. Baker EA, Tian Y, Adler S, Verbalis JG (2000) Blood-brain barrier disruption and complement activation in the brain following rapid correction of chronic hyponatremia. Exp Neurol 165:221–230
109. Kleinschmidt-DeMasters BK, Norenberg MD (1981) Rapid correction of hyponatremia causes demyelination: relation to central pontine myelinolysis. Science 211:1068–1070
110. Adler S, Verbalis JG, Meyers S, Simplaceanu E, Williams DS (2000) Changes in cerebral blood flow and distribution associated with acute increases in plasma sodium and osmolality of chronic hyponatremic rats. Exp Neurol 163:63–71
111. Soupart A, Penninckx R, Stenuit A, Perier O, Decaux G (1992) Treatment of chronic hyponatremia in rats by intravenous saline: comparison of rate versus magnitude of correction. Kidney Int 41:1662–1667
112. Verbalis JG, Martinez AJ (1991) Neurological and neuropathological sequelae of correction of chronic hyponatremia. Kidney Int 39:1274–1282
113. Sterns RH, Thomas DJ, Herndon RM (1989) Brain dehydration and neurologic deterioration after rapid correction of hyponatremia. Kidney Int 35:69–75
114. Soupart A, Penninckx R, Namias B, Stenuit A, Perier O, Decaux G (1996) Brain myelinolysis following hypernatremia in rats. J Neuropathol Exp Neurol 55:106–113
115. Ayus JC, Arieff AI (1993) Pathogenesis and prevention of hyponatremic encephalopathy. Endocrinol Metab Clin North Am 22:425–446
116. Goldszmidt MA, Iliescu EA (2000) DDAVP to prevent rapid correction in hyponatremia. Clin Nephrol 53:226–229
117. Perianayagam A, Sterns RH, Silver SM, Grieff M, Mayo R, Hix J, Kouides R (2008) DDAVP is effective in preventing and reversing inadvertent overcorrection of hyponatremia. Clin J Am Soc Nephrol 3:331–336
118. Bernstein SA, Williford SL (1997) Intranasal desmopressin-associated hyponatremia: a case report and literature review. J Fam Pract 44:203–208
119. Das P, Carcao M, Hitzler J (2005) DDAVP-induced hyponatremia in young children. J Pediatr Hematol Oncol 27:330–332
120. Ayus JC, Arieff AI (2002) Therapy of dDAVP-associated hyponatremia can lead to permanent brain damage. J Am Soc Nephrol 13:PUB002
121. Hasegawa H, Okubo S, Ikezumi Y, Uchiyama K, Hirokawa T, Hirano H, Uchiyama M (2009) Hyponatremia due to an excess of arginine vasopressin is common in children with febrile disease. Pediatr Nephrol 24:507–511
122. Don M, Valerio G, Korppi M, Canciani M (2008) Hyponatremia in pediatric community-acquired pneumonia. Pediatr Nephrol 23:2247–2253
123. Hoorn EJ, Geary D, Robb M, Halperin ML, Bohn D (2004) Acute hyponatremia related to intravenous fluid administration in hospitalized children: an observational study. Pediatrics 113:1279–1284
124. Arnon K, Riordan A, Playfor S, Millman G, Khader A (2008) Hyponatraemia and hypokalaemia during intravenous fluid administration. Arch Dis Child 93:285–287
125. Wattad A, Chiang ML, Hill LL (1992) Hyponatremia in hospitalized children. Clin Pediatr (Phila) 31:153–157
126. Cansick J, Rees L, Koffman G, Van't Hoff W, Bockenhauer D (2009) A fatal case of cerebral oedema with hyponatraemia and massive polyuria after renal transplantation. Pediatr Nephrol 24:1231–1234
127. Neville KA, Verge CF, O'Meara MW, Walker JL (2005) High antidiuretic hormone levels and hyponatremia in children with gastroenteritis. Pediatrics 116:1401–1407
128. Mehta S, Kumar P, Narang A (2005) A randomized controlled trial of fluid supplementation in term neonates with severe hyperbilirubinemia. J Pediatr 147:781–785
129. Neville KA, Verge CF, Rosenberg AR, O'Meara MW, Walker JL (2006) Isotonic is better than hypotonic saline for intravenous rehydration of children with gastroenteritis: a prospective randomized study. Arch Dis Child 91:226–232
130. Dearlove OR, Ram AD, Natsagdoy S, Humphrey G, Cunliffe M, Potter F (2006) Hyponatraemia after postoperative fluid management in children. Br J Anaesth 97:897–898; author reply 898
131. Stewart PC, McGrath K (2007) Paediatric maintenance fluids. Br J Anaesth 98:406; author reply 406
132. Coulthard MG, Cheater LS, Long DA (2007) Perioperative fluid therapy in children. Br J Anaesth 98:146–147
133. Singhi S, Jayashre M (2009) Free water excess is not the main cause for hyponatremia in critically ill children receiving conventional maintenance fluids. Indian Pediatr 46:577–583
134. Neville KA, Sandeman DJ, Rubinstein A, Henry GM, McGlynn M, Walker JL (2009) Prevention of hyponatremia during maintenance intravenous fluid administration: a prospective randomized study of fluid type versus fluid rate. J Pediatr doi:10.1016/j.jpeds.2009.07.059

Answers

1. a
2. c
3. d
4. e
5. b

HER MAJESTY'S CORONER

DISTRICT OF GREATER BELFAST

John L Leckey LL.M.
H.M. Coroner
Coroner's Office
Courthouse
Old Town Hall Building
80 Victoria Street
Belfast BT1 3GL
Northern Ireland

Telephone: (028) 9072 8202
Fax: (028) 9072 4559
E-mail: jleckey.rcj@courtsni.gov.uk

Dr E Sumner MA, BM, BCh, FRCA
Consultant Paediatric Anaesthetist
[redacted]

3rd March 2003

Dear Ed,

LUCY CRAWFORD, DECEASED

I am writing to ask your assistance in connection with the death of another child where hyponatraemia is a material factor. Dr Peter Crean, who gave evidence at the Raychel Ferguson inquest, has looked at the medical records for me and is of the opinion that the issues regarding Lucy are not as clear cut as those concerning Raychel. However, he has concerns about the management of Lucy whilst a patient at the Erne Hospital.

I am enclosing a copy of the post-mortem report and a copy of a letter I have received from Mr Stanley Millar who is the Chief Officer of the Western Health & Social Services Council. I would suggest you contact him direct for access to medical records. I am arranging to obtain statements from those concerned with the care and treatment of Lucy both in the Erne Hospital and the Royal Belfast Hospital for Sick Children and I will forward copies to you once these are available.

The death was reported to my office on 14th April 2000. The office note gives a history of gastroenteritis, dehydration and brain swelling. On behalf of my office Dr Michael Curtis who is Assistant State Pathologist spoke to Dr Hanrahan, the Consultant in charge at the Children's Hospital. Dr Curtis was satisfied that a post-mortem examination was unnecessary and the office note indicates that a Death Certificate was to be issued giving the cause of death as Gastroenteritis. Apparently a post-mortem examination was then carried out by Dr Denis O'Hara who is a Consultant Paediatric Pathologist at the Royal Victoria Hospital. This was not a

coroner's post-mortem. In retrospect Dr O'Hara should have reported his findings to me and I would then have made this a coroner's case. If it had not been for the letter from Mr Millar I would have been unaware of the fact that a post-mortem examination had been carried out. For your information I am enclosing a copy of the letter I received from Mr Millar and the post-mortem report of Dr O'Hara.

I am assuming that you are willing to undertake this task. Should you decide that you have had enough of inquests in Belfast please let me know. However I sincerely hope that you will feel able to assist me once again.

With best wishes.

Yours sincerely

J L LECKEY
HM CORONER FOR GREATER BELFAST

Enc

THE ROYAL GROUP OF HOSPITALS AND DENTAL HOSPITAL
HEALTH AND SOCIAL SERVICES TRUST

Trust Policy **TP 9/00**

Adverse Incident Reporting

Rationale

Adverse events can be defined as "any unexpected or untoward event that has a detrimental effect on an individual patient, member of staff or public." This definition includes near miss reporting. Events related to clinical treatment and outcomes, patient care, working practices, health, safety, fire, security (including data protection) and events involving property (1,2,) are covered by this policy.
Incident and near miss reporting can be used as a means of identifying the risks to which patients, staff and members of the public may be exposed.

Objectives

- To provide staff with an opportunity to participate in and effect changes in practice and procedures
- To provide information to allow effective evaluation and monitoring of patient care and procedures
- To provide formal documentation to assist in the management of complaints, claims and investigations by statutory bodies.

Policy

This policy applies to all staff and any other employers whose activities may directly or indirectly affect patients, staff or visitors.
All staff must report adverse events as outlined in the procedure for adverse events reporting (3).
Line managers are responsible for implementing the policy within each ward and department and staff must follow the recognised procedures. These are summarised as follows:

- ensuring all staff are aware of the policy and procedures
- ensuring incident documents and reports are available
- acting appropriately on all reports received liasing with Risk Management and others as necessary.

The Risk and Occupational Health Directorate is responsible for:

- reviewing incidents and actions taken by wards and departments
- following up on actions taken as deemed necessary
- notifying appropriate persons or government agencies where required (4)
- ensuring information is up to date and available to relevant personnel
- managing incident information on behalf to include the evaluation and monitoring of incidents and maintaining a central record of events
- maintaining records, database and archive files.

The monitoring and review of adverse event reporting will form part of ward and department audit activities in line with Clinical Governance and Controls Assurance.

William McKee

W McKee
Chief Executive
May 2000

Review Date

Authors: John Orchin, Health & Safety manager
June Champion, Clinical Risk Manager

REFERENCES

1 Fire Precaution Policy TP 4/00
2 Information Systems Security TP 26/98
3 Procedure for Adverse Incident Reporting April 2000
4 Reporting of Injuries, Diseases and Dangerous Occurrence (NI) 1997

Procedure for Adverse Incident Reporting – IR 1 Form

1.0 Introduction

When an adverse incident occurs, a record of what happened must be completed. Each incident will require a review of what happened, why it occurred, and steps taken to resolve the incident and to prevent recurrence. Line managers will ensure that incident forms – IR 1 forms – are available in each area for this purpose. ***(order as stock item WGA 6439)***

2.0 Definition

An adverse incident is *any unexpected or unplanned incident that has a short or long term detrimental effect on patients, staff or others, which results in material loss or damage, loss of opportunity or damage to reputation. This definition includes 'near miss' reporting.*

3.0 Procedure for Reporting an Adverse Incident

3.1 Secure the location and ensure that further immediate harm is prevented. Where first aid is required this should be instituted, referral to A&E or Occupational Health should be considered. Inform line manager.

3.2 A list of non-clinical incidents which must be reported to the Health & Safety Executive (N.I.) is attached in appendix 1. Also attached is a list of clinical and other incidents which should be reported. This list is not comprehensive but should give an indication of what should be reported.

3.3 Where problems arise outside the Line Managers competence he/she should contact Mr John Orchin, Health & Safety Manager/Mrs June Champion, Clinical Risk Manager exts: 3928 / 2371 or the Communication Centre.

3.4 Legibly document all the information in black pen or ink on the incident report (IR 1 form). As these forms are three part carbonated forms, ensure that addressograph labels, if used, are applied to each form, otherwise print firmly using a separation board between each set of forms.

3.5 Document fact only, not opinion. It is important to complete all parts of the form. State N/A (not applicable) where it is appropriate to do so.

3.6 For patient related incidents, make a comprehensive entry covering relevant clinical details in the patient's medical record. The IR 1 form **should not** be filed in the medical record.

3.7 For staff incidents, make an entry in the yellow accident book (BI 510) to cover requirements for industrial injuries benefit as required by the Social Security Act (NI) 1967.

3.8 In the event of a sharps injury follow the procedure in the Trust Policy Manual – 'Exposure to Body Fluids – Policy for Management of (including Sharps injuries) TP8/98'.

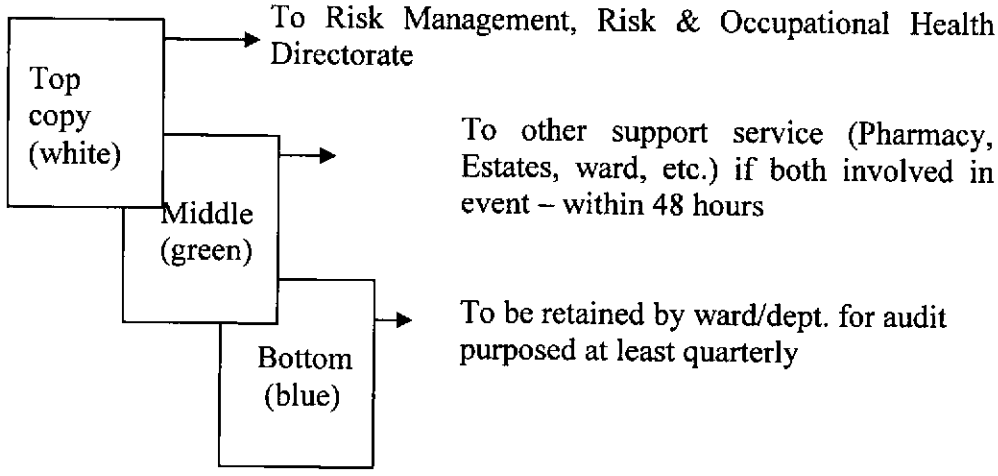
4.0 Grade the incident

4.1 The IR 1 report form requires you to grade each incident as to severity. These grades are outlined as follows:

Severity	Can be defined as:
Major	• life threatening • long-term significance to person • outcome could have serious consequences
Moderate	• serious morbidity • intermediate with some significance to person • significant disruption in time, service
Minor	• self limiting • minimal interruption of activities • short term
Insignificant	• probable risk in time • no interruption
Near miss	• no adverse outcome but risk potential evident

5.0 Forward the report:

5.1 Once the IR 1 form is complete, you will need to send it on for review and action if required. The diagram below outlines the procedure to follow:



5.1.1 The middle (green) copy is used as a mechanism for two services to resolve a particular incident, e.g.:

- a drug dispensing error is picked up on the ward and an IR 1 form would be completed, the top copy (white) is sent to Risk Management, the middle copy (green) should go to pharmacy to notify that an error was made and bottom copy (blue) retained by the ward/dept.

- following a staff tripping incident on a damaged floor the middle (green) copy should go to the Estates Department.

5.1.2 If the green copy does not need to be forwarded to another service, then send it with the white copy to Risk Management who will hold it with the original top copy.

5.2 Further advice can be obtained from the Health & Safety Manager or Clinical Risk Manager on ext: 3928 / 2371. Out of hours further advice can be obtained from the line manager or the Bed Management Co-ordinator.

6.0 What happens after an incident is reported?

6.1 Initially there should be discussions within the Directorate, normally by the departmental manager, about the incident and any follow-ups that should be undertaken by staff themselves.

6.2 If another support service was involved or needs to be involved in the incident follow up, the second (green) copy will initiate a response by the manager of that service. This is particularly true for the following:

- radiation (Medical Physics will lead on investigations for radiation)
- microbiological exposure (e.g. Hepatitis B)
- medication errors
- facilities and environmental issues (i.e. building maintenance, clinical waste, non-medical clinical equipment)

6.3 The top copy will be received by the Risk Management, Risk & Occupational Health Directorate, and an acknowledgement of receipt for **major/moderate incidents** sent. This will identify when the IR 1 form was received, who is dealing with it and indication of follow up by Risk Management. If the second (green) copy was sent to another service and was indicated on the form itself (see 'action' section on form), then Risk Management may seek further information from that Department on the event as part of the overall follow ups.

6.1.1 In the event of verbal notification, the Risk Management staff will take basic details from you and ask that the top copy be sent and if appropriate, advise that the second copy (green) be sent to others who may need to be involved in follow ups.

6.1.2 You may also be advised to provide supporting statements about the incident especially if it is serious, i.e. if a report to the Coroner or the Health & Safety Executive is required, or lastly, if there is a view by staff that a complaint or litigation may ensue, then the Litigation Management will require statements.

6.2 Incidents requiring notification to government organisations (i.e. Health and Safety Executive, Environmental Health, RUC and Coroner will be co-ordinated by Risk Management/Litigation Management.

- **Exceptions for others to notify government organisations: Radiation**

Notification will be undertaken by the Trust Radiation Protection Adviser based in Medical Physics who will oversee any investigation from then on and report to the appropriate government organisation.

- **Exceptions for others to notify government organisations: Medicines**

The Pharmacy Department will undertake investigations and notification to the Department of Health. Where involvement of Medical Physics is also required, Pharmacy and the Radiation Protection Adviser will liaise.

6.3 Risk Management will follow up on specific reported incidents. This may involve liaising with other Directorates, researching other types of incidents, developing guidelines and/or notification to Directors of potential risks, options for risk reduction and required resources.

6.4 Each incident is categorised by the Risk Management into person category (e.g. patient, staff), type and cause of incident, any contributory factors and severity of the incident.

6.5 The information is entered into a managed database system registered under the Data Protection Act. Each entry is made using a unique identifier number. Information is reviewed to determine trends or patterns within the Trust and to initiate research or project work which would help to further identify and reduce risks. An example of this would be reviewing manual handling injuries to severity and locations to assist in developing strategies with line managers to reduce risks.

6.6 Statistical information will routinely be made available to the Risk Management Steering Group, Trust Health & Safety Committee, Directorate Risk Management Group. This information is anonymous and confidential.

6.7 The Risk Management Steering Group may choose through this review to establish a task group to assess and evaluate risks identified through incident reports as part of the Trust strategy for risk management.

7.0 Procedure for managing major/moderate incidents.

7.1 Events graded major or moderate require further immediate action. These may be serious incidents, but generally will not require activation of the Trust's disaster plans.

8.0 Guidelines for dealing with major/moderate incidents

8:1 Follow the Trust procedure for incident reporting. The Directorate Management Team will take action immediately to prevent any further harm/potential harm to patients, staff or others if required. This may involve shutting down equipment, suspending treatments or operations, withdrawing facilities.

NOTE: Out of normal office hours i.e. between 5.00 p.m. & 8.00 a.m. weekdays and 24 hours at weekends and public holidays the following procedure should be followed.

8.2 Contact the Bed Manager immediately by telephone, stating the urgency of the situation. The Bed Manager will then contact the Risk Management Team (Health & Safety Manager/Clinical Risk Manager, as per rota). He/she will also notify the Clinical Director/Director, the Medical Director and the Director of Nursing and Patient Services. The Risk Management Team will notify Occupational Health and all external bodies such as the Health & Safety Executive, R.U.C. etc.

8.3 The Bed Manager will mobilise communications support through the Directorate of Corporate Affairs, they will base the initial response on a verbal report. Under no circumstances should employees talk directly to the media. All enquiries should be referred to Corporate Affairs.

8.4 The Bed Manager will identify the group/s of people likely to be involved, gather supporting information listed below. This will need to be given to the Risk Management Team once complete,

8.5

- Witness statements.
- Documents which may relate to the incident (e.g. batch numbers),
- Name of medical staff involved including named consultant.
- Treatment/technique used.
- Type of equipment/machinery involved.
- Clinical diagnosis.
- Indications of support including counselling for patients and staff.
- Additional staffing requirements necessary to maintain the service.

8.5 Depending on the nature of the incident and the type of patient/staff involved, full consideration should also be given as to whether it would be helpful for the clinical team to inform the patient's relatives of the incident at the same time. This will be decided by the Clinical Director in consultation with the staff involved and decide on the most appropriate method for informing them.

8.6 The Risk Management Team must consider the need for staff support and critical incident debriefing. The Occupational Health Adviser on call should be notified of the incident early in order that appropriate critical debriefing of staff can be planned.

8.7 Press statements should be released through the Corporate Affairs Directorate in conjunction with Trust Policy, i.e. Media Information about Patients and Confidentiality Policy. Patients must be notified before any press statement is released.

8.8 If major media attention is involved, the Directorate of Corporate Affairs will make arrangement to accommodate them away from patient areas and will be the liaison with them.

8.9 The Risk Management Team will co-ordinate investigation, monitoring and evaluation of the incident providing a written report to Directors on process, outcome and recommendations for change if required.

8.10 The Risk Management Team will liaise with the Legal Services Directorate notifying the Associate Medical Director and named Director for actions. They will also liaise with staff involved, supported by the Risk Management Service, to gather relevant information. All records, materials, documents and equipment related to the incident are to be retained for an indefinite period.

8.11 For patient incidents it is advisable to inform the patient's GP as soon as possible by telephone or by fax. The Clinical Director of the service involved will contact the GP and give the following information:

- The nature of the incident.
- The patients involved.
- How contact is being made.
- Written confirmation of actions.

If there has been a time interval between the incident and its discovery, the surgery should be contacted first to ensure that the patient is still alive and their current address. **It is imperative that GPs are kept informed and up-to-date, particularly, where their patient's welfare has been adversely affected.**

9.0 Monitoring and Evaluation

This will form part of Directorate audit activities

10.0 Version Control

Version 5
Mr John Orchin and Mrs June Champion for Risk & Occupational Health Directorate

Non-clinical Adverse Incidents which must be reported

Health and safety incidents involving staff, patients and visitors *must be reported to Risk Management within 5 working days for legal purposes*

- physical assault resulting in injury
- exposure to body fluids, chemicals, cytotoxics or other potentially harmful substance
- any injury where a person at work is off **for more than three (3)** days after the incident
- any injury to a person NOT at work, but which results from an incident arising out of or in connection with work and results in them being taken to hospital for treatment
- any injury to a person who is NOT at work on hospital premises as a result of an incident if it falls into any of the categories listed below
- fracture of any bone other than fingers, thumbs or toes
- dislocation of shoulder, hip, knee or spine
- any amputation
- loss of sight of an eye (whether temporary or permanent); a penetrating injury to the eye, or a chemical or hot metal burn to the eye
- any injury resulting from electric shock or electrical burn leading to unconsciousness or needing admission to hospital for more than 24 hours
- any other injury requiring resuscitation or admission to hospital for more than 24 hours, or leading to hypothermia, heat induced illness or unconsciousness
- loss of consciousness caused by asphyxia or by exposure to a harmful substance or biological agent
- acute illness requiring treatment or causing loss of consciousness caused by breathing in or swallowing any substance or absorbing it through the skin
- acute illness needing medical treatment where there is reason to believe it resulted from exposure to a pathogen or infected material
- dangerous occurrences related to lifting machinery, electric short circuit, explosion, fire, collapse of a building/structure, escape of a pathogen or substance (e.g. mercury) and other similar incidents.

Radiation

For Radiation incidents, contact the Radiation Protection Adviser (RPA) via Medical Physics, tel: 028 90793681 ext; 2383 or the switchboard immediately. An incident form will need to be completed as per guidelines. Any further advice as to procedure will be given by the RPA.

- any radiation incident involving staff or patients.

Clinically Related Adverse Incidents which should be reported

Procedure

- Thrombosis including deep vein thrombosis as a result of treatment/procedure
- Exposure including overexposure or over-treatment with radiation **see list of Non-clinical incidents*
- Stroke/CVA as a result of treatment/procedure
- Cardiac arrest as a result of treatment/procedure
- Unexpected death as a result of treatment/procedure
- Unexpected wound infection as a result of treatment
- Damage to adjacent tissues, organs, etc.
- Consent not obtained prior to treatment
- Extravasation of cytotoxics and other potential harmful medications
- Missing items of equipment and/or items after invasive procedure
- Miscount of equipment and/or items which may have an effect on patient
- Sepsis as a result of treatment/procedures
- Use of unsterile equipment in situations where sterile equipment is required
- Operating or undertaking a procedure on wrong body part or area

Equipment

- Equipment failure or misuse
- A fault or failure of equipment

Drug

- Unexpected and/or serious side effects of medications including antidotes
- Errors in dispensing, prescribing and/or administration of medication, for example when:

    1 an antidote had to be, or needs to be given to reverse the effects of drugs given by a doctor or nurse or self administered by a patient excluding overdoses taken in the community
    2 an incorrect drug has been administered
    3 more than the dose prescribed of an IV drug has been given or where adverse clinical effects have occurred due to improper administration by excessive rate of infusion
    4 during administration of an IV, an incompatibility becomes apparent
    5 these are errors involving drugs given by intrathecal and epidural routes
    6 omissions of doses that may lead to serious clinical consequence.

- Any out of date products such as IV products prepared by Pharmacy, oral and parenteral chemotherapy products or otherwise which have been administered or could have been administered.

Other

- Perforation of any tissue, organ, etc. not as part of a procedure
- Any incident which may lead to serious clinical or non-clinical consequences /outcomes
- Any fracture sustained by a patient not associated with a pathological condition
- Unexpected damage to arteries, vessels and/or nerves
- Excessive bleeding and/or haemorrhage requiring transfusion
- Pressure sores
- Unexpected return to theatre
- Unqualified staff performing treatment/procedures
- Service delays
- Confidentiality issues
- Incidents which may affect patient care management (staffing levels, skills mix)
- Mislabelled specimens
- Wrong results given out
- Where a complaint or claim may arise from treatment or actions
- ANY OTHER CATEGORY WHICH GIVES CAUSE FOR CONCERN

Organisational/Business Risks

Information Technology

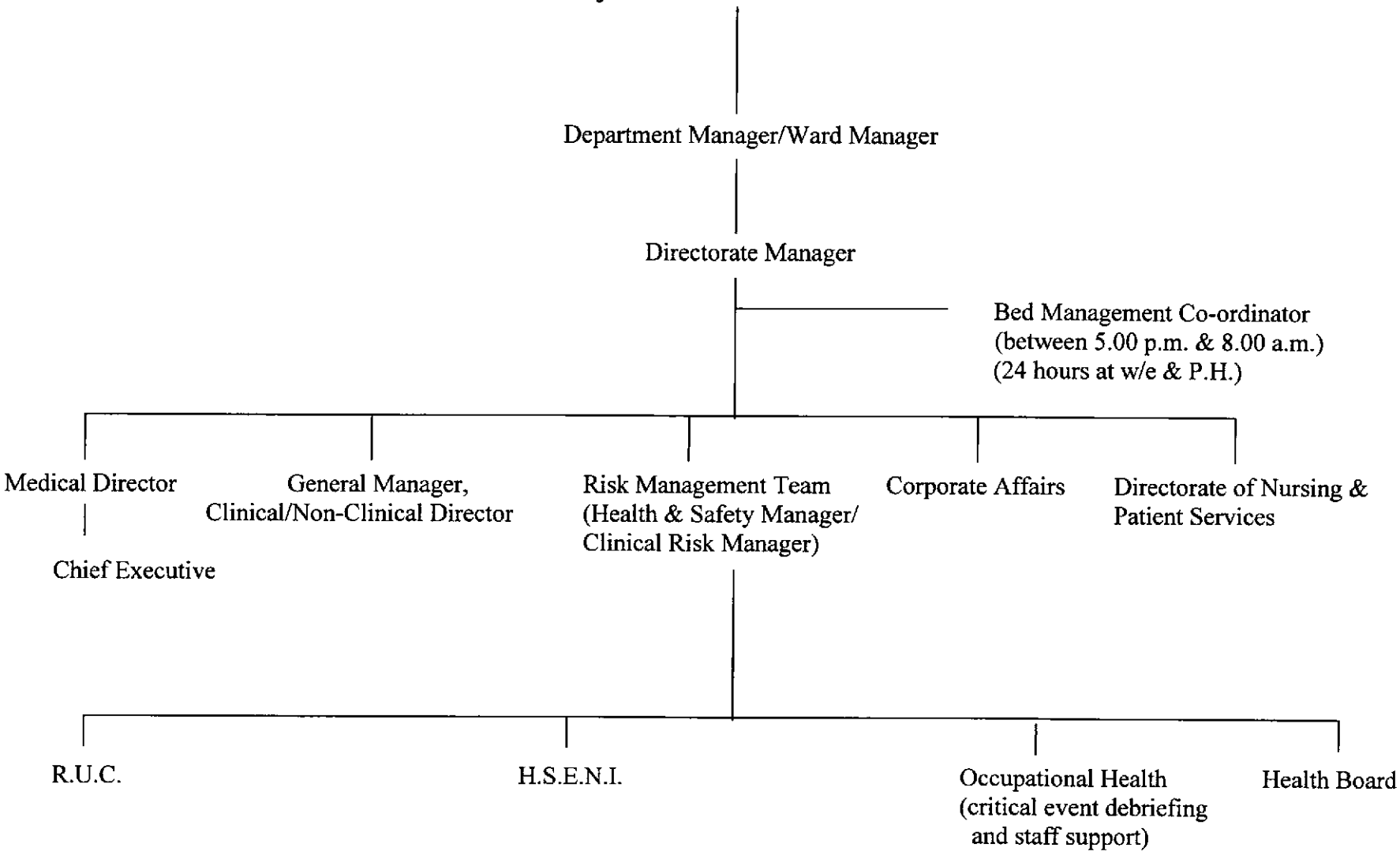
- the disclosure of confidential information to any unauthorised individual
- the integrity of the system or data being put at risk
- the availability of the system or information being put at risk
- an adverse impact, for examples:
  - embarrassment to the NHS
  - threat to personal safety or privacy
  - legal obligations or penalty
  - financial loss
  - disruption of activities
- denial of access to data
- destruction of data or equipment
- unauthorised modification of data

Business associated risks

- security incidents (theft, breach of confidentiality, threats, etc)
- damage to property, personal or Trust belongings
- service issues (delays, unavailable, inappropriate, inadequate)

FLOW CHART
FOR

Major/Moderate Adverse Incidents



Patient' name and address	Patient's Hospital no.	Patient's GP	Check pts Circs (4)	Date & time & method of contact	Contacted by	Response to contact	Noted in record (4)	GP informed of contact (4)

F/Procedure/AdvEv/Feb2000/V5

HSC Business Services Organisation

Directorate of Legal Services
PRACTITIONERS IN LAW TO THE HEALTH & SOCIAL CARE SECTOR

2 Franklin Street, Belfast, BT2 8DQ
DX 2842 NR Belfast 3

Your Ref: INQ-4194-13 Our Ref: HYP B04/04

Date: 8th May 2013

Ms A Dillon
Solicitor to the Inquiry
Arthur House
41 Arthur Street
Belfast
BT1 4GB

Dear Madam,

RE: INQUIRY INTO HYPONATRAEMIA RELATED DEATHS – RAYCHEL FERGUSON PRELIMINARY

I refer to the above and in particular to Dr Crean's witness statement WS292/2.

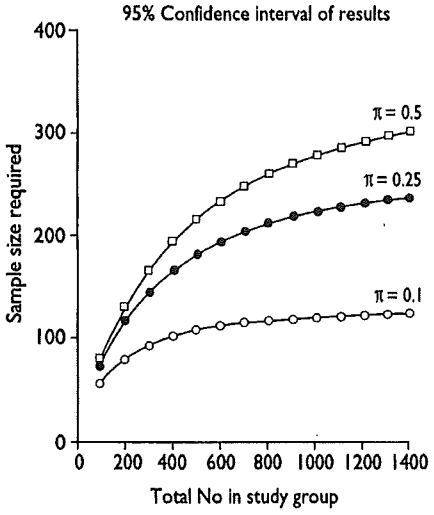
Please note that, in addition to the papers referred to therein, Dr Crean will also be referring to a letter from Simon J. Ellis in the BMJ entitled "Management of Hyponatraemia: Differentiate between acute and chronic", which relates to an earlier article in that journal by Arieff AI. (Management of Hyponatraemia. BMJ 1993;307:305-8), and the response to that letter by Alan I. Arieff.

I enclose a copy of BMJ 1993;307:736 (18 September) for your attention.

Yours faithfully,

JR Bolton

Joanna Bolton
Solicitor Consultant



Graph used to calculate sample size

the asthmatic patients would need to be sampled, at random.

The chart may seem counterintuitive in that the sample required to estimate $\pi=0{\cdot}1$ is smaller than that required to estimate $\pi=0{\cdot}5$ and yet one would expect a larger sample to be needed to estimate a smaller proportion. This arises because the variance of an estimated proportion is largest at $\pi=0{\cdot}5$. The width of the confidence interval, however, is fixed at 0·05, and so if $\pi=0{\cdot}1$ the allowable error is 50% of the estimate whereas if $\pi=0{\cdot}5$ the allowable error is only 10% of the estimate. The formula given by Machin and Campbell should be used for confidence intervals with other widths.[2]

This formula should not be used to test hypotheses. For example, to test the hypothesis that 50% of asthmatic patients had had their peak flow recorded in the past year one would use conventional tables, as described by Daly, in which the concept of the power of the test is also involved.[3]

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1 Peters L. Audit in primary medical care paediatrics. *BMJ* 1993;307:51-3. (3 July.)
2 Machin D, Campbell MJ. *Statistical tables for the design of clinical trials.* Oxford: Blackwell Scientific, 1987.
3 Daly LE. Confidence intervals and sample sizes: don't throw out all your old sample size tables. *BMJ* 1991;302:333-6.

Management of hyponatraemia

Differentiate between acute and chronic

EDITOR,—Allen I Arieff is correct to draw attention to the dangers of hypotonic fluids in the postoperative period.[1] He is incorrect, however, to state that neither the magnitude nor the rate of fall in serum sodium concentration is important in the genesis of brain damage. In his own series of 15 women who died or had permanent brain injury all had profound hyponatraemia and had been made acutely hyponatraemic.[2] Conversely, chronic severe hyponatraemia may be asymptomatic and minor perturbations of sodium do not cause damage.

Of most concern is Arieff's advocacy of hypertonic saline with loop diuretics for correcting hyponatraemia by up to 25 mmol/l in the first 24 hours. Sodium chloride is not innocuous, and correction of chronic hyponatraemia at a rate greater than 10 mmol/l/24 h risks long term neurological complications.[3] In addition, it is misleading to suggest that calculations of sodium deficit can be used to control the rate of correction accurately. Even in Arieff's own hands the rate of correction varied widely.[4] Rehydration with isotonic saline has resulted in rapid correction producing central pontine myelinolysis.[5] Even spontaneous correction can be rapid. Few authors would agree with Arieff that central pontine myelinolysis has nothing to do with hyponatraemia in most cases. In the 406 cases of central pontine myelinolysis that I identified in the literature severe hyponatraemia (≤120 mmol/l) had occurred in 179, moderate hyponatraemia in 69, normonatraemia in 12, and hypernatraemia in 24; the natraemic state was not recorded in the remaining 122.

Arieff fails to differentiate between acute and chronic cases in his treatment regimen or to address the underlying causes of the hyponatraemia. The opinion that "the rate of correction is not a factor in the genesis of hyponatraemic brain injury" is a minority view.

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1 Arieff AI. Management of hyponatraemia. *BMJ* 1993;307:305-8. (31 July.)
2 Arieff AI. Hyponatremia convulsions, respiratory arrest and permanent brain damage after elective surgery in healthy women. *N Engl J Med* 1986;314:1529-35.
3 Ellis SJ. The neurological complications of hyponatraemia [abstract]. *Neurology* 1993;43:A271.
4 Ayus JC, Krothapalli RK, Arieff AI. Treatment of symptomatic hyponatremia and its relation to brain damage: a prospective study. *N Engl J Med* 1987;317:1190-5.
5 Lundbom N, Laurila O, Laurila S. Central pontine myelinolysis after correction of chronic hyponatraemia. *Lancet* 1993;342: 247-8.

Author's reply

EDITOR,—Simon J Ellis's concerns seem largely to reflect anecdotally generated opinions rather than documented information. For example, data showing that either the magnitude or the rate of development of hyponatraemia correlates with brain damage do not exist. On the contrary, a recent prospective study of 739 patients who were hyponatraemic postoperatively clearly shows that neither factor has any relation to brain damage.[1]

Ellis expresses concern that treatment with hypertonic saline "risks long term neurological complications." Although earlier anecdotal reports speculated on this possibility, confounding variables, such as alcoholism and hypoxic brain damage, were not considered. Data are available on 164 consecutive hyponatraemic patients studied prospectively worldwide, in whom confounding variables were not present.[2] Rates of correction ranged up to 20 mmol/l/h. No patient suffered any neurological complication, which shows that the rate of correction is not a factor in the occurrence of brain damage.[2]

The contention that serum sodium deficit cannot be accurately controlled during correction of hyponatraemia is unsupported by any data. In over 200 consecutively treated patients the change in serum sodium concentration was essentially identical with that predicted from the suggested calculations,[3] and worldwide reports from virtually all other investigators over 40 years yield identical results.[3]

Ellis then suggests that treatment of hyponatraemia with hypertonic saline may cause central pontine myelinolysis. A few such anecdotal reports exist. Retrospective review of hyponatraemic patients diagnosed as having central pontine myelinolysis shows, however, that the diagnosis was incorrect about 85% of the time, while among patients with central pontine myelinolysis other conditions known to be associated with cerebral demyelination were present.[4] Central pontine myelinolysis has never occurred in any prospective trial of the treatment of hyponatraemia.[2] It is associated not with hyponatraemia but with other major medical illness, such as cirrhosis, alcoholism, cachexia, and burns.[2]

Ellis's belief that my statement that "the rate of correction [of hyponatraemia] is not a factor in the genesis of hyponatraemic brain injury" is a minority view is erroneous. In fact, when only controlled studies rather than anecdotal data are considered it is a unanimous view. All prospective studies have found no relation between the rate of correction of hyponatraemia and brain injury.[2] Ellis cites an unreviewed abstract in support of his undocumented claims.[5] The statistical test he used, however, is invalid for the available sample size, negating the conclusions.[5] Given that Ellis's overall mortality of 31% (26 of 84 patients died) is the highest ever reported worldwide,[5] I urge him to re-evaluate his nihilistic approach to the treatment of hyponatraemia.

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1 Ayus JC, Wheeler JM, Arieff AI. Postoperative hyponatremic encephalopathy in menstruant women. *Ann Intern Med* 1992; 117:891-7.
2 Ayus JC, Arieff AI. Pathogenesis and prevention of hyponatremic encephalopathy. *Endocrinol Metab Clin North Am* 1993;22:425-46.
3 Arieff AI. Management of hyponatraemia. *BMJ* 1993;307:305-8. (31 July.)
4 Tien R, Arieff AI, Kucharczyk W, Wasik A, Kucharczyk J. Hyponatremic encephalopathy: is central pontine myelinolysis a component? *Am J Med* 1992;92:513-22.
5 Ellis SJ. The neurological complications of severe hyponatremia [abstract]. *Neurology* 1993;43:A271.

Generalised seizure due to terfenadine

EDITOR,—We recently reported on a 27 year old man who suffered his first tonic-clonic seizure while taking the antihistamine terfenadine.[1] In the absence of any other relevant precipitants or history, and in view of the temporal coincidence, we proposed a causal relation between the drug and the seizure. Twelve months later he has now had a second unprovoked seizure, which was not related to any drug use. It is therefore likely that he has primary generalised tonic-clonic epilepsy; terfenadine may not have been the cause of his original seizure.

This case illustrates the importance of long term follow up in the assessment of possible adverse drug reactions.

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1 Tidswell P, d'Assis-Fonseca A. Generalised seizure due to terfenadine. *BMJ* 1993;307:241. (24 July.)

Unexpected cardiac abnormalities in Lyme disease

EDITOR,—Evidence is growing that cardiac abnormalities may occur as a late complication of infection with *Borrelia burgdorferi* (Lyme disease).[1,2] We carried out detailed cardiac investigations on a series of patients with Lyme disease after a man developed reversible complete atrioventricular block and aortic valve regurgitation four and a half years after his initial, untreated illness.

We studied eight outpatients at the infectious diseases unit at Ruchill Hospital. The diagnosis of Lyme disease was based on clinical features of disseminated Lyme disease; a positive result of an