Witness Statement Ref. No. 178/5

**NAME OF CHILD: Claire Roberts**

**Name: Ian S.Young**

**Title: Professor**

**Present position and institution:**

**Professor of Medicine, Queen's University Belfast**

**Consultant in Clinical Biochemistry, Belfast Health and Social Care Trust**

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

**Senior Lecturer in Clinical Biochemistry, Queen's University Belfast**

**Consultant in Clinical Biochemistry, Royal Group of Hospitals, Belfast**

**Membership of Advisory Panels and Committees:**
*[Identify by date and title all of those between January 1995-December 2004]*

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

096-007-039 Statement to the PSNI

091-010-060 4/5/2006 Deposition to the Coroner

WS 178-01

30/10/12 Response to reports of Dr.R MacFaul on Claire Roberts

**OFFICIAL USE:**
**List of previous statement, depositions and reports attached:**

| Ref: | Date: | |
|---|---|---|
| | | |

**Other points you wish to make including additions to any previous Statements, Depositions and or Reports**
*[Please attach additional sheets if more space is required]*

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

**Signed:** **Ian Young** **Dated: 26/11/12**

**Response to Dr.MacFaul's statement dated 7/11/12 and related discussion in his oral evidence**

Professor Ian S.Young

The purpose of this report is to address issues raised in Dr.MacFaul's response of 7/11/12 to my earlier statement (30/10/12) and during his oral evidence. My aim is to confirm for the Inquiry those areas where, in my opinion, Dr.MacFaul and I are in agreement and disagreement, and to indicate why in the latter case I believe that my position is the appropriate one.

As a result of comments made by Dr.MacFaul, I believe that he has not given sufficient weight to contemporary publications in the early 1990s relating to fluid management in children with cerebral disease. There is a clear body of contemporary evidence which favours my view and, furthermore, the majority of experts who have commented on Claire's management are also aligned with my position rather than that adopted by Dr.MacFaul, as summarized below.

**Chairman's summary of the Royal's position:**

Before addressing Dr.MacFaul's position I want to comment on the summary made by the Chairman of the Royal's position in relation to Claire's condition and fluid management. This is recorded on page 5/6 on the evidence of 14/11/12 in the following terms: "So the Royal's position is this that, in 1996, when Claire was felt to be suffering from SIADH and when she had a sodium level of less than 135, which she did from Monday night, the practice would have been to restrict fluid intake and to consider administering fluid of a higher content of sodium. But that wasn't done; isn't that right?"

While some elements of this statement are correct, I do not agree that it correctly summarises the position of the Royal. Certainly, it is not my position or the position which I have put forward at any stage in 2004 or recently. It may be helpful to break this summary down into its component parts and implications in order to be completely clear about this:

1) "In a patient suffering from SIADH it is appropriate to restrict fluid intake and to consider administering fluid with a higher content of sodium." I agree with this statement.
2) "Claire was felt to be suffering from SIADH". This is correct, but only from Tuesday night at 11 PM. It is not the Royal's position or my position that Claire was felt to be suffering from SIADH on Monday night on admission. With hindsight it is possible to say that had

additional tests been done during the day on Tuesday it is likely that a diagnosis of SIADH would have been made then. However, in 1996 this was only considered at 11pm on the Tuesday.

3) "A sodium less than 135 should have triggered consideration of SIADH." SIADH is a diagnosis which should be considered in a patient with hyponatraemia. Contemporary paediatric sources defined hyponatraemia as a serum sodium <130 mmol/l (Paediatric Vade Mecum quoted by Dr.MacFaul at 238-002-035). Claire's sodium on admission was slightly below the lower reference interval (135) but above the level defined as hyponatraemia (<130) in 1996, a point on which Dr.MacFaul and myself agree (see for instance P64 lines 19 -21, 12/11/12). Therefore, there was no indication for the clinicians to make a diagnosis of SIADH on Monday evening or hence to take any measures to treat SIADH at that time.

**Position of Dr. MacFaul:**

**Areas of agreement:**

Dr.MacFaul and I agree about the requirement to restrict fluid intake in the presence of established SIADH, whether in 1984, 1996 or 2004, and to consider the administration of fluids with a higher sodium content.

Once this diagnosis became part of the stated differential (at indicated in the clinical notes at 11 pm on Tuesday), then fluid restriction was initiated and consideration was given to the administration of fluids with a higher sodium content, although a decision was made not to do this.

**Key area of disagreement:**

**The requirement to routinely restrict fluids and use fluids with a higher sodium content in a child with encephalopathy presenting in 1996.**

Dr.MacFaul and I disagree on whether there was a generally understood requirement to restrict fluid intake and use routinely a fluid of higher sodium content in a child presenting with an encepahlopathic illness in 1996.

In asserting that this was the case, Dr.MacFaul relies, firstly, on the explicit statement in the 1984 edition of Forfar and Arneil. He has accepted that this statement was no longer present in the 1992

edition but considers it important as it reflects what Drs.Webb and Steen may have learnt during their training.

I cannot comment on the training of Drs.Webb and Steen, but the suggestion that doctors rely on what they learn during training and should not update this in light of changing information is one which I find very strange. I wish to reiterate my view that any doctor continuing to follow guidance in an out-of-date textbook once this had been changed would, rightly, be subject to severe criticism.

Dr.MacFaul then proceeds to argue from various disparate and non-specific statements taken from a range of textbooks current in 1996 that it would have been obvious to a clinician and was generally understood that fluids should be restricted and fluids of a higher sodium content administered in a child presenting with encephalopathy. I do not believe that this argument stands up at all, and Dr.MacFaul's view on the need to restrict fluids when Claire initially presented is not shared by most of the other experts who have commented on fluid management in this complex case, as discussed in my report of 30/10/12.

Specifically I wish to highlight for the inquiry the following comments on the initial fluids given to Claire in this case:

1) Professor Neville at **232-002-008**, commenting on the nature and volume of intravenous fluids prescribed in 1996 "What was given was routine, but should have been carefully monitored in the circumstances" compared with the current time "Now I think a higher sodium content and fluid restriction would be routine".
2) Dr. Scott-Jupp at **234-002-002** says, in relation to the choice of intravenous fluids for Claire, "The IV fluid given was 0.18% Sodium Chloride in 4% Dextrose. This was absolutely the standard IV fluid given to most children needing fluids for any reason in 1996. This policy has changed over the last few years. Although now policy is universally to give either 0.45% or 0.9% Sodium Chloride, there would have been no reason in these circumstances to have deviated from the normal policy. Even when the results of the electrolytes were available and the low sodium of 132 was noted, I believe at the time most practitioners would have continued with 0.18% Saline. The quantity prescribed was 65mls per kg per 24 hours. I believe that this was appropriate as at the time there was no particular reason to impose fluid restriction as a means of preventing Cerebral Oedema."

3) Dr.Bingham, Consultant at Great Ormond Street, in his report to the coroner at **091-006-026**:

> I feel that Claire's initial diagnosis and management was reasonable. A viral illness was a common and likely diagnosis and although her serum sodium was low it was not excessively so. Her fluid prescription was in line with the practice of the time and although current guidance would be to use fluid with higher sodium content in this situation, this advice did not exist in 1996.

If Dr.MacFaul is correct about Claire's initial fluid management, then the three expert witnesses above (and myself) must be wrong. It is much more likely that Dr.MacFaul is incorrect in his assertion about Claire's initial fluid management.

In 1996 a doctor seeking information about how to manage fluids in a child presenting with encephalopathy would have turned to contemporary textbooks or recent medical journal articles. Where there is clear consensus on important issues in medical practice then clear statements about those issues are made in textbooks. There is no clear statement in any of the contemporary sources quoted by Dr.MacFaul to indicate that fluids should be routinely restricted or fluids with a higher sodium content used when managing a child presenting with encephalopathy. To suggest that there was consensus, or even clear guidance, on this important issue or widespread recognition of the problem in 1996 flies in the face of the evidence. If there was a consensus then there would be specific statements to that effect; a doctor would not be expected to infer this requirement from statements about "maintaining homeostasis".

Dr.MacFaul says (P2 of evidence on 12/11/12) that many of the previous papers to which I referred are not relevant since they do not specifically deal with children with encephalopathy. I do not believe that this is correct. Many of the papers deal with management of fluids in children generally, and there is no statement in any of the papers to say that they exclude children admitted with neurological problems. Given that the papers deal with the clinical settings in which hyponatraemic encephalopathy develops, it is inconceivable to me that encephalitis would not have been mentioned if there was general recognition that it was a predisposing factor.

Furthermore, in some cases the papers I have cited specifically refer to neurological conditions.

a) Arieff's 1993 BMJ review specifically refers to "structural lesions of the central nervous system" as a risk factor for hyponatraemia. The failure to mention encephalitis in this key review is a clear indication of lack of awareness of the problem at that time.
b) Kirkham in 2001 in Arch Dis Child is entirely concerned with non-traumatic coma in childhood, exactly the condition under consideration in this case. The recommendations for fluid management are completely different from those of Dr.MacFaul. Specifically, in relation to fluid restriction this review states: "There is considerable controversy over fluid

restriction, which has been shown to be potentially harmful in patients with sub-arachnoid haemorrhage and meningitis." This statement is referenced to a 1990 paper which is discussed further below.

In light of the evidence above I do not believe that Dr.MacFaul's position (that restriction of intravenous fluids and use of fluids of higher sodium content in a child of encephalopathy was routine in 1996) is correct or can be sustained.

Ultimately, however, I think that even Dr. MacFaul accepts grudgingly that the overnight fluid management in Claire's case was acceptable: Day 58, P65, lines 7-9 "I think it was not inappropriate for the junior doctors on the evening of admission and overnight to use fifth normal saline"

There was a clear change in the position, therefore, between 1996 and 2004, as in 2004 Claire would have been given 0.45% saline.

**Changes in fluid recommendations for encephalopathy between 1984 and 1996:**

Dr.MacFaul says that he is not aware of any reason why the wording of the Forfar and Arneil textbook and practice changed between 1984 and 1996, and therefore argues that the 1984 advice still widely applied. However, he does refer to a paper from 1990 as potentially important (p62, day 58). This is a paper by Powell et al. in the Journal of Paediatrics and I deal with it in more detail below. In addition to this key publication, there was increasing awareness of cerebral salt wasting as a mechanism leading to hyponatraemia around this time. I believe that the Powell publication and awareness of cerebral salt wasting may explain the change in wording in Forfar and Arneil and the removal of routine fluid restriction as a recommendation in that textbook and elsewhere, and I will therefore summarise the evidence relating to these two issues.

1) **Emerging evidence about fluid deficits in cerebral infections in the early 1990's:**

Dr.MacFaul in several places in his evidence highlights similarities between meningitis and encephalitis in relation to fluid balance, requirements and cerebral oedema. In 1990 Powell et al. published a paper entitled "Normalization of plasma arginine vasopressin concentrations when children with meningitis are given maintenance plus replacement fluid therapy" (J Pediatr. 1990 Oct; 117(4):515-22.) This is the 1990 paper referred to above and referenced by Kirkham in 2001 in

relation to the controversy about fluid restriction in a child presenting with coma. This study showed that fluid restriction appeared to be harmful in these patients. It indicated that serum ADH concentrations were elevated in patients with meningitis because of hypovolemia and became normal when sufficient fluids were given to facilitate reabsorption of water by the proximal tubule of the kidney. It was recommended that patients with meningitis should be given maintenance plus replacement fluids rather than fluid restriction. It was suggested that replacement fluids should contain 0.9% saline and that maintenance fluids should be hypotonic, and that patients should be monitored carefully for emergence of SIADH.

The results of this study were picked up and discussed by other authors. For instance, Lambert published a review on the management of meningitis in 1994 (J Neurol Neurosurg Psych 1994; 57:405-15): "A common error in management is to limit fluid intake unduly with the aim of controlling inappropriate secretion of antidiuretic hormone and, it is supposed, thus reducing the likelihood of cerebral oedema. It has been shown in childhood meningitis, however, that the observed high levels of arginine vasopressin are an appropriate response to hyponatraemia and that levels return to normal when fluid replacement is achieved. Fluid deficits in meningitis should be corrected with the appropriate replacement fluids and normal maintenance requirements provided."

It is therefore clear that, based on research evidence between 1986 and 1992, that there was a swing away from fluid restriction in cerebral infections and this new evidence may have led to the change in the recommendations in Forfar and Arneil in the 1992 edition. When the 1992 textbook was published, this new knowledge had entered the literature and it was no longer appropriate to recommend routine fluid restriction in this setting.

On page 94, day 58, lines 20-21 Dr.MacFaul says "The debates about fluid restriction have emerged in the early 2000's". As I have shown above, this is simply incorrect. On all counts I believe that Dr.MacFaul is wrong to suggest that routine fluid restriction was a general standard in 1996. Although it remained part of the protocol in his unit, I believe that others had taken on board emerging evidence and had moved away from this approach, reflected by the change in wording in Forfar and Arneil.

**2) Cerebral Salt Wasting as part of the differential diagnosis:**

Dr.MacFaul did not mention cerebral salt wasting (CSW) as a potential cause of hyponatraemia in his original opinion. He deals with this condition briefly in oral evidence on pages 93/94 of 13/11/12, where he states that he excluded cerebral salt wasting because of changes in potassium and lack of tachycardia in Claire. The statements he makes here about potassium and tachycardia are simply incorrect. Cerebral salt wasting cannot be excluded on this basis and Dr.MacFaul is wrong to make this assertion. In addition, Dr.MacFaul states that he associates CSW with prolonged coma; however, approximately 40% of cases in children have their onset within two days of the cerebral insult and just under one quarter are associated with meningoencephalitis (Bettinelli et al. 2012)

The possibility of cerebral salt wasting is important, because fluid management is completely different from that required in SIADH. Specifically, fluid restriction is likely to worsen the situation in cerebral salt wasting. Treatment of cerebral salt wasting requires administration of increased volumes of sodium containing fluids, while treatment of SIADH requires fluid restriction. In many ways, therefore, the treatment of the two conditions, which are difficult to distinguish, is diametrically opposed. I believe that the shift away from fluid restriction in a child presenting with encephalopathy in the early 1990s was in part due to emerging awareness of cerebral salt wasting.

There is an extensive literature on cerebral salt wasting going back to the 1950s. However, the key issues, including historical aspects, are dealt with in a recent review by Yee et al. (Cerebral salt wasting: pathophysiology, diagnosis and treatment Neurosurg Clin N Am 2010; 21:339-52). In particular, I would like to highlight the following statements about cerebral salt wasting from this review:

- "it occurs not infrequently in a variety of conditions affecting the CNS such as head trauma, malignancy and CNS infections."
- "further proof of an association between cerebral salt wasting and meningitis is provided by the observation of a trend toward more adverse outcomes in children with meningitis-associated hyponatraemia who were treated with fluid restriction."
- "the challenge lies in the differentiation of cerebral salt wasting from SIADH, because both disorders caused similar serum and urine laboratory abnormalities and occur in the same neurologic and neurosurgical diseases. Accurately distinguishing between these two disorders is crucial, because misdiagnosis can lead to inappropriate therapy, often with serious consequences. Volume restriction instituted for a presumptive diagnosis in SIADH with aneurysmal subarachnoid haemorrhage and cerebral salt wasting, for example, has been shown to increase the risk of delayed ischaemic deficits and

mortality. Treatment based on an inaccurate diagnosis can also lead to progressive worsening of hyponatraemia and its direct neurologic complications."

Table 1 in this review which I reproduce below highlights the difficulty in distinguishing cerebral salt wasting from SIADH.

**Table 1**
**Differential diagnosis of CSW and SIADH**

| Variable | CSW | SIADH |
|---|---|---|
| Urine osmolality | ↑ (>100 mOsm/kg) | ↑ (>100 mOsm/kg) |
| Urine sodium concentration | ↑ (>40 mmol/L) | ↑ (>40 mmol/L) |
| Extracellular fluid volume | ↓ | ↑ |
| Body weight | ↓ | ↔ or ↑ |
| Fluid balance | Negative | Neutral to slightly + |
| Urine volume | ↔ or ↑ | ↔ or ↓ |
| Heart rate | ↔ or ↑ | ↔ |
| Hematocrit | ↑ | ↔ |
| Albumin | ↑ | ↔ |
| Serum bicarbonate | ↑ | ↔ or ↓ |
| Blood urea nitrogen | ↑ | ↔ or ↓ |
| Serum uric acid | ↔ or ↓ | ↓ |
| Sodium balance | Negative | Neutral or + |
| Central venous pressure | ↓ (< 6 cm $H_2O$) | ↔ or slightly + (6–10 cm $H_2O$) |
| Wedge pressure | ↓ | ↔ or slightly ↑ |

*Abbreviations:* CSW, cerebral salt wasting; SIADH, syndrome of inappropriate antidiuretic hormone secretion.
*Adapted from* Rabinstein AA, Wijdicks EF. Hyponatremia in critically ill neurologic patients. Neurologist 2003;9: 290–300; with permission.

Basic laboratory tests and clinical features cannot distinguish the two conditions. In practice, measurement of central venous pressure is required.

I would be happy to provide further contemporary literature about cerebral salt wasting if required. This would certainly have been considered as part of the differential diagnosis by someone with expertise in hyponatraemia in 1996 and it is not possible to exclude it as the explanation of the hyponatraemia in Claire's case based on the results I have seen, although I believe that SIADH was a more likely cause of her hyponatraemia.

**Additional issues emerging from Dr.MacFaul's evidence:**

a) At various places in oral evidence, Dr.MacFaul makes statements about hyponatraemia which are at best misleading and on occasions simply wrong. For instance, in discussing hyponatraemia in relation to Kirkham's paper about coma in 2001 (day 59, page 15, lines 14-

21) he says that the only cause of hyponatramia in coma could be SIADH or fluid overload with water. This is clearly wrong, given the very obvious possibility of cerebral salt wasting in this setting as discussed above.

b) On day 59, p156 Dr. MacFaul discusses the low serum osmolality and when asked what this means says "water overload of the syndrome of inappropriate ADH secretion". Again, this is simply incorrect. The only information provided by a low serum osmolality result is the exclusion of physiological or pseudohyponatraemia. It provides no information as to the causation of hyponatraemia beyond this.

c) Throughout the oral evidence of day 59 there are repeated references to fluid overload as a possible cause of Claire's hyponatraemia separate and distinct from SIADH. I am unclear what is meant by this phrase and believe that there is considerable risk of confusion as a result of its use. In the context of hyponatraemia, fluid overload is generally used to in reference to hypervolaemic hyponatraemia (for instance, in heart failure or liver failure). There has been no suggestion that Claire suffered from hypervolaemic hyponatraemia. The evidence points mainly to euvolaemic hyponatraemia, most commonly caused by SIADH. SIADH is described as a volume expanded state, not a fluid overload state. At no stage did Claire receive more than maintenance fluids; there is no way that she would have developed hyponatraemia in the absence of SIADH or cerebral salt wasting. Therefore, to talk about fluid overload as a possible cause of her hyponatraemia is at best loose use of terminology and potentially misleading.

**The concept of the "normal range" and hyponatraemia:**

In oral evidence, there has been considerable discussion about the significance of a sodium level of 132 mmol/l. Often the terminology used to discuss and describe this has been unclear and inconsistent. For instance, on day 58, p95, 14-15 Dr.MacFaul says "I think when you have hyponatraemia, even if it's just a low sodium outside the normal range, you're triggered into maintaining homeostasis". There are several things potentially misleading about this statement:

1) A sodium level of 132 mmol/l did not constitute hyponatraemia by the textbook definitions of the time. I do not believe any doctor would have said that Claire had hyponatraemia on admission.
2) The term "normal range" is an incorrect term which some clinicians use inappropriately to describe a reference interval for a laboratory result. It is an inappropriate term because it

implies that any result outside the reference interval is abnormal. This is not the case. A reference interval covers the middle 95% of a healthy population. In other words, if you measure sodium in 1000 entirely healthy individuals, 950 of them will fall within the reference interval, with 25 having values below the lower limit and 25 having values above the upper limit. Therefore a sodium level which is a little below the lower reference interval will be found in a small percentage (2.5%) of an entirely healthy population. In 1996, based on the quoted reference interval, 25 entirely healthy children out of 1000 would have had a sodium level below 135. The further away from the lower reference interval a value falls the more likely it is to be associated with a pathological process. A sodium result less than 130 is very unlikely to be found in a healthy individual, which is one reason why that cut off has often been used to define hyponatraemia. Interestingly, the current paediatric reference interval for sodium which is recommended for national use in the UK is 133-136 mmol/l (Pathology Harmony document, 2011), implying that it is currently believed that 25 healthy children out of 1000 will have a serum sodium of 132 mmol/l or less.

**Anticipatory care and maintenance of homeostasis:**

In order to justify his assertion that fluid restriction and use of fluids with a higher sodium content should have been utilised once Claire was noted to have a sodium level of 132 mmol/l, Dr.MacFaul refers to the requirement to "maintain homeostasis". This is a very general phrase which could be used in relation to a patient who is ill from any cause. It is so non-specific that I do not believe it would be of any help at all to junior doctors in the context of Claire's management when considering what specific actions to take. As discussed above, and acknowledged by almost all of the expert witnesses in this case, most doctors would take no action in response to a sodium of 132 mmol/l. Even when frank hyponatraemia develops, the correct course of action is critically dependent on identifying the cause of the hyponatraemia as discussed below. Increasing the sodium content of fluids may appear an obvious course of action, but in some settings may actually worsen the patient's clinical condition as discussed below.

**Investigation and management of hyponatraemia in 1996:**

To clarify the issues above, I would like to outline the approach which I would ideally have expected to be taken if a further blood sample on Tuesday demonstrated Claire to have significant hyponatraemia (Na < 130 mmol/l). This approach would have been in line with best practice at that

time based on my extensive clinical experience of dealing with patients with hyponatraemia and knowledge of the literature.

1) Consider and exclude the possibility of physiological hyponatraemia or pseudo-hyponatraemia by measuring serum osmolality and glucose.
2) Send urine to the biochemistry laboratory for urinary osmolality and electrolytes, including urinary sodium.
3) Look for any evidence of an osmolal gap (the difference between measured serum osmolality and calculated serum osmolality (2xNa + 2xK + glucose + urea).
4) Assess Claire's volume status and document when she was felt clinically to be hypovolaemic (dehydrated), euvolaemic (no clinical evidence of fluid overload or dehydration) or hypervolaemic (fluid overloaded).
5) Decisions about fluid management or other treatment would then be critically dependent on the clinical assessment and cause of the hyponatraemia. In each case it is important to identify and treat the underlying cause, but the following general approach would have been taken.

a) For hypovolaemic hyponatraemia (including cerebral salt wasting) the general approach would have been to administer increased amounts of fluids with a higher sodium content (0.9% saline, for instance). It is important to note that fluid restriction would be harmful in this setting.
b) Euvolaemic hyponatraemia is most commonly SIADH, and the standard approach would have been to fluid restrict and to provide modest sodium supplements as has been discussed elsewhere.
c) Hypervolaemic hyponatraemia is characterised clinically by evidence of tissue swelling (oedema) and is typically observed in conditions such as heart and liver failure. In this case the general approach would have been to restrict fluid intake but also to restrict sodium intake, and to use diuretics to help get rid of excess water. It is important to note that switching to fluids containing a higher sodium concentration (such as 0.9%) saline would worsen the situation and lead to increased fluid overload.

The steps outlined above are sufficient to deal with the vast majority of cases of hyponatraemia. However, when a patient is suffering from acute neurological symptoms which are believed to be due to hyponatraemia then consideration needs to be given to administering a small amount of hypertonic saline (1.8 – 3% saline), regardless of the cause of the hyponatraemia. The purpose of

this intervention is to raise serum osmolality by a few mosmol/l, which is sufficient in most cases to reduce cerebral oedema.

When I reviewed the notes in 2004, I concluded that at 11/11.30 pm on the Tuesday the clinicians took the view that the neurological symptoms could be explained by status epilepticus / encephalitis. The presence of hyponatraemia was noted by Dr.Stewart, but there was no indication that this was considered to be the cause of Claire's neurological symptoms. Therefore, since the doctors did not believe that the hyponatraemia was the cause of neurological problems and considered that SIADH was the most likely cause of the hyponatraemia, they determined that fluid restriction alone was the correct course of action.

Index to enclosures - Statement of Professor Ian S. Young dated 26th November 2012

1. Neurosurgery.theclinics.com 2010; 339-352 - Alan H. Yee et al. – Cerebral Salt Wasting: Pathophysiology, Diagnosis, and Treatment.
2. Journal of Neurology, Neurosurgery, and Psychiatry 1994; 57:405-415 - H P Lambert – Neurological Management – Meningitis.
3. The Journal of Pediatrics; October 1990; Volume 17 Number 4; 515-522 Keith R Powell et al. – Normalization of plasma arginine vasopressin concentrations when children with meningitis are given maintenance plus replacement fluid therapy.
4. Pediatric Nephrology; 2012; Volume 27 Issue 5; 733-739 – Alberto Bettinelli et al. – Renal salt-wasting syndrome in children with intracranial disorders.
5. Pathology Harmony Group, Clinical Biochemistry Outcomes, January 2011 – Harmonisation of Reference Intervals.

# Cerebral Salt Wasting: Pathophysiology, Diagnosis, and Treatment

Alan H. Yee, DO[a,*], Joseph D. Burns, MD[b], Eelco F.M. Wijdicks, MD, PhD[a]

**KEYWORDS**

• Natriuresis • Natriuretic factors • Hyponatremia • SIADH

Hyponatremia can be a vexing problem for those who care for critically ill neurologic patients. Although seemingly simple at first glance, the accurate diagnosis and effective treatment of hyponatremia can be complex. The chief difficulty in this setting often lies in determining what is driving the fall in serum sodium concentration. Cerebral salt wasting (CSW) is a disorder of sodium and water handling that occurs as a result of cerebral disease in the setting of normal kidney function. It is characterized by hyponatremia in association with hypovolemia and, as the name implies, is caused by natriuresis. In routine clinical practice, distinguishing this condition from the more familiar syndrome of inappropriate secretion of antidiuretic hormone (SIADH) can be quite difficult. Nonetheless, this task is crucial because treatments for the two conditions are fundamentally different. Accordingly, it is important for physicians caring for critically ill neurologic patients to have a thorough understanding of this disorder. This article reviews the pathophysiology of CSW. Building on these basic concepts, a rational approach to its diagnosis and treatment is outlined.

## HISTORICAL ASPECTS

Early studies of hyponatremia in patients with cerebral disease published in the 1950s described the presence of polyuria, elevated urinary sodium levels, and dehydration despite the presence of a low serum sodium concentration and adequate fluid intake. This syndrome was termed "cerebral salt wasting." At the time, CSW was suspected to be the major cause of hyponatremia in patients with central nervous system (CNS) injury. Shortly after its original description, however, a syndrome of euvolemic hyponatremia associated with normal urine output and inappropriately high levels of antidiuretic hormone (ADH) was described in a patient with bronchogenic carcinoma.[1] This was later termed as the "syndrome of inappropriate antidiuretic hormone release." Following this discovery and over the subsequent 30 years, hyponatremia that developed in patients with neurologic diseases, such as subarachnoid hemorrhage (SAH), was generally attributed to SIADH.[2–6] Beginning in the 1980s, several key studies[7–9] challenged this concept by demonstrating in patients with aneurysmal SAH a syndrome of low blood volume, natriuresis with a net negative sodium balance, and high urinary output, which was consistent with CSW and not SIADH. These publications led to the modern acceptance of CSW as an important cause of hyponatremia in patients with brain injury and to important research that followed investigating the pathophysiologic disturbances of salt and water homeostasis in patients with neurologic disease.

## CLINICAL RELEVANCE

Hyponatremia is frequently encountered in patients with neurologic disease. A recent analysis

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neurosurgery.theclinics.com

of 316 patients with aneurysmal SAH detected hyponatremia in 57% of patients.[10] Although previous investigators have reported lower frequencies,[11–13] it is still the most commonly encountered electrolyte disturbance in the neurologic intensive care unit. Adding to its importance are the occasional serious consequences of severe hyponatremia, which include seizures and worsening of cerebral edema. Although hyponatremia is most reliably encountered in patients with aneurysmal SAH,[7,11,14–30] it occurs not infrequently in a variety of other conditions affecting the CNS, such as head trauma,[31–43] malignancy,[44–51] and CNS infections,[14,52–60] and it has been reported in the postoperative neurosurgical setting.[61–64]

The proportion of patients with hyponatremia related to neurologic disease who have CSW, as opposed to SIADH or some other etiology of hyponatremia, is substantial, although the exact frequency is not clear. This issue has been studied most rigorously in patients with aneurysmal SAH.[7,11,14–30] In one study, up to 67% (six of nine) of patients with hyponatremia after rupture of an intracranial aneurysm had CSW as the etiology of low sodium levels[7] and 75% (six of eight) of SAH cases in other reports.[8] A study by Sherlock and colleagues,[10] however, found that only 6.5% (4 of 62) of patients who presented with spontaneous SAH and subsequent hyponatremia had CSW as the cause of abnormally low sodium levels in their unselected cohort.

The discrepancy between reported prevalence rates may be a result of differences in study population size. Much has to do with how CSW and volume depletion are defined, however, when comparing the available data. There is no universally accepted gold standard in defining extracellular volume status or the specific parameters that classify cerebral-induced salt wasting, leading to significant variability between studies in the definition of low intravascular volume. For example, some authors have measured central venous pressure (CVP),[10] whereas others have used isotope-labeled albumin.[65] This difference in method of volume assessment and inclusion criteria could result in varying frequencies of affected subjects among studies, and it is unclear whether direct comparisons can be made between such trials when identifying CSW as an underlying etiology in hypovolemic hyponatremic patients. An additional confounding variable underlying the variability of CSW frequency in the literature is the manner in which sodium depletion is defined. Single versus multiple day cumulative sodium balance measurements often yield significantly different results.[66]

CSW has been associated with a host of other CNS diseases in addition to aneurysmal SAH. Although the precise frequency of CSW in traumatic brain injury is unknown, an association has been described in a number of case reports, small case series, and studies with greater sample size that incorporate several categories of neurologically injured patients of which small numbers of traumatic brain injury patients are included.[8,31–33,67,68] The best estimate can be found in a study by Vespa,[35] in which 5% to 10% of traumatic brain injury patients were found to have salt wasting. The hyponatremia that frequently occurs in patients with infectious meningitis is most often attributed to SIADH. In several studies of this condition, however, a number of patients with moderate to severe volume contraction in association with decreased serum sodium levels, a combination that is most consistent with CSW, were identified. Further proof of an association between CSW and meningitis is provided by the observation of a trend toward more adverse outcomes in children with meningitis-associated hyponatremia who were treated with fluid restriction.[52,59,69,70] Other conditions in which natriuresis with volume contraction and hyponatremia occur include transsphenoidal pituitary surgery and cerebral malignancies, such as primitive neuroectodermal tumors with intraventricular dissemination, carcinomatous meningitis, glioma, and primary CNS lymphoma.[44–51,61,62]

## PATHOPHYSIOLOGY OF CSW

Despite the clear association between the presence of CSW and severe neurologic disease, the mechanism underlying this association has not yet been clearly identified. Maintenance of body sodium and water homeostasis is a vital physiologic process. It is largely governed by intricate interactions between the autonomic nervous system and humoral factors that influence the kidney's handling of sodium and water. Disruption of the normal interactions between these systems can generate sodium and water dysregulation at the level of the nephron, thereby leading to more global alterations in sodium and water homeostasis. It has been postulated that interference of sympathetic input to the kidney and the presence of abnormally elevated circulating natriuretic factors noted after cerebral injury can lead to CSW (**Fig. 1**).

### *Physiology of the Renin-Angiotensin-Aldosterone System*

The renin-angiotensin-aldosterone system (RAAS) is a hormonal pathway involving several enzymatic

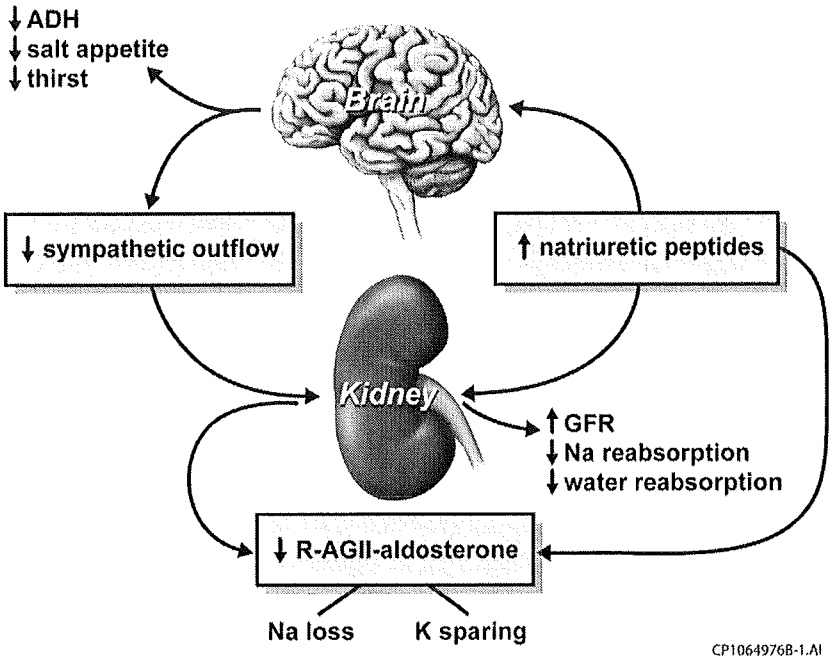


**Fig. 1.** Proposed mechanisms responsible for the production of CSW syndrome. ADH, antidiuretic hormone; GFR, glomerular filtration rate; K, potassium; Na, sodium; R-AG II, renin-angiotensin II. (*From* Rabinstein A, Wijdicks E. Hyponatremia in critically ill neurologic patients. Neurologist 2003;9:6; with permission.)

steps and humoral factors that serve a central role in maintaining whole-body sodium and water homeostasis. Renin is a circulating enzyme produced and stored within the kidney and released in response to low systemic and renal arterial perfusion. Once released, it initiates a series of intricate sequential enzymatic steps involving the well known angiotensin-converting enzyme, the ultimate product of which is the formation of angiotensin II (AT II). This potent vasopressor agent has immediate effects on blood pressure by influencing the constrictive properties of peripheral vasculature, increasing sympathetic tone, and stimulating the release of ADH.[71] Moreover, AT II augments renal blood flow to maintain an appropriate rate of glomerular filtration and the percentage of sodium to be filtered. AT II activity is not only critical in the immediate phases of hemodynamic control but is also instrumental in maintaining serum sodium homeostasis by stimulating the release of aldosterone, a key mineralocorticoid released from the adrenal gland that regulates extracellular fluid volume and serum potassium concentration (eg, nephrogenic excretion). Aldosterone ultimately causes sodium retention and a subsequent increase in serum sodium concentration by binding to specific intracellular receptors at the distal tubule and collecting ducts, leading to a cascade of protein synthesis of sodium channels, sodium-potassium pumps, and their regulatory proteins all of which are critical in transepithelial sodium transport.[72]

In large part, effective extracellular fluid volume and sodium concentration are maintained by the degree of RAAS activity and aldosterone bioavailability. These are increased during periods of low circulating fluid volume and decreased when total circulating volume is sufficient or elevated. A cerebrally mediated mechanism for influencing the RAAS system, and renal salt and water handling, may exist.[73–75] Several publications have documented the scientific progress and understanding of a local intrinsic tissue-specific RAAS model within the CNS and its influence on renal physiology.[71,76,77] As detailed in a key review by DiBona,[78] intrinsic cerebral AT II production likely exists and its presence within the CNS conceivably can influence renal sympathetic nerve activity and baroreflex control. More specifically, neuronal synthesis of this hormone within the paraventricular nucleus is released in the rostral ventrolateral medulla, a critical structure in the autonomic neural control of circulation. Tonic excitation of the rostral ventrolateral medulla influenced by endogenous AT II has been postulated to result in increased peripheral sympathetic tone.

### *Sympathetic Nervous System Hypothesis*

The sympathetic nervous system plays an important role in the regulation of sodium and water

handling in the kidney.[78–80] In the face of intravascular volume contraction, the autonomic nervous system responds by increasing sympathetic nervous system tone. This in turn induces secretion of renin from the kidneys, subsequently leading to elevations in the bioavailability of AT II and aldosterone, stimulating sodium and water retention. By way of a positive feedback mechanism, AT II itself may have a role in regulating sympathetic nervous system activity.[71,72] Data from animal studies suggest that this circulating hormone can directly affect the sympathetic nervous system by binding to specific receptors located within discrete subcortical brain structures, specifically the subfornical organ and area postrema.[78,81,82] Direct projections from the subfornical organ to the paraventricular nucleus are thought to influence rostral ventrolateral medulla activity indirectly. Activation of these circumventricular regulatory centers leads to an increase in the activity of the sympathetic nervous system by their projections to preganglionic sympathetic neurons within the intermediolateral cell column of the spinal cord[82,83]; the ultimate effect is an increase in mean arterial pressure and retention of sodium and water by the kidney.

Peters and coworkers[14] originally hypothesized that disruption of CNS influence on renal salt and water balance mechanisms could potentially disturb the kidney's ability to maintain proper sodium homeostasis. Specific renal innervation by the sympathetic nervous system, however, was not discovered until nearly 20 years later.[79] Peters' theory was then expanded on to explain more specifically the mechanism underlying CSW.[15,21,22,84] According to this theory, loss of adrenergic tone to the nephron has two important consequences. First, it leads to a decrease in renin secretion by the juxtaglomerular cells, thereby causing decreased levels of aldosterone and decreased sodium reabsorption at the proximal convoluted tubule. Second, it causes dilatation of the afferent arteriole, leading to increased glomerular filtration of plasma and sodium. The failure of renin and aldosterone levels to rise in the setting of CSW-associated volume contraction has been considered to be evidence in favor of this hypothesis. This hypothesis has one crucial flaw: acute CNS injury typically leads to a surge and not a decrease in sympathetic tone during the immediate phases of injury. This is demonstrated by such phenomena as neurogenic pulmonary edema and myocardial dysfunction, which occur because of dramatic sympathetic outflow during periods of severe CNS stress.[85] It has yet to be demonstrated that the changes in the interactions between the autonomic nervous system and the kidneys that are needed to produce a salt-wasting state actually occur in the setting of acute cerebral injury.

### *Natriuretic Peptide Theory*

Natriuretic peptides were initially discovered in the early 1980s after it was demonstrated that atrial myocardial extracts induced a potent natriuretic response when infused into rats.[86] At about the same time, early studies investigating the pathogenesis of sodium and extracellular volume disturbances in patients with SAH led to the hypothesis that a natriuretic factor may be involved.[8,9,17] Subsequently, a number of specific natriuretic substances were identified and their biologic effects have been intensely studied.

Natriuretic peptides are molecules that normally defend against periods of excess water and salt retention by antagonizing the RAAS system, promoting vascular relaxation, and inhibiting excess sympathetic outflow and the generation of vasoconstrictor peptides.[87] Four main natriuretic peptides with purported associations with CSW have been identified: (1) atrial natriuretic peptide (ANP); (2) brain-natriuretic peptide (BNP); (3) C-type natriuretic peptide (CNP); and (4) the more recently discovered dendroaspis natriuretic peptide (DNP).[88,89] Although the former three natriuretic peptides have shown some expressivity within the CNS, each peptide has a unique predominant tissue-specific site of production: ANP and DNP from the myocardial atria; BNP from within the ventricles of the heart; and CNP from the telencephalon, hypothalamus, and endothelium.[90–93]

The natriuretic peptides all have similar, potent effects on the regulation of cardiovascular homeostasis by influencing vascular tone and sodium and water homeostasis. They cause relaxation of vascular smooth muscle thereby leading to dilatation of arteries and veins, most likely by dampening vascular sympathetic tone.[94–96] A similar effect on the nephron's afferent tubule leads to increased filtration of water and sodium through the glomerulus. These molecules also have direct renal tubule natriuretic and diuretic effects by inhibiting angiotensin-induced sodium reabsorption at the proximal convoluted tubule and antagonizing the action of vasopressin at the collecting ducts, respectively.[97,98] Interestingly, local production of natriuretic peptides within the adrenal medulla[99,100] has been demonstrated and might have paracrine inhibitory effects on mineralocorticoid synthesis.[100] This paracrine mechanism might explain why in patients with CSW aldosterone and renin levels fail to rise

despite the presence of hypovolemia. Clearance and inactivation of circulating natriuretic peptides occurs by two main mechanisms: endocytosis once bound to a C-type natriuretic receptor (which has equal affinity for the family of peptides),[101,102] and degradation and cleavage by endopeptidases within the vasculature and renal tubular system.[87]

These characteristics of natriuretic peptides make them ideal candidate mediators that may serve as a key link between CNS injury and the development of CSW. Several studies have demonstrated that a rise in serum BNP concentration is evident after SAH.[19–21,103,104] McGirt and colleagues[19] demonstrated the existence of a temporal relationship between elevated BNP levels and the presence of hyponatremia in patients with SAH. Interestingly, in this same study abnormally high levels of BNP correlated well with the presence of cerebral vasospasm, suggesting that BNP may have a direct causal link to the secondary complications often observed in SAH. Besides BNP, other members within this peptide family, ANP in particular, have also been suspected to contribute to the development of CSW.[16,17,28] The caveat to this, however, is that BNP was not measured in these earlier studies, leaving open the possibility that it, rather than ANP, was responsible for the CSW.[28,105] Additionally, more recent evidence has shed light on a new member of the natriuretic peptide family, DNP, as a potential additional causative agent of hyponatremia in patients with aneurysmal SAH.[24] Further investigation is needed to better define the roles played by the different natriuretic peptides in the pathogenesis of CSW.

Several hypotheses have been offered to explain how an intracranial insult could lead to elevations of serum concentrations of these peptides. One plausible hypothesis is that direct damage to cortical and subcortical structures where BNP exists[106] leads to inadvertent release of hormone directly into the circulation.[14] Some investigators have proposed that generation and release of natriuretic peptides from the hypothalamus in disease states, such as SAH, may serve a protective role against elevated intracranial pressure. This cerebral induction of natriuresis could limit further impending rise in intracranial pressure and its subsequent potential unfavorable outcomes.[21,107]

Myocardial tissue has also been proposed to be a source of elevated natriuretic peptide levels in CSW.[104,105] Surges in sympathetic outflow typically occur as a result of acute CNS injury.[85] This increase in sympathetic tone may lead to catecholamine-induced myocardial ventricular strain, thereby causing release of BNP from the atrial myocardium.[85,103] Additionally, the presence of excess catecholamine as a result of acute intracranial disease may be excitotoxic to cardiac myocytes,[85] also potentially causing transient myocardial dysfunction. Related neurohumoral findings have also been demonstrated in other forms of acute cerebral injury, such as ischemic stroke, also implying that like mechanisms are at play.[108] Some authors have speculated that hypervolemic therapy itself, which is frequently administered after SAH, can lead to myocardial chamber stretch with resultant peptide release.[23] Regardless of which individual or combination of molecules is responsible, the mechanistic cause-and-effect link between cerebral damage and natriuretic peptide release with ensuing renal sodium loss has yet to be identified.

### *Miscellaneous Hypotheses*

Kojima and colleagues[26] suggest that a mechanism or mechanisms other than one involving ANP, BNP, or ADH exists that may be responsible for CSW. In an experimental rat model, they measured serum concentrations of these hormones and urinary volume and sodium excretion at several time intervals after induction of SAH while controlling the degree of volume therapy to exclude this as a confounding variable. Findings consistent with CSW occurred in the SAH rats: a significant elevation in urinary volume and sodium excretion, decreased body weight, and an increase in hematocrit. Interestingly, levels of ANP decreased, whereas the BNP and ADH concentrations were unchanged. They concluded that a novel, undefined mechanism, or one that involves DNP, likely underlies the etiology of CSW.

Adrenomedullin (AM) is a more recently discovered endogenous peptide that has been proposed as a mediator of CSW.[30,109,110] Originally discovered in pheochromocytoma tissue[111] and later revealed in human brain matter,[112,113] AM is a potent vasodilator with natriuretic and diuretic properties. Elevation in plasma levels of this peptide has been shown to be high immediately after SAH and may reflect the severity of hemorrhage; however, its levels do not seem to correlate with the presence angiographic vasospasm.[25] Conversely, cerebrospinal fluid concentrations of AM do seem to parallel the development of hyponatremia and delayed ischemic neurologic injury for at least 8 days after the onset of hemorrhage.[27] The release of this hormone in the setting of aneurysmal SAH might serve a protective role against the development or worsening of cerebral vasospasm through its vasoactive properties. The site of CNS production of AM within the hypothalamus extends neuronal

projections to regions within the brainstem and spinal cord, which can ultimately effect sympathetic tone.[113] Interestingly, a decrease in renal sympathetic activity with subsequent natriuresis and diuresis has been demonstrated in an animal model after AM was introduced into the cerebral ventricular system.[114] Although new molecules and mechanisms have been described, BNP and ANP continue to be implicated as the main offenders toward the development of CSW, of which the former continues to be of primary suspect.[21]

## DIAGNOSIS OF CSW

Differentiating CSW from most other common causes of hyponatremia (diuretic use, adrenal insufficiency, extrarenal-induced volume-deplete states, hypothyroidism, congestive heart failure)[115] is typically not difficult. Obtaining a meticulous history and inventory of recent medications and laboratory studies often reveals the correct diagnosis. The challenge lies in the differentiation of CSW from SIADH, because both disorders cause similar serum and urine laboratory abnormalities and occur in the same neurologic and neurosurgical diseases.[116,117] Accurately distinguishing between these two disorders is crucial, because misdiagnosis can lead to inappropriate therapy, often with serious consequences. Volume restriction instituted for a presumptive diagnosis of SIADH in patients with aneurysmal SAH and CSW, for example, has been shown to increase the risk of delayed ischemic deficits and mortality.[11] Treatment based on an inaccurate diagnosis can also lead to progressive worsening of hyponatremia and its direct neurologic complications.[115] Despite the availability and general ease in obtaining tests for the determination of electrolyte concentrations and osmolality in the serum and urine, only the careful determination of volume status in the hyponatremic patient accurately differentiates CSW from SIADH (**Table 1**).

SIADH is a syndrome of euvolemic hyponatremia. It is characterized by (1) euvolemia and an even fluid balance; (2) hyponatremia (serum sodium <135 mmol/L[115,117]) and hypo-osmolality (serum osmolality <275 mOsm/kg $H_2O$ in an adult); (3) a urine osmolality that is greater than that of maximally dilute urine (>100 mOsm/kg $H_2O$ in an adult); and (4) the presence of an elevated urinary sodium concentration (>40 mmol/L) in an individual with normal salt and water intake.[117] This constellation of findings is a result of excessive ADH-induced water reabsorption from the glomerular filtrate at the distal nephron, which produces inappropriately concentrated urine despite serum hypo-osmolality. CSW, however, is a syndrome of hypovolemic hyponatremia. Its major clinical features are (1) hypovolemia, often with a net

**Table 1**
**Differential diagnosis of CSW and SIADH**

| Variable | CSW | SIADH |
|---|---|---|
| Urine osmolality | ↑ (>100 mOsm/kg) | ↑ (>100 mOsm/kg) |
| Urine sodium concentration | ↑ (>40 mmol/L) | ↑ (>40 mmol/L) |
| Extracellular fluid volume | ↓ | ↑ |
| Body weight | ↓ | ↔ or ↑ |
| Fluid balance | Negative | Neutral to slightly + |
| Urine volume | ↔ or ↑ | ↔ or ↓ |
| Heart rate | ↔ or ↑ | ↔ |
| Hematocrit | ↑ | ↔ |
| Albumin | ↑ | ↔ |
| Serum bicarbonate | ↑ | ↔ or ↓ |
| Blood urea nitrogen | ↑ | ↔ or ↓ |
| Serum uric acid | ↔ or ↓ | ↓ |
| Sodium balance | Negative | Neutral or + |
| Central venous pressure | ↓ (< 6 cm $H_2O$) | ↔ or slightly + (6–10 cm $H_2O$) |
| Wedge pressure | ↓ | ↔ or slightly ↑ |

*Abbreviations:* CSW, cerebral salt wasting; SIADH, syndrome of inappropriate antidiuretic hormone secretion.
*Adapted from* Rabinstein AA, Wijdicks EF. Hyponatremia in critically ill neurologic patients. Neurologist 2003;9: 290–300; with permission.

negative fluid balance; (2) hyponatremia and serum hypo-osmolality; (3) an elevated urine osmolality (>100 mOsm/kg); and (4) elevated urinary sodium (>40 mEq/L). In contrast to SIADH, the findings in CSW are caused by excessive renal sodium and water excretion. Because sodium excretion is disproportionately higher than that of water, the urine is inappropriately concentrated for the degree of serum hypo-osmolality. Salt wasting typically occurs early following acute cerebral injury and can persist beyond 5 days. Hyponatremia often follows and develops by the first week following the insult.[8,9,11,17]

It is not possible to distinguish CSW from SIADH based on serum and urine laboratory findings alone, because their associated abnormalities are identical. For this reason, accurate determination of the patient's volume status is the key to differentiating these syndromes. Unfortunately, determination of volume status is notoriously difficult to perform accurately in routine clinical practice. Despite the use of complex, labor intensive, and elegant methods of determining intravascular volume status in experimental studies of CSW, no universally accepted standard exists for this purpose.[118] Precisely because of this difficulty in conclusively and consistently differentiating hypovolemic hyponatremia from euvolemic and hypervolemic hyponatremia, Sterns and Silver[118] have recently suggested that differentiating between CSW and SIADH is not currently possible. Rather, they suggest that because hyponatremia from any cause in a brain-injured patient is best treated with hypertonic saline, the two conditions should be considered a single entity called the "cerebral salt wanting syndrome." This idea is intriguing, but needs to be tested to determine its value in clinical practice.

Classical signs and symptoms of hypovolemia including hypotension, orthostatism, lassitude, increased thirst, and muscle cramps all lack specificity, particularly in critically ill patients; however, in the appropriate clinical context (eg, vomiting, diarrhea, diaphoresis, diuretic use, and polyuria), these symptoms can provide clues that the patient is hypovolemic. Weight loss, the absence of jugular venous distention, prolonged capillary refill time or diminished skin turgor, or the presence of dry mucous membranes can be suggestive of diminished extracellular fluid volume. Unfortunately, physical examination provides limited sensitivity in the assessment of hypovolemia.[119,120] Similarly, measurement of serum concentrations of the conventional biochemical markers that normally reflect hypovolemia (renin and aldosterone) is unreliable because these substances are abnormally suppressed in CSW.[22,62,121] Other more common laboratory data used to support a volume-contracted state are the presence of an elevation in serum bicarbonate, blood urea nitrogen concentration, or hematocrit, but none of these is independently diagnostic and all lack specificity. Elevated serum uric acid levels can be seen in the hypovolemic state, but uric acid levels have surprisingly been found to be low in both CSW and SIADH.[122,123]

Measurement of CVP can be useful for estimating intravascular volume status when clinical and laboratory data are nondiagnostic and accurate intravascular volume evaluation is critical. Damaraju and colleagues[124] assessed the intravascular volume status in 25 neurosurgical patients who fulfilled the diagnostic criteria for SIADH by monitoring CVP. Hypovolemia was defined as a CVP less than 5 cm $H_2O$. Patients with a CVP less than 5 cm $H_2O$ received 50 mL/kg/d of volume replacement and an initial sodium intake of 12 g per day. The main outcome measured was an improvement in serum sodium concentration from two consecutive measurements 12 hours apart or within 72 hours of initiation of therapy. Nineteen of their 25 patients were found to be both hypovolemic and able to achieve normal serum sodium values (defined as >130 mEq/L) within this time frame after therapy. The authors concluded that neurosurgical hyponatremic patients with natriuresis were more likely to be affected by CSW rather than SIADH and that CVP-directed treatment of hyponatremia and volume status in such patients is effective. Although the CVP is a very useful estimate of intravascular volume status, key limitations to its use exist.[125] Placement of a CVP catheter is an invasive procedure associated with rare but important complications.[126] Also, CVP measurements can be inaccurate in the setting of abnormal cardiac function, which is not uncommon in acute cerebral injuries. For example, despite high pulmonary wedge pressures, the CVP can be falsely low-normal in patients with isolated left or right-sided heart failure. Conversely, patients with cor pulmonale can have a falsely elevated CVP.

An accurate and timely diagnosis of CSW relies on several clinical and laboratory features when considered in the appropriate context (eg, SAH). The disorder is characterized by hyponatremia with increased urinary sodium concentration and hypovolemia in the setting of acute intracranial disease. Because other features of CSW are identical to SIADH, the key in distinguishing the two disorders lies in determining the patient's volume status. An estimation of volume status can often be made on the basis of simultaneous consideration of the symptoms, signs, and laboratory

parameters discussed previously. Of these, meticulously recorded fluid balance values are probably most informative. In rare patients with hyponatremia in whom precise management of intravascular volume is essential, placement of a central venous catheter for measurement of CVP can be useful.

## TREATMENT

The mainstay of therapy for CSW is replacement of the sodium and water that is lost as a result of pathologic natriuresis and diuresis. This is in direct contrast to the treatment of SIADH, the crux of which is free water restriction. Patients with CSW typically have significant extracellular volume depletion and a total-body sodium deficit of at least 2 mmol of sodium/kg body weight.[66] In patients who are hypovolemic, a reasonable initial management strategy is administration of normal saline with the intent of restoring intravascular volume. This is particularly important in patients with aneurysmal SAH, because the risk of vasospasm and its downstream complications is increased in the setting of hypovolemia.[11,17–20,127] Cautiously aggressive administration of intravenous fluids has become the mainstay of initial therapy in patients with SAH and has been shown to prevent volume contraction but not the development of hyponatremia.[128]

Once euvolemia is achieved, attention should be directed to the correction of hyponatremia. One method for augmenting both serum sodium concentration and intravascular volume is the use of mineralocorticoids. One should be mindful that although correction of hyponatremia and hypovolemia can often be achieved,[65,129–132] these medications have not been shown to be beneficial in preventing additional secondary complications of SAH, such as cerebral vasospasm.[131] The authors typically use fludrocortisone, 0.1 to 0.2 mg orally twice a day, starting once the diagnosis of CSW is made and continuing until serum sodium concentrations and intravascular volume remain stably normal, typically 3 to 5 days later. Especially when the serum sodium approaches dangerously low levels (<125 mEq/L) or when large volumes of intravenous fluid are required to maintain euvolemia, intravenous hypertonic saline can also be a useful adjunctive therapy in CSW. A dose of 1.5% sodium chloride can be administered through peripheral veins, and can safely and effectively restore and maintain intravascular volume and serum sodium concentration when administered at rates that are titrated to achieve a normal to slightly positive fluid balance. The authors routinely use 1.5% sodium chloride in patients with CSW at rates between 50 and 150 mL per hour. The use of 3% saline in CSW should be reserved for uncommon patients with CSW who have severe hyponatremia (<120 mEq/L) because it must be administered through a central vein and cannot be given at rates high enough to effectively restore or maintain intravascular volume.

Treatment with hypertonic saline and mineralocorticoids has important side effects. To gage the efficacy of treatment and to avoid osmotic myelinolysis as a consequence of overly rapid correction of hyponatremia, the serum sodium concentration should be carefully and frequently monitored during treatment. In general, the serum sodium concentration should not be increased by more than an average of 0.5 mEq/L/h.[115] Similarly, it is useful to use a serum sodium concentration of 130 mEq/L or greater rather than restoration of a normal concentration of 135 to 145 mEq/L as an end point for treatment. In most patients, this strategy effectively treats the negative consequences of hyponatremia while minimizing the likelihood of causing osmotic myelinolysis. Aggressive fluid and sodium administration and the use of mineralocorticoids can also cause volume overload, hypertension, pulmonary edema, and renal medullary washout,[65] warranting vigilance for these important complications during treatment. Finally, mineralocorticoid-like drugs also frequently cause hypokalemia and, because of their steroid properties, can promote hyperglycemia. Serum glucose and potassium concentration should be carefully monitored during such therapy.[65,129,131,132]

A novel treatment strategy for hyponatremia that has only recently become available highlights the need to differentiate CSW from SIADH. Conivaptan is a nonselective antagonist at the V1a and V2 vasopressin receptor subtypes. By antagonizing the action of vasopressin in the renal collecting duct, it promotes electrolyte-free water excretion (a process termed "aquauresis"), thereby raising serum sodium levels. As its mechanism of action indicates, conivaptan is a highly specific and effective treatment for SIADH caused by a number of conditions.[133] It has recently been approved by the US Food and Drug Administration for the treatment of euvolemic and hypervolemic hyponatremia[133,134] for which it has demonstrated a satisfactory safety profile.[135] Conversely, this medication should not be used to treat hypovolemic hyponatremia, of which CSW is an important cause, because of its tendency to induce a negative fluid balance. The use of this medication in patients with neurologic injury has been examined in only small, uncontrolled retrospective studies.[134] Murphy and colleagues[134] assessed

the efficacy of intermittent bolus doses of 20 or 40 mg of intravenous conivaptan to correct acute euvolemic or hypervolemic hyponatremia that developed within 48 hours of admission to the neurologic intensive care unit. The studied patients had a variety of primary neurologic diagnoses, but patients with SAH who were suspected of having CSW were excluded. Patients who received the drug were those who had symptomatic hyponatremia, were at high risk of developing cerebral edema, or had low serum sodium levels refractory to traditional therapy. A 4 to 6 mEq/L rise in serum sodium concentration by 12 hours after a single dose was seen in 59% of patients and there were no adverse effects, including intravenous site reactions or hypotension. Conivaptan clearly shows promise in treating refractory hyponatremia in critically ill neurologic patients. A careful determination of the likely cause of hyponatremia must take place, however, before administering this drug to such patients. Patients with CSW are volume depleted in addition to being hyponatremic, and conivaptan causes volume loss by aquauresis. Because poor outcome has been associated with volume depletion in SAH patients with hypovolemic hyponatremia, conivaptan should not be administered to patients in whom CSW or a high likelihood for cerebral vasospasm is suspected.[11]

## SUMMARY

CSW is a syndrome of hypovolemic hyponatremia caused by natriuresis and diuresis. Once thought of as a rare novelty, recent clinical and basic science research has shown that CSW exists, is not uncommon in patients with certain types of brain injury, and can have significant negative consequences if not properly diagnosed and treated. The mechanisms underlying this syndrome have yet to be precisely delineated, although existing evidence strongly implicates abnormal elevations in circulating natriuretic peptides as the key pathophysiologic event. Nonetheless, several fundamental questions have yet to be answered, the most important of which are how cerebral injury leads to the release of excessive amounts of natriuretic peptides and why this occurs in only a small subset of cerebral injury types. The key in diagnosis of CSW lies in distinguishing it from the more common SIADH, although the value of this often imprecise process has recently been called into question.[118] Volume status, but not serum and urine electrolytes and osmolality, is crucial for making this distinction. Volume and sodium repletion are the goals of treatment of patients with CSW, and this can be performed using some combination of isotonic saline, hypertonic saline, and mineralocorticoids.

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NEUROLOGICAL MANAGEMENT

# Meningitis

H P Lambert

Three organisms predominate in causing community-acquired bacterial meningitis, *Neisseria meningitidis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*. Meningococcal meningitis is most common in childhood but also affects adolescents and adults. A total of 1302 cases were notified in England and Wales in 1992, 71% of them caused by group B strains against which no vaccine is yet available. *Haemophilus influenzae* meningitis chiefly affects children less than five years old, although a few older patients are encountered. In 1992, 1089 blood or CSF isolates, or both, were recorded and a seven-year study in the Oxford region has estimated the cumulative risk by the fifth birthday as 1:800.[1] Invasive haemophilus infections are already showing a gratifying reduction following the introduction of HIB conjugate vaccines in October 1992.

The pattern of pneumococcal meningitis is more complex. It is seen at all ages but affects particularly the extremes of life and is also especially associated with immune defects such as asplenia, as in sickle cell disease, and with fractures of the skull or congenital defects allowing entry of bacteria to the CNS. This infection carries a high mortality, rarely recorded as less than 20%. The overall mortality from meningococcal and haemophilus meningitis is 5–6% in Britain, but the picture is often complicated by inclusion of acute meningococcal septicaemia, with a much higher death rate than that seen in meningitis alone. The overall mortality from childhood meningitis over a 10-year period in Nottingham[2] was 11·6% and at least one in 10 of the survivors suffered permanent sequelae; these consequences of meningitis are discussed later. In developing countries the incidence and mortality from meningitis are often much higher than in wealthier countries.

Meningitis caused by other bacteria is less common but important, as these infections often cause serious difficulties in diagnosis and management. The need to consider other agents has increased with the increasing number of patients with immune defects, especially HIV infection, and the associated resurgence of tuberculosis. To these bacterial causes must be added the problem of cryptococcal meningitis in association with HIV infection. In nosocomial meningitis, Gram-negative organisms such as *Escherichia coli*, Klebsiella and pseudomonas have to be considered in the differential diagnosis, as also does *Listeria monocytogenes*. A similar distribution of organisms is seen in neonatal meningitis, a special problem not dealt with in this review.

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## Clinical diagnosis

In most patients the initial diagnosis of meningitis, or at least its possibility, is obvious from the combination of systemic and neurological features. Malaise, fever, severe headache, photophobia, and neck stiffness are common and sometimes consciousness is disturbed. The discussion will therefore mainly be concerned with difficulties in diagnosis and, as so often, these are greatest at the extremes of life. The problem of diagnosis in infancy is beyond the ambit of this review, but similar difficulties are sometimes encountered in the elderly. Consciousness may become rapidly depressed and soft neurological signs may lead diagnostic thoughts in the direction of a cerebrovascular accident. Fortunately meningism is a sign not easily masked and is usually, but not always, maintained even in comatose patients.

Meningococcal disease may present in several atypical and deceptive ways. At one extreme, fulminating meningococcal septicaemia, the illness may run its short course from onset to death with no element of meningitis. At the other end of the scale of severity patients, especially children, may experience a period of hours, or even days, of febrile illness with no meningeal features before the symptoms and signs of meningitis appear. This sequence has often led to medicolegal problems when a claim of delayed or missed diagnosis may rest on this point. One especially deceptive presentation of meningococcal meningitis, seen in adolescents and young adults, is as acute mania, directing the diagnosis towards acute psychosis, possibly drug-induced.[3] Neck stiffness may not yet have developed or may be impossible to test for.

The rash of meningococcal septicaemia, when present, is a valuable feature, as the combination of petechial-purpuric rash and meningitis is virtually diagnostic for this

organism. The rash may vary from a few inconspicuous petechiae to extensive purpura with skin necrosis. Non-purpuric rashes—and occasionally petechial ones—are seen in some patients with enteroviral rashes, but this aetiology should never be assumed, as the early rash of meningococcal disease may be macular and unimpressive.

Focal neurological signs are relatively uncommon in pyogenic meningitis in previously healthy patients. Ocular palsies usually resolve within days or weeks. In sharp contrast, labyrinthine damage, which often develops early in the illness, is usually permanent. The frequency of convulsions varies greatly between different forms of meningitis, and is much higher in infancy than in older age groups. They are most frequent in pneumococcal meningitis, less common in haemophilus meningitis, and uncommon in meningococcal disease.[4] Fits are also distinctly uncommon in community-acquired meningitis in adult life, in patients with no underlying neurological abnormality. When focal signs, convulsions, or disturbance of consciousness are prominent in the clinical picture, the possibility of an encephalitis as the primary diagnosis should be considered.

In community-acquired meningitis in previously healthy patients there is often no specific aetiological clue such as rash, recent otitis media, or head injury. In such cases the patient's age may be the sole diagnostic pointer, as haemophilus meningitis is rare after the first few years of life, meningococcal meningitis is the most common form at school age and in young adults, whereas in the elderly *S pneumoniae* becomes more frequent. There are many exceptions to these generalisations, especially now that many reasonably well people in the community may have various forms of immune suppression, notably HIV infection or treatment with immunosuppressive drugs, and may present with uncommon forms of meningitis. Early and accurate laboratory diagnosis therefore remains important and should be achieved as often as possible.

## LUMBAR PUNCTURE

Until recently, suspicion of meningitis was accepted as an almost invariable indication for lumbar puncture, although it was always recognised that it should be avoided or deferred if there was suspicion of an alternative diagnosis that might mimic meningitis, such as brain abscess, cerebral haemorrhage, encephalitis, or posterior fossa tumour. In the last few years, however, concern about the possibility of coning has led to a more cautious approach to lumbar puncture in meningitis. The risk of coning is variously estimated. A recent retrospective survey, from an Australian paediatric referral centre receiving a preponderance of complicated or seriously ill children, noted cerebral herniation in 19 of 445 children (4·3%).[5] There was a strong suggestion that lumbar puncture led to this complication in some patients, although it can certainly occur in patients with meningitis when no lumbar puncture has been done. On the other hand, there are great advantages in making an accurate and early diagnosis, and a Gram-stained smear of the CSF deposit is still the most common way in which this can be achieved. Certainly 'blind' treatment is often successful but if the responsible organism is unusual or antibiotic-resistant, or the patient's progress is unsatisfactory in any way, failure of identification creates an uncertain and unsatisfactory situation.

The dilemma can be resolved by defining genuine risk factors for coning while accepting that lumbar puncture is normally indicated in suspected meningitis. A common injunction is to avoid lumbar puncture if there is suspicion of raised intracranial pressure, a distinctly unhelpful precept as intracranial pressure is raised in nearly every patient with meningitis.[6] More realistic guidelines can be set using known clinical correlates of impending coning, namely coma or rapidly increasing depression of consciousness, focal neurological signs, and tonic or prolonged fits. Fits are common in childhood meningitis in some communities and are not an invariable contraindication to lumbar puncture although, as Mellor points out in a thoughtful review,[7] it is sensible to defer lumbar puncture for 30 minutes after a fit because of the transient cerebral oedema that accompanies it. Papilloedema is a contraindication but is very rare in meningitis and its presence should in any case indicate a wider diagnostic sweep.

Another indication for avoiding or delaying lumbar puncture is unrelated to the question of coning. This is the need for urgent treatment of patients with established or threatened bacterial shock (usually meningococcal septicaemia). The window of opportunity closes rapidly in these patients and treatment should on no account be delayed in order to do a lumbar puncture.

CT or MR scans are usually normal or mildly and non-specifically abnormal in meningitis and are not generally helpful in detecting coning.[7]

## TUBERCULOUS MENINGITIS

In countries with a high prevalence of tuberculosis, tuberculous meningitis acts as one of the markers of the frequency of infection, and the diagnosis is in question in any patient, especially a child, with meningitis. Where tuberculosis has declined the diagnosis is hard to bear in mind, and the problem is compounded by the often deceptive ways in which this disease presents. Its importance is again increasing with the spread of HIV infection and the high prevalence in many countries of the poor social conditions and crowding that are associated with tuberculosis. The relationship of success in treatment to the stage at presentation has rightly been stressed.

There is usually a prodromal illness of days or weeks, with low fever, malaise, and headache before meningeal features develop.

The multiple pathology of tuberculous meningitis, with basal arachnoiditis, vasculitis, infarction, and obstructive hydrocephalus leads to an immense variety of possible focal features; most frequent are cranial nerve palsies and papilloedema. Spinal involvement may take a number of different forms, and rare presentations include a mainly encephalopathic picture. It is important, however, to remember that tuberculous meningitis may present as a meningeal illness with no specific features, so that the diagnosis must be entertained in any patient with non-purulent meningitis. Some persistent myths must be abandoned; the onset may be acute, the CSF glucose is within the normal range in about 20% of cases, and the tuberculin test initially negative in a similar proportion. Because of these protean manifestations, laboratory diagnosis is particularly important (see below), but unfortunately tubercle bacilli are seen in the CSF in only a few cases, depending on the technical skills available, and cultures are not always positive. Indicative features in the clinical presentation include slow onset, contact or family history, ethnic origin, or immigrant status from an area of high prevalence, while a primary lung complex or any evidence of miliary tuberculosis will obviously virtually establish the diagnosis.

CRYPTOCOCCAL MENINGITIS

Cryptococcal meningitis also varies widely in its mode of onset. In immunocompromised patients the course tends to be more rapid than in the immunocompetent but in both groups onset may be insidious, with general malaise, low fever, and headache, This subtle form of presentation is common now that HIV infection is the most frequent type of immune abnormality preceding cryptococcal meningitis.[8] Indeed, features indicative of CNS involvement may be entirely absent and the indications for lumbar puncture must be more widely set in these patients than in the immunocompetent. Lumbar puncture in HIV-infected patients should be preceded by CT because of the possibility of a silent mass lesion. A small proportion of patients with cryptococcal meningitis show focal neurological signs, including early visual loss.[9] In some patients the course of the illness is much more protracted, extending over many months before a diagnosis is reached, and sometimes greatly fluctuating in severity.

LISTERIA MENINGITIS

This is most frequently seen in the neonate but also has a predilection for the immunocompromised and the elderly. Presentation is usually as an acute purulent meningitis with no particular distinguishing features, but the subtle presentations mentioned in the context of cryptococcal meningitis are seen here also. Neurological signs and disturbance of consciousness are common with a mixed meningitic and encephalitic picture, which is more commonly seen with listeria than with other forms of bacterial meningitis. Listeria also causes a range of other CNS conditions, including single or multiple brain abscess, diffuse encephalitis and, rarely, brain stem encephalitis.

## Laboratory diagnosis

This topic can be discussed only briefly, chiefly to stress its importance and the need for efficient and prompt acquisition of correct specimens by the clinician and for good liaison between ward and laboratory. Gram staining of the centrifuged CSF deposit remains the gold standard for early diagnosis, with occasional help from other specimens such as smears from skin lesions. Later, results of blood and CSF cultures provide the main diagnostic yield. Many methods of early diagnosis have been developed, the most useful of which are antigen detection methods, especially latex particle agglutination, which can be employed using CSF, serum, or urine. These techniques are not generally superior to traditional staining, but have definite value in reducing the diagnostic gap in patients who have been given antibiotics before admission.

Diagnosis of tuberculous meningitis still depends mainly on traditional staining methods on the CSF deposit, but new techniques are being developed, notably the polymerase chain reaction, which may greatly improve the low sensitivity of current diagnostic methods.[10]

Diagnosis of cryptococcal meningitis rests largely on cryptococcal antigen detection in CSF (but not blood), on India ink preparations of CSF to detect capsulated *Cryptococcus neoformans*, and on culture using large volumes of CSF.

## Treatment (see Table 1 for doses)

Treatment of the three common forms of pyogenic meningitis has been greatly complicated by increasing prevalence of several types of antibiotic drug resistance. Until these changes became widespread, antibiotic treatment of meningitis caused by these organisms could be accomplished using two safe, easily administered and cheap agents, benzylpenicillin (or ampicillin), and chloramphenicol. Benzylpenicillin is still appropriate for meningococcal and pneumococcal disease in most countries, but haemophilus meningitis, and meningitis of uncertain aetiology must now often be treated with extended spectrum cephalosporins, a particular tragedy in developing countries in which meningitis is common and in which the cost of these compounds is beyond the reach of publicly funded health budgets. It is therefore important to remember that penicillin and chloramphenicol remain agents of first choice in many areas, and may indeed be the only agents available. Table 1 gives the dosages of antibiotics commonly used.

Meningococcal meningitis can be treated with equal efficacy by high dose penicillin or ampicillin given intravenously or by chloramphenicol, given by intravenous injection

*Table 1 Dosage of antibiotics commonly used in meningitis*

| Agent | Total dose per 24 hours: Adult (g) | Total dose per 24 hours: Child (mg per kg) | Dose interval (hours) | Route |
|---|---|---|---|---|
| Benzylpenicillin | 14·4 | 180–300 | 4 | Intravenous |
| Ampicillin | 12 | 200 | 4 | Intravenous |
| Chloramphenicol* | 3 | 50–100 | 6 | Intravenous or oral |
| Cefotaxime | 8 | 200 | 8 | Intravenous |
| Ceftriaxone | 4 | 80 | 24 | Intravenous |
| Vancomycin† | 2 | 40 | 6 | Intravenous |

*Dosage unsuitable for neonates, †Control by blood levels required.

initially, and by mouth as soon as practicable. The role of cephalosporins was at first controversial, as the earlier compounds were relatively ineffective, but the newer compounds, although most widely used in *H influenzae* meningitis, are also of established efficacy in meningococcal infections. An important caveat is the emergence of penicillin resistance in meningococci, especially in Spain, but also increasingly recorded elsewhere. The level of risk of encountering a resistant strain that would necessitate a change from penicillin or ampicillin must be kept under review. One important difference between meningococcal and other forms of meningitis is the relative ease with which the organism can be eradicated. Although 10–14 day courses of treatment have traditionally been used in all forms of meningitis, shorter courses are fully adequate in meningococcal disease. Successful trials have included durations of seven, five, and even four days with penicillin.[11] Chloramphenicol is the best choice in patients allergic to penicillin. In field conditions in tropical Africa, several studies have been made of treatment in one or two doses using a long acting preparation of chloramphenicol in oil. For example, in a large, randomised trial involving 528 patients in Mali and Niger, the success of a two-dose scheme of this sort equalled that achieved by intravenous ampicillin given four times daily for five days, and was clearly much more simple to administer. The mortality in all groups in these trials was much higher than that found in the West, again demonstrating the great impact of meningitis in these areas.[12]

Penicillin is also still the best agent for the treatment of pneumococcal meningitis, but pneumococci resistant to penicillin have become widespread and are now common enough in several countries, including Spain and Hungary, to preclude the use of penicillin in treatment. The treatment of penicillin-resistant pneumococcal meningitis presents a difficult and partly unsolved problem. The chief alternative, chloramphenicol, may be successful but has failed to eradicate infection in a number of cases. It has been shown, in work from South Africa, that many penicillin-resistant pneumococci, although susceptible to chloramphenicol on disc testing, require high minimum bactericidal concentrations of penicillin, and that this form of partial resistance is associated with poor results of treatment.[13] Vancomycin, although a difficult drug to use, has had some success, but a number of treatment failures have led to the suggestion that it should be used in penicillin/chloramphenicol-resistant pneumococcal meningitis only if high-dose cephalosporins have failed or if the patient has anaphylactic reactions to $\beta$-lactam agents.[14]

*H influenzae* meningitis has its main impact in children less than four years old, but is seen occasionally in older children and adults. Ampicillin, formerly widely used alone or together with chloramphenicol, has now lost its role because resistance to its action is now present in a large number of isolates, 15–25% in most countries. Chloramphenicol is still the best agent in many areas, but resistance is increasing, and many ampicillin-resistant strains are also resistant to chloramphenicol. For these reasons extended spectrum cephalosporins such as cefotaxime and ceftriaxone have become the chosen agents in haemophilus meningitis or meningitis of uncertain aetiology. Treatment may be modified when laboratory results are available. Although active against the three common pathogens,[15] cephalosporins have limited or no activity against some of the more unusual causes of meningitis, notably listeria and some of the less common Gram-negative organisms. If the patient has an underlying disease that places him or her at risk for these unusual pathogens and treatment has to be started without microbiological information, the initial regimen should include ampicillin together with the cephalosporin.

Antibiotic treatment before admission diminishes the prospects of obtaining a positive finding by CSF microscopy or culture. Occasionally the CSF is altered more profoundly, with a lymphocytic picture. If partly treated pyogenic meningitis is in question (as well as other diagnoses such as brain abscess and tuberculous meningitis), it would be reasonable to begin provisional treatment with a cephalosporin in full dosage while other investigations are in train.

### TUBERCULOUS MENINGITIS

Tuberculous meningitis stands apart from other forms of meningitis in many important ways. Diagnosis can be difficult, the course of the disease variable and prognosis uncertain. These and other factors have led to a deficiency of the extensive controlled clinical trials that have established well validated regimens for the treatment of pulmonary and some forms of non-pulmonary tuberculosis. Treatment tends therefore to be based on limited trial data, the empirical opinion of physicians with experience of the disease, and on knowledge of the pharmacokinetics of antituberculous agents.[16] The broad relationship of prognosis to neurological deficit demands that treatment should be started as soon as possible, even when there is still uncertainty about the diagnosis. Fear that diagnosis will then be impossible to establish is largely unfounded, because it can often be made from post-treatment specimens of CSF, or from later results of culture of pre- or

post-treatment specimens. Alternatively, a different diagnosis may later be established—for example, by virological findings that allow the provisional treatment for tuberculosis to be discontinued.

The pharmacokinetics of antituberculous agents in the CSF are well established. Pyrazinamide shows excellent penetration into the CSF. The CSF/serum ratio in Chinese patients is about 75% two hours after the dose is given, and about 110% after five and eight hours. Isoniazid too penetrates well, with concentrations in CSF approaching those in serum. Rifampicin concentrations in CSF are 10–15% those in serum, representing the unbound moiety of the drug. Streptomycin achieves adequate concentration in the CSF after standard intramuscular dosage only when the meninges are inflamed, and this is true also of ethambutol, given orally. Ethionamide and prothionamide, by contrast, penetrate the CSF well, whether or not the meninges are inflamed, although their value is limited by gastrointestinal and other unwanted effects. Initial treatment should employ at least a triple regimen of pyrazinamide, isoniazid, and rifampicin. It is still uncertain whether streptomycin is needed as an addition to this scheme. Workers in Hong Kong with great experience of the disease recommend its inclusion during the first two or three months of treatment, and it should certainly be used if rifampicin cannot be obtained because of its cost.[16] The three principal agents are all given by mouth in once daily dosage, or by gastric tube if the patient cannot swallow. The dose of pyrazinamide is 35 mg/kg for a child, 2 g for an adult, that of rifampicin 10 mg/kg. Isoniazid has customarily been given in higher dosages, 10 mg/kg, than are used in other forms of tuberculosis, but the conventional dose of 300 mg or 4–5 mg/kg is probably adequate. Pyridoxine 10 mg daily is given to prevent isoniazid neuropathy. Streptomycin is administered by intramuscular injection in a dose of 20 mg/kg to a maximum of 1 g daily but careful and continued attention should of course be paid to renal function. Intrathecal treatment can no longer be recommended, although there was evidence of its value in treatment regimens which preceded the use of rifampicin and pyrazinamide.

The optimal duration of treatment is unknown. Because the disease is so serious, it has been customary to use long courses of treatment. This is perhaps illogical because, despite the devastating pathology of the condition, the bacterial population concerned is small compared with that found, say, in cavitating pulmonary tuberculosis. Most authors continue treatment for one year, but shorter courses have been used, for example, a nine-month regimen.

The role of steroids has been debated for decades, but rigorous analysis by controlled trial has never been achieved. A mixture of open studies, anecdotal evidence and possibly shaky inference from the known effects of steroids on inflammatory processes has led to their use in the more neurologically advanced grades of the disease, in infants, in generally very ill patients, and in impending spinal block, which may nevertheless progress even during their administration. The situation with raised intracranial pressure in tuberculous meningitis is more clear cut. CSF block leading to hydrocephalus requires urgent control by shunting. Clinicians working in areas of high prevalence believe that early shunting is an important factor in improving prognosis. Rising intracranial pressure from enlarging tuberculoma can be controlled in most patients by high-dose dexamethasone, and surgical decompression is rarely necessary.

### CRYPTOCOCCAL MENINGITIS

Before the advent of HIV infection and AIDS, cryptococcal meningitis was rarely seen in Britain, and then mainly in association with defects of cellular immunity—for example, in patients with lymphoma, those receiving substantial doses of steroids, and in patients with sarcoid whether or not on steroids. In some other countries a substantial number of patients with cryptococcal meningitis had no overt predisposing factors. This picture changed dramatically with the spread of HIV infection and cryptococcal meningitis is now seen as one of the most common CNS infections associated with AIDS. Treatment is difficult and demanding. Failure and relapse are common even in patients without HIV infection; in the presence of HIV, as with other infections, eradication is especially difficult and for this reason much thought has been given to devising practical methods of long-term prevention as well as to improving treatment of established infections.

Agents available for chemotherapy include amphotericin in various forms, flucytosine and some of the more recently developed triazole compounds, of which fluconazole has been most extensively studied. Trials completed before the onset of HIV established the value of amphotericin, despite its formidable toxicity, and showed how the unwanted effects could be partly mitigated by using the synergy, demonstrable in vitro and in vivo, between this agent and flucytosine. A major multicentre study showed that a combination of amphotericin in a dose of 0·3 mg/kg daily together with flucytosine in a dose of 150 mg/kg daily given for six weeks gave results at least as good as with amphotericin alone at 0·4 mg/kg per day for 10 weeks. The patients given combination therapy showed superior results at a non-significant level by a number of criteria; eight of 34 patients in the combination group died compared with 15 of 32 given amphotericin alone.[17]

Since this trial the methods of using amphotericin have been to some extent refined, with a trend to give larger doses, 0·5–0·7 mg/kg daily, or 1·0–1·2 mg/kg on alternate days. Duration of treatment may also be varied. Four weeks may prove adequate for patients with no adverse prognostic factors. These factors include underlying

immune defects (and therefore all those with cryptococcal meningitis superimposed on HIV infection), neurological deficit, a high cryptococcal antigen titre (>1:32) in the CSF and a low (<20 $mm^3$) CSF leucocyte count. Treatment may, however, fail even in patients with no identifiable adverse features.

The onerous nature and limited success of these methods of treatment is even more notable in AIDS-associated cryptococcal meningitis, in which marrow suppression by disease or by other drugs used in therapy may limit or prevent the use of flucytosine. The potential of triazole compounds, with lower toxicity and the advantage of oral administration, is therefore especially interesting in this group of patients. After favourable early results, a formal comparison of fluconazole and amphotericin was made in a randomised, multicentre trial.[18] Fluconazole was given in a dose of 200 mg daily, amphotericin at 0·4–0·5 mg/kg daily. The gravity of this infection is clearly revealed, with successful treatment in only 40% of 63 patients in the amphotericin group and in 34% of 131 patients given fluconazole. There was no significant difference in overall mortality, but deaths were more frequent in the fluconazole group during the first two weeks of treatment and CSF culture reverted to negative more slowly than in the amphotericin group. Comments on this trial emphasised that dosage of both drugs might now be thought too low. Other schemes being evaluated use a higher (0·7 mg/kg) dose of amphotericin with or without flucytosine at 100 mg/kg, either as definitive treatment or for the first two weeks followed by fluconazole. Other studies involve higher doses: 400 mg or 800 mg of fluconazole. Favourable results are also being reported with itraconazole,[19] although this compound does not reach the CSF in detectable concentrations.

The prospects for preventing recurrence of cryptococcal meningitis after initial successful treatment are more promising. A comparison of fluconazole 200 mg daily, with amphotericin 100 mg weekly showed clearly superior results for fluconazole, with relapse in 2% compared with 18% in the amphotericin group.[20] The high relapse rate in patients with AIDS and other forms of immune suppression make it essential to use long-term prophylaxis following initial treatment. What is still uncertain is whether, at least in areas where cryptococcal meningitis is a common feature of AIDS, primary prophylaxis should be attempted. A retrospective study reported only one patient with cryptococcal meningitis of 329 given daily fluconazole as against 16 in 329 historical "controls". This type of primary prevention may come to be vitiated by the development of fluconazole resistance, already emerging in *Candida albicans* infections.

## ROLE OF STEROIDS

There is now abundant evidence that endogenously released factors play an important role in causing the inflammatory changes of meningitis, and increasing interest in the possibility that measures aimed at inhibiting this response might be beneficial.

Although much detail remains to be filled in, the relevant processes can be summarised briefly. In the case of meningococci and *H influenzae*, the initiating factor is endotoxin, a lipopolysaccharide component of the cell wall released in the form of vesicles from the bacteria. Similar processes are induced in pneumococcal infection by the release of other cell wall components, mainly teichoic acid and peptidoglycan. After a time lag of a few hours, pro-inflammatory cytokines are induced, including tumour necrosis factor (TNF), and interleukins (IL) 1, 6, and 8. These and other factors produced from macrophages and from platelets have been shown in experimental systems to induce the changes of acute inflammation in the CNS. An additional complicating factor is that neutrophils, although an important component of the defence systems against pyogenic infection, themselves contribute to the inflammatory process when, after adhesion and migration, they degranulate and produce pro-inflammatory factors including reactive oxygen species.[21]

The link between inflammatory mediators and the timing and intensity of CSF changes is well established in experimental work, and there is increasing evidence of their relevance to human meningitis. For example, the outcome of meningitis can be correlated with levels of endotoxin and pro-inflammatory cytokines in the CSF.[22,23] These relationships are also clearly established in septicaemic meningococcal infection, in which there is a close relationship between plasma endotoxin levels and prognosis, and between endotoxin levels and levels of TNF-$\alpha$, IL-1, and IL-6.[24]

An especially taxing question is whether lytic antibiotics, given to cure the infection, might themselves have an adverse effect by causing rapid release of bacterial products and thus provoking an increased inflammatory burst. In experimental models of meningitis it is clear that an increase of several mediators, and a consequent inflammatory burst, follows the administration of lytic antibiotics such as $\beta$-lactams.[25] This increased inflammatory response can be significantly mitigated by dexamethasone if given at the same time as, but not one hour later than, the antibiotic.[26] Again, the evidence from human meningitis is necessarily more fragmentary. In one study, eight children with *H influenzae* meningitis had repeat lumbar puncture two to six hours after their initial dose of antibiotic, ceftriaxone. The second specimens showed increased concentration of endotoxin correlated with the decrease in viable bacteria, together with increase in lactate and decrease in glucose concentration in the CSF. In some cases TNF concentration in the CSF rose about four hours after starting treatment.[27] It is therefore possible that diminishing the endogenously mediated inflammatory processes might be beneficial and that some or all of this benefit might

accrue from diminishing a possible adverse consequence of essential treatment, the sudden lysis of large numbers of bacteria.

It is against this background that the current renewed interest in a role for steroids in pyogenic meningitis has arisen, after a 20-year lapse since their first trial.[28 29] The first favourable evidence of a beneficial effect on outcome was gained from two trials involving 200 children, predominantly with haemophilus meningitis,[30] In one trial the antibiotic used was cefuroxime (not now considered entirely satisfactory as the cephalosporin of choice in meningitis), in the other ceftriaxone. In both, patients were randomly allocated to receive placebo or dexamethasone in a dose of 0·15 mg/kg six hourly for four days. The dexamethasone group showed a significant increase in the speed with which abnormal CSF findings resolved, and, at follow up, substantial hearing loss was found in 15 placebo and three dexamethasone recipients; hearing aids were needed in 12 and one respectively. A smaller trial of 60 patients gave similar, although non-significant results.[31] Notable reductions in the IL-1 $\beta$ concentration were also demonstrated, together with improved prognosis, in dexamethasone-treated children. An open study in Egypt involved adults and children with meningitis, alternate patients being given dexamethasone. Seven of 52 patients with pneumococcal meningitis given dexamethasone died, compared with 22 of 44 controls. Sequelae were also less common in the dexamethasone group.[32]

Two more substantial controlled trials in childhood meningitis have taken account, in their design, of the importance of timing in experimental models. Children in Costa Rica[33] were given placebo or dexamethasone in the same dose as in the previous studies (0·15 mg/kg six hourly for four days) but beginning 15–20 minutes before the first dose of the antibiotic, cefotaxime. At 12 hours the dexamethasone-treated group showed improvement compared with the controls in CSF pressure and in inflammatory indices and cytokine concentrations in the CSF. At follow up seven of 51 dexamethasone-treated children (14%), and 18 of 48 controls (38%) had neurological or audiological sequelae (relative risk 3·8, 95% CI 1·3 to 11·5). A Swiss trial[34] differed in the dose and duration of dexamethasone administration, 0·4 mg/kg 12 hourly for two days, starting 10 minutes before the first dose of antibiotic, ceftriaxone. Follow up at 3, 9, and 15 months showed sequelae in three of 60 dexamethasone recipients (5%) and nine of 55 placebo recipients (16%) relative risk 3·27, 95% CI 0·93 to 11·47. Table 2 summarises the results of these important studies.

*Table 2 Neurological and audiological sequelae of meningitis. Trials of dexamethasone*

| | | *Neurological sequelae (no.(%))* | | *Moderate or severe deafness (no.(%))* | |
|---|---|---|---|---|---|
| *Reference* | *No. in study* | *Dexamethasone* | *Placebo* | *Dexamethasone* | *Placebo* |
| 30,31 | 260 | 3(4) | 9(12) | 11(9) | 21(19) |
| 33 | 101 | 5(10) | 15(31) | 3(6) | 7(16) |
| 34 | 115 | 3(5) | 5(9) | 3(5) | 7(13) |

The trials also showed few adverse effects in the dexamethasone groups, mainly a higher incidence of gastrointestinal bleeding, usually detected only by investigation rather than by a significant clinical event. Moreover, cases of viral meningitis inadvertently treated with dexamethasone showed no adverse effects. It is reasonable to conclude that steroids, given in high dosage for a short time, and initiated early and preferably shortly before starting antibiotics, have a beneficial effect on outcome in childhood haemophilus meningitis, with lesser but suggestive evidence of benefit in other forms and at other ages.

Several other modes of damping the inflammatory response and its adverse pathophysiological consequences have been successful in experimental systems. They include non-steroidal anti-inflammatory agents, monoclonal antibodies against some of the cytokines involved, and antibody inhibiting leucocyte adhesion to endothelium. No method of modulating the inflammatory process, however, other than administration of steroids, is yet available for use in human meningitis.

**Other aspects of management**

Might any aspects of therapy other than antibiotics and steroids help to mitigate the continued high mortality and residual morbidity associated with bacterial meningitis? Fits must, of course, be brought under control as promptly as possible, and mannitol infusions are of established value if signs of increasing intracranial pressure appear. Changes in the cerebral circulation in meningitis may be important, and certainly in experimental models, the inflammatory process leads to a complex interaction of brain oedema and raised intracranial pressure with changes in cerebral blood flow and perfusion. Especially notable is loss of autoregulation so that the cerebral blood flow becomes passively responsive to the systemic blood pressure.[35] Few measurements of the cerebral circulation have been made in human meningitis, and these largely in infants and children. Two important studies by non-invasive techniques are notable. Goh and Minns[36] made serial measurements of cerebral blood flow velocity using transcranial Doppler ultrasound. They found an increase in flow velocity as meningitis resolved with a decrease in the final resistance index, suggesting a decrease in cerebral perfusion during the acute phase of the illness. Mannitol infusion, by reducing intracranial pressure, increased cerebral perfusion pressure with a resultant decreased resistance index and increase in blood flow velocity. Another study, involving seriously ill children, employed stable xenon CT.[37] This showed diminished blood flow in only a few patients (five as against 18 with normal cerebral blood flow) but did reveal marked

regional variations in flow changes. Determinations in artificially ventilated patients at different $pCO_2$ tensions showed that hyperventilation to low $pCO_2$ tension could reduce regional blood flow below ischaemic thresholds. In these and other studies cerebral autoregulation appeared to be generally preserved and pressure passivity was only seen in some very ill children with grossly abnormal neurological signs.

Some tentative conclusions relevant to clinical management may be drawn from these studies. It would seem sensible, in patients seriously ill with meningitis, to aim at avoiding fluctuations of blood pressure in either direction which might lead to changes in cerebral blood flow. In particular, hyperventilation with the aim of reducing intracranial pressure may sometimes prove disadvantageous and it may be preferable to maintain the $pCO_2$ within the normal range.

A common error in management is to limit fluid intake unduly with the aim of controlling inappropriate secretion of antidiuretic hormone and, it is supposed, thus reducing the likelihood of cerebral oedema. It has been shown in childhood meningitis, however, that the observed high levels of arginine vasopressin are an appropriate response to hypovolaemia and that levels return to normal when fluid replacement is achieved.[38] Fluid deficits in meningitis should be corrected with the appropriate replacement fluids and normal maintenance requirements provided.

## Communication

The diagnosis of meningitis brings with it enormous fear and anxiety for many reasons. Will the patient die? Will the patient be brain damaged? Will other members of the family or other people "catch" meningitis? All these questions must be discussed as often as necessary. Especially difficult is the oft-expressed question, why did this particular person develop meningitis? A simple account of how these bacteria spread is often helpful to the family and needs including with discussion of the patient's progress. To this must be added the common anxiety of health service staff about the possibility of infection when treating patients with meningococcal meningitis or septicaemia. The consultant in communicable disease control must be informed as soon as possible so that preventive measures (see below) can be rapidly brought into operation. Close liaison with the laboratory is of course essential, to ensure the best possible quality of specimens and thus the best chance of identifying the causal organism and its antibiotic sensitivity.

*Table 3 Permanent hearing loss after bacterial meningitis*

| *Type of meningitis* | *No. in study* | *Permanent sensorineural hearing loss of any degree (no. (%))* |
|---|---|---|
| Unselected | 1175 | 113 (9·6) |
| *Haemophilus influenzae* | 876 | 99 (11·4) |
| Meningococcal | 398 | 30 (7·5) |
| Pneumococcal | 66 | 21 (31·8) |

After Fortnum.[32]

## Sequelae

Most previously healthy survivors of community-acquired meningitis recover completely but an important minority is left with residua ranging from mild neurological or audiological defects to profound and lifelong disability. Bacterial meningitis is the most common cause of acquired sensorineural deafness. Its frequency has been analysed in a thoughtful review by Fortnum[39] accepting only published series with well-defined criteria avoiding the many possible confounding factors in such studies (table 3). Deafness complicates meningitis in about 10% of patients, and will be bilaterally profound or total in 1–4%.

Pneumococcal meningitis is generally reported to carry a much higher risk of deafness than the other two common forms, although the difference may not be as great as has been supposed. Certainly the risk of deafness exists in all forms of meningitis and at all ages, and no reliable predictors of this complication are available. Whether the trend towards steroid treatment will make an impact on the frequency of deafness remains to be seen.

The likelihood of other serious long-term sequelae is hard to estimate but may occur at about the same frequency as severe deafness—for example, four of 48 children who survived haemophilus meningitis in Wales suffered long-term neurological sequelae (8%).[40]

### RELATION BETWEEN DURATION OF ILLNESS AND OUTCOME

The relationship between clinical features and the known pathophysiology of meningitis is important to our understanding of the disease. The question is also important in the medicolegal context as actions about neurological damage following meningitis often centre on a claim of missed or delayed diagnosis. Inflammatory changes in the CNS are related to bacterial load, which suggests a connection between prognosis and delayed diagnosis, but attempts to analyse the point reveal a more complex picture. One prospective analysis[41] showed that children with a history of less than 48 hours illness did significantly worse than those with longer histories. A recent exhaustive examination of 22 studies involving 4707 patients with meningitis attempted to analyse the question in more detail.[42] Many of the studies were unsuitable for formal meta-analysis, but the previous finding that children with a slow and insidious presentation had a better outlook than those with acute illness was confirmed. At the other extreme, in a small subgroup with fulminant meningitis, the influence of antibiotics seemed minimal. Between these lies the group with clinically overt meningitis but without septicaemic shock; data were

insufficient to analyse these, the very patients in whom it would seem plausible that early treatment would be beneficial. These analyses reflect a familiar clinical observation, that there is often a substantial prodromal illness of hours to days before features of meningitis appear, especially in children. Although the entire illness is subsequently designated as meningitis, presumably the early phase corresponds with the bacteraemic illness preceding localisation to the meninges, or perhaps in some cases a preceding viral infection. In either case the host–parasite relationship is more evenly balanced, and the illness less severe than in fulminant meningococcal septicaemia.

A further point bearing on the complex relation between duration of illness and outcome is that deafness, the most common adverse event leading to longterm disability, often develops very early in the course of meningitis.

## Prevention

### VACCINATION

The persistently high mortality and residual morbidity from meningitis make it likely that substantial further progress can be made only by improvements in prevention. Recent years have seen encouraging advances in vaccination, with the promise of more to come.

Capsular antigen plays an important role in pathogenesis for all the common causes of bacterial meningitis, and anticapsular antibody is correspondingly important in protection. Unfortunately children less than two years old show poor and transient responses to these polysaccharide antigens.[43] This serious deficiency in the value of these antigens in immunisation programmes has been successfully addressed in the case of *H influenzae* by formulating conjugates of the capsular antigen with various protein moieties that render them fully immunogenic in infancy as well as in older age groups. The problem is complex as different conjugates so far devised vary in their immunological properties and in their potency as antigens in infancy. There are also variations in host response dependent on ethnic, nutritional, and demographic factors. Despite these intricacies, several conjugate vaccines have been developed and widely used in many countries including Great Britain.[44] Their introduction has been followed by rapid reduction in the incidence of haemophilus meningitis and an additional, unexpected benefit, reduction of the nasopharyngeal carrier rate. In Finland, which has been in the forefront of immunisation against haemophilus meningitis, this form of meningitis has been almost eliminated.[45]

The great majority of invasive haemophilus infections are caused by one serotype, group b. The situation is more complex in meningococcal infection. Capsular polysaccharide vaccines have been developed against groups A and C strains, and are available for use in contacts and for outbreak control when one of these strains is responsible, for travellers to areas of high prevalence, and for individuals at special risk of meningococcal disease.[46] The development of vaccine against meningococci of group B, the predominant group in Britain, has proved difficult, but several approaches to this problem are now being pursued. One involves developing conjugate vaccines, another using outer membrane proteins (OMPs) rather than the polysaccharide capsular material as antigen. As these OMPs are strain specific, this approach necessitates the development of multivalent vaccines. Trials of OMP vaccines have been achieved in several countries, including Norway, Brazil, and Cuba, with overall efficacy rates varying between 50% and 90%, but with less efficacy in children.[47 48]

Pneumococcal vaccines[49] are relevant mainly in the prevention of respiratory disease and otitis media, but here too the successful development of conjugate vaccine against a high proportion of important serotypes might in future contribute to a general vaccine against the main types of bacterial meningitis. Alternatively, other antimeningitis components may come to be added to combinations, already being developed, of diphtheria, pertussis, tetanus with HIB vaccine.

### CHEMOPROPHYLAXIS

The risk of meningococcal and of haemophilus meningitis is significantly higher in certain contact groups than in control populations. For this reason chemoprophylaxis is used in these contacts to eradicate nasopharyngeal carriage of the causal organism and thus diminish the likelihood of disease.[50 51] Although the alarm which is engendered by the diagnosis of meningitis leads naturally to great emphasis on treatment of contacts, it has to be emphasised that chemoprophylaxis is a control measure of very limited value, compared with preventive vaccination, or early diagnosis and treatment of cases. There are several reasons for this, chiefly that in most patients with meningitis the source is unknown, and the patient could therefore not have received chemoprophylaxis. In addition, spread of both *H influenzae* and the meningococcus between carriers may be quite slow, and the risk to contacts extends long beyond any practicable period of chemoprophylaxis.[52] Moreover, sometimes the carrier state is not eradicated, and resistance may develop to the agent used.

Rifampicin is used for contacts of both these forms of meningitis, although there are important differences in dose and duration (10 mg/kg 12 hourly for two days for meningococcal contacts, 20 mg/kg daily for four days for haemophilus contacts, maximum 600 mg per dose). Two other authenticated forms of chemoprophylaxis are available, ciprofloxacin in a single oral dose, or ceftriaxone as a single injection. In general, close family, household, and nursery contacts are given chemoprophylaxis, and also the index case before leaving hospital, as, paradoxically, successful chemotherapy for

meningitis does not eradicate the carrier state.

It is most important that contact between health professionals and families of patients with meningitis should include careful discussion of possible early features of meningitis, and the limitations of chemoprophylaxis.

## Resource implications

Hospital management of meningitis requires well trained and well staffed medical and paediatric units with easy access to the relevant supporting services. Most essential is liaison with the laboratory on a 24-hour basis, and with the relevant clinical specialists, including especially neurological and infectious disease services. Access to a fully staffed intensive care unit may become essential for some very ill patients, with facilities for safe transfer if this is not available on site. Outside the hospital, communication with the relevant specialist in public health medicine should extend beyond the legal requirements of notification and should include detailed discussion of possible contacts and control measures. Audit of services for meningitis might measure, in addition to mortality and morbidity, such factors as completeness of notification, duration of illness before admission, whether antibiotics were given before admission, time between admission and definitive treatment and appropriateness of treatment regimens employed.

At a later stage, rehabilitation facilities will be needed for patients with residual disability. The needs of children with hearing problems have been well studied.[53] Early skilled assessment is required because, although some hearing loss in the acute illness and during recovery is conductive and may be transient, early identification of sensorineural loss is essential so that rehabilitation can begin promptly. It has been strongly argued that all children who have had meningitis should have auditory assessment, initially 4–6 weeks after discharge from hospital. This would involve 30–40 appointments annually for a health district with a population of 250 000. This requirement may well change with successful vaccination programmes, although there is evidence that at present not all patients who need assessment are referred.


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## ORIGINAL ARTICLES

# Normalization of plasma arginine vasopressin concentrations when children with meningitis are given maintenance plus replacement fluid therapy

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**We hypothesized that plasma arginine vasopressin (AVP) concentrations in children with meningitis are appropriate for the children's degree of hypovolemia, even though the concentrations were higher than expected for the serum osmolality. A randomized study was conducted to compare the effect on plasma AVP concentrations of giving maintenance fluid requirements plus replacement of any deficit versus restricting fluids to two thirds of maintenance requirements for 24 hours. Plasma AVP concentrations and serum osmolality were measured before fluid therapy was begun and again after 24 hours. Nineteen children, 2 months to 17 years of age, were studied; 13 had bacterial meningitis (12 with *Haemophilus influenzae* type b). Ten children (seven with bacterial meningitis) received a mean of 1.42 times the calculated maintenance fluid requirements, and nine (six with bacterial meningitis) were restricted to a mean of 0.65 times maintenance. Children in the maintenance group also received significantly more sodium (mean = 6.3 mEq/kg/24 hr) than children in the fluid-restricted group (mean = 2.0 mEq/kg/24 hr). The two groups were comparable for plasma AVP concentration and serum osmolality before fluid therapy was begun. The plasma AVP concentration was significantly lower after 24 hours of**

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**maintenance plus replacement fluids than after fluid restriction ($p = 0.005$), and the change in AVP concentration correlated with the amount of sodium given ($p < 0.02$). This study supports the hypothesis that serum AVP concentrations are elevated in patients with meningitis because of hypovolemia and become normal when sufficient sodium is given to facilitate reabsorption of water by the proximal tubule of the kidney. Patients with meningitis can be given maintenance plus replacement fluids but should be monitored for the development of the syndrome of inappropriate secretion of antidiuretic hormone. (J PEDIATR 1990;117:515-22)**

Fluid restriction is generally considered a standard part of supportive care for patients with bacterial meningitis who are neither hypotensive nor hypovolemic.[1] This practice of fluid restriction has evolved from three observations: (1) The syndrome of inappropriate secretion of antidiuretic hormone can occur in patients with meningitis[2]; (2) plasma and cerebrospinal fluid arginine vasopressin (antidiuretic hormone) concentrations are elevated in patients with bacterial meningitis[3, 4]; and (3) the treatment of SIADH is fluid restriction.[5] However, no one has demonstrated that the restriction of fluids to two thirds or three fourths of maintenance requirements will prevent SIADH.

The purpose of our study was to test the hypothesis that plasma AVP concentrations in children with meningitis are appropriately elevated for their extracellular fluid volume and will become normal after appropriate maintenance therapy plus replacement fluids are administered.

## METHODS

Previously healthy children aged 3 weeks to 16 years, in whom the diagnosis of meningitis was made on the basis of physical examination and cerebrospinal fluid cytologic and chemistry studies, were considered for enrollment. Patients with central nervous system diseases other than meningitis or with renal disease, endocrinopathy, a history of prematurity (<36 weeks of gestation), congestive heart failure, chronic pulmonary disease, malignancy, immunodeficiency, or hepatic disease, and patients being treated with phenytoin, lithium, morphine, phenobarbital, or dexamethasone, were excluded from the study. Patients who received undocumented volumes of fluid during transport to our hospital and patients who were judged to require fluid resuscitation were also excluded from the study. When the diagnosis of meningitis was made, patients were given one or more antibiotics; fluids were administered intravenously at the slowest rate that is compatible with keeping the intravenous catheter patent until patients could be enrolled in the study. Informed consent was obtained, and patients were randomly assigned to receive either two thirds of their maintenance fluid requirement for 24 hours or their maintenance fluid requirements plus the replacement of any estimated deficit for 24 hours. Random assignments were made by opening an envelope containing a card saying "restrict" or "maintenance" that had been prepared with a table of random numbers. The study was approved by the research subjects review board of the University of Rochester.

**Clinical and laboratory assessment.** The initial assessment of all patients entering the study included obtaining a history and performining a physical examination, including asking questions about oral intake during the previous 24 hours and a clinical assessment of hydration. Weight loss, based on the most recent weight recalled by the parents less the child's weight on arrival at the emergency department, was used as one estimate of fluid deficit. Other indexes included thirst, absence of tears, dry mucous membranes, depressed anterior fontanelle, sunken eyeballs, soft eyeballs, skin turgor, hyperpnea, hypotension, and history of urination.[6] On the basis of this assessment (performed by one of us), patients were judged to be normally hydrated or mildly (1% to 5%), moderately (6% to 10%), or severely (11% to 15%) dehydrated. All patients had a routine laboratory assessment that included serum concentrations of electrolytes, glucose, creatinine, and blood urea nitrogen, and a urinalysis. Laboratory assessment performed specifically for the study included measurement of the plasma AVP concentration.

| | |
|---|---|
| AVP | Arginine vasopressin (antidiuretic hormone) |
| SIADH | Syndrome of inappropriate secretion of antidiuretic hormone |

As soon as informed consent was obtained, 2 ml of blood was obtained by phlebotomy and placed in a heparinized glass tube on ice for measurement of the plasma AVP concentration.

**Fluid therapy.** Daily maintenance fluid requirements were calculated as 100 ml/kg for the first 10 kg of body weight, plus 50 ml/kg for the next 10 kg (10 to 20 kg), plus 20 ml/kg for each kilogram in excess of 20 kg. Patients randomly assigned to the fluid-restriction regimen were given two thirds of their daily maintenance requirements for

Table I. Selected laboratory and clinical findings at the time of patient entry into the study

| | Meningitis | Maintenance | Restricted | p* |
|---|---|---|---|---|
| No. of patients | Bacterial | 7 | 6 | — |
| | All | 10 | 9 | — |
| Laboratory findings | | | | |
| Plasma AVP concentration (pg/ml) | Bacterial | 11.2 ± 2.9† | 6.0 ± 1.2‡ | NS |
| | All | 9.0 ± 2.3 | 6.5 ± 1.0 | NS |
| Serum osmolality§ | Bacterial | 277 ± 2 | 273 ± 4 | NS |
| | All | 278 ± 2 | 279 ± 4 | NS |
| Serum $Na^+$ concentration (mEq/L) | Bacterial | 135 ± 1 | 132 ± 2 | NS |
| | All | 135 ± 1 | 135 ± 2 | NS |
| Clinical findings | | | | |
| Dehydration (%) | Bacterial | 4.2 ± 1.2 | 0.8 ± 0.5 | 0.028 |
| | All | 3.6 ± 0.9 | 0.5 ± 0.3 | 0.007 |
| Vomiting | Bacterial | 6/7 | 4/6 | NS |
| | All | 8/10 | 4/9 | NS |

*NS*, Not significant.
*Student *t* test was used for all except vomiting, for which the Fisher Exact Test was used; $p \leq 0.05$ was considered significant.
†Mean ± SEM.
‡ADH concentration and serum osmolality of the fluid-restricted patient with a zero-time ADH concentration of 54.7 pg/ml were deleted for these calculations.
§Serum osmolality = (Serum $[Na^+]) \times 2 + [Glucose]/18 + [BUN]/2.8$ mOsm/kg $H_2O$.

24 hours; no extra fluids were given to correct any estimated deficit. Patients randomly assigned to receive maintenance fluids received the full daily maintenance requirement, plus the replacement of any estimated deficit, during a 24-hour period. The clinical estimate of the percentage of dehydration was multiplied by the premorbid weight to arrive at the volume deficit. Rehydration was begun by administering 10 or 15 ml/kg by rapid intravenous infusion. This amount was then subtracted from the calculated deficit and the remainder was given during a 24-hour period, half during the first 8 hours and the remainder during the next 16 hours. The composition of fluids administered to study patients was determined by the attending physician and not by study protocol. Fluids given rapidly to replace calculated deficits usually contained 0.9% saline solution. Other intravenous fluid solutions consisted of either 0.2%, 0.3%, 0.45%, or 0.9% saline solution in 5% dextrose. After the patient had voided, potassium chloride was added to a final concentration of 10 to 20 mEq/L.

For the 24 hours after the initial AVP determination, the ratio of the volume of fluid received to the maintenance fluid requirements for each patient was calculated. The amount of sodium given to each patient was calculated on the basis of the sodium content and volume of fluid administered plus the amount of sodium in the antimicrobial agents administered (ampicillin 3.12, chloramphenicol 2.25, ceftriaxone 3.6, and cefotaxime 2.2 mEq $Na^+$ per gram). No attempt was made to estimate the sodium content of the small volume of fluids taken orally.

Fluid intake and urine output were documented for at least 24 hours after entry into the study. Patients were reweighed when admitted to the inpatient service and weighed on the same scale within 24 hours. Urine specific gravity was measured at least once every 8 hours. After 24 hours of hospitalization, measurements of plasma AVP and serum electrolyte concentrations were repeated.

**Plasma AVP concentration.** The AVP concentration was measured by radioimmunoassay,[7] with antiserum generously provided by Drs. Jacques A. Durr and Marshall D. Lindheimer, University of Chicago, Chicago, Ill. The antibody is highly specific for AVP and has negligible cross-reactivity with oxytocin (0.001%). Plasma was extracted before assay by the acetone-ether procedure of Robertson et al.[8] Recovery from extraction was determined from each set of samples and averaged 63 ± 22% (mean ± SD). Values were corrected for the percentage of recovery during extraction on the basis of standards extracted with each batch assayed. Interassay variation was 15.6%. All samples from an individual patient were measured in the same assay.

**Statistical analysis.** Statistical analyses were performed with the Student *t* test, Fisher Exact Test, and correlation analyses. Data are expressed as mean ± SEM. Data were analyzed for all study patients combined and for patients with bacterial meningitis as a separate group.

## RESULTS

From July 1985 through June 1988, of approximately 74 children treated for meningitis at the University of Rochester Medical Center, 24 were enrolled in the study. More than half of the patients not enrolled had received intravenous fluid while in transport from an outlying hospital.

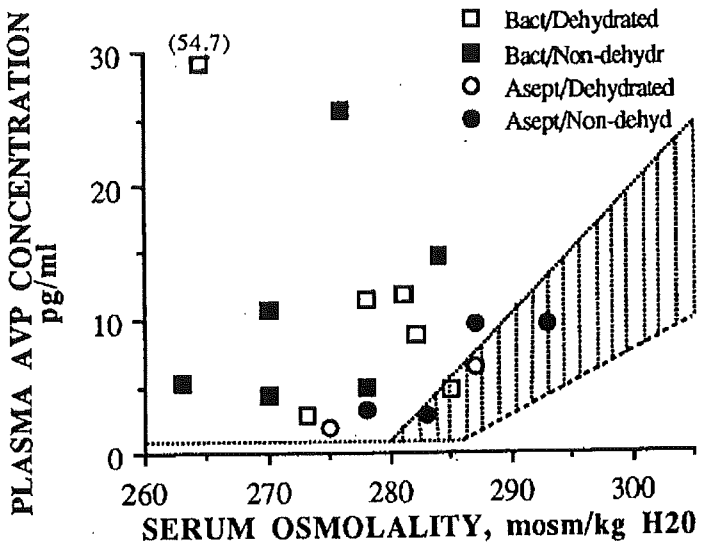


**Fig. 1.** Plasma AVP concentration versus serum osmolality at time of hospitalization. *Hatched area* represents relationship between plasma AVP concentration and serum osmolality in normally hydrated adults.[8] *Bact*, Bacterial; *Asept*, aseptic.

**Table II.** Interventions and selected laboratory findings on the day after hospitalization

| | Meningitis | Maintenance | Restricted | p* |
|---|---|---|---|---|
| No. of patients | Bacterial | 7 | 6 | — |
| | All | 10 | 9 | — |
| Intervention | | | | |
| Volume given† | Bacterial | 1.50 ± 0.1‡ | 0.63 ± 0.3 | 0.000 |
| | All | 1.42 ± 0.07 | 0.65 ± 0.2 | 0.000 |
| mEq $Na^+$/kg/24 hr | Bacterial | 7.8 ± 1 | 2.2 ± 0.3 | 0.000 |
| | All | 6.3 ± 1 | 2.0 ± 0.2 | 0.001 |
| Outcome | | | | |
| Plasma AVP concentration (pg/ml) | Bacterial | 2.5 ± 0.9 | 6.3 ± 1.3§ | 0.025 |
| | All | 2.4 ± 0.6 | 5.7 ± 0.8 | 0.005 |
| Change in AVP concentration (pg/ml) | Bacterial | −8.7 ± 2.2 | 0.5 ± 1.7§ | 0.011 |
| | All | −6.6 ± 1.8 | −0.7 ± 1.5 | 0.026 |
| Serum osmolality‖ | Bacterial | 286 ± 1 | 282 ± 5§ | 0.157 |
| | All | 287 ± 2 | 282 ± 2 | 0.080 |
| Serum $Na^+$ concentration (mEq/L) | Bacterial | 139 ± 1 | 136 ± 1 | 0.067 |
| | All | 140 ± 1 | 137 ± 1 | 0.063 |

*Student $t$ test; $p < 0.05$ was considered significant.
†Fluid given is the volume of fluid administered in 24 hours divided by the calculated maintenance volume.
‡Mean ± SEM.
§ADH concentration and serum osmolality of the fluid-restricted patient with a zero-time ADH concentration of 54.7 pg/ml were deleted for these calculations.
‖Serum osmolality = (Serum $[Na^+]$) × 2 + [Glucose]/18 + [BUN]/2.8 mOsm/kg $H_2O$.

Technical difficulties with the extraction step in the plasma AVP assay resulted in the loss of specimens from four children. One child enrolled in the study was excluded from data analysis because the nephrotic syndrome was diagnosed approximately 12 hours after hospitalization for *Streptococcus pneumoniae* meningitis.

Of the 19 children included for data analysis, 12 were female, 18 were white, and their ages ranged from 2 months to 17 years. Thirteen children had bacterial meningitis (12 *Haemophilus influenzae* type b, one *Neisseria meningitidis*), and six had aseptic meningitis.

Ten patients, seven with bacterial meningitis, were randomly assigned to receive maintenance fluids plus replacement of any estimated deficit; nine patients, six with

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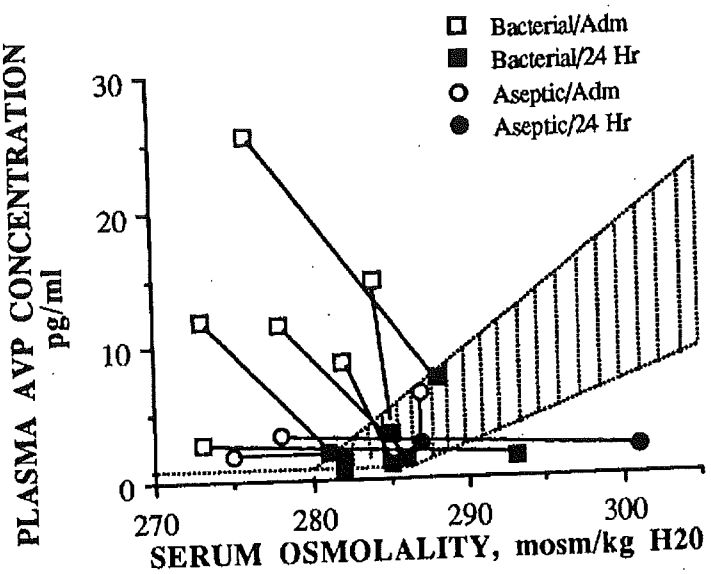


**Fig. 2.** Maintenance fluid therapy. *Clear symbols* represent relationship between plasma AVP concentration and serum osmolality at time of hospitalization for individual patients and are connected by *rule* to *dark symbols*, which represent this relationship after 24 hours of maintenance-plus-replacement-fluid therapy. *Adm*, Admission.

bacterial meningitis, were randomly assigned to the fluid-restriction regimen. At entry into the study, patients who were to receive maintenance plus replacement fluids were clinically estimated to be significantly more dehydrated than patients assigned to the fluid-restriction group (Table I). However, there were no significant differences between the fluid-restriction and maintenance-fluid groups for plasma AVP concentration, serum sodium concentration, serum osmolality, or the incidence of vomiting before hospitalization (Table I). The clinical estimate of the percentage of dehydration did not correlate with plasma AVP concentration, serum osmolality, serum sodium concentration, or temperature at the time of enrollment into the study.

Changes in selected laboratory findings approximately 24 hours after hospitalization are detailed in Table II. The volume of fluids given to children in the maintenance-plus-replacement group ranged from 1.11 to 1.87 times calculated maintenance requirements (mean 1.42 ± 0.07 × maintenance). Children who had fluid restriction received from 0.49 to 0.87 times maintenance requirements (mean 0.65 ± 0.2 × maintenance). The amount of sodium given during the first 24 hours ranged from 1.4 to 12 mEq/kg (mean 6.3 ± 1 mEq/kg) in the maintenance-plus-replacement group compared with 1.4 to 3.4 mEq/kg (mean 2.0 ± 0.2 mEq/kg) in the fluid-restriction group. Plasma AVP concentrations approximately 24 hours after the start of fluid therapy were significantly lower in patients who received maintenance plus replacement fluid than in patients who had fluid restriction, for patients with bacterial meningitis ($p = 0.025$) as well as for all patients ($p = 0.005$), and the difference remained significant if the patient in the fluid-restricted group with the outlying serum AVP concentration (54.7 pq/ml; Fig. 1) was included. The change in plasma AVP concentration from the time of admission to 24 hours later was also significantly different if the AVP values for the patient in the fluid-restriction group with an initial AVP of 54.7 pq/ml were excluded ($p = 0.026$). The change in plasma AVP concentration was significantly correlated with the amount of sodium administered ($r = 0.54$; $p < 0.02$) but not with the volume of fluid given ($r = 0.31$; not significant). Serum osmolality and serum sodium concentration after 24 hours of fluid therapy tended to be higher in patients receiving maintenance plus replacement fluid than in those who were fluid restricted ($p = 0.08$ and 0.063, respectively), but no significant change in serum sodium concentration or change in serum osmolality occurred in either group. Thus there was no correlation between the amount of sodium given and the change in serum sodium concentration or the change in serum osmolality.

In healthy adults, plasma AVP is maximally suppressed when plasma osmolality is <280 mOsm/kg $H_2O$.[8] When plasma osmolality is >280 mOsm/kg $H_2O$, the plasma AVP concentration is positively correlated with plasma osmolality.[8] At the time of entry into the study, 11 of 12 patients with bacterial meningitis (data incomplete on one patient) and three of six patients with aseptic meningitis had

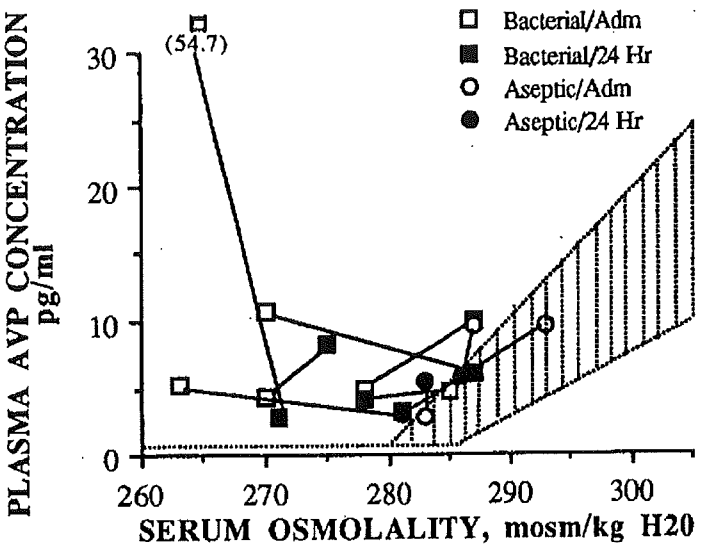


**Fig. 3.** Fluid restriction. *Clear symbols* represent relationship between plasma AVP concentration and serum osmolality at time of hospitalization for individual patients and are connected by *rule* to *dark symbols*, which represent this relationship after 24 hours of fluid restriction. *Adm*, Admission.

plasma AVP concentrations that were elevated in comparison with the relationship between plasma AVP concentration and plasma osmolality in healthy, normally hydrated adults (Fig. 1). The plasma AVP concentration of one child with bacterial meningitis was far higher than any other observations at entry into the study. In all patients who received maintenance plus replacement fluids, the 24-hour plasma AVP concentration was lower than the admission AVP concentration, and was within or below the range indicated by their serum osmolality (Fig. 2).

In contrast, the plasma AVP concentration was higher at 24 hours than at the time of hospitalization in four of nine patients who had fluid intake restricted (Fig. 3). Furthermore, after 24 hours of fluid restriction, the plasma AVP concentration was elevated in comparison with the value expected on the basis of the corresponding serum osmolality in seven of nine patients (Fig. 3), and was significantly higher in these patients than in those who received maintenance plus replacement fluids.

## DISCUSSION

The SIADH results in excessive free water retention despite a falling extracellular fluid osmolality. The syndrome is characterized by "(1) hyponatremia with corresponding hypoosmolality of the serum and extracellular fluid; (2) continued renal excretion of sodium; (3) absence of clinical evidence of fluid volume depletion, that is, normal skin turgor and blood pressure; (4) osmolality of the urine greater than that appropriate for the concomitant tonicity of the plasma, that is, urine less than maximally dilute; (5) normal renal function; and (6) normal adrenal function."[5] However, the reported incidence of these characteristics in patients with bacterial meningitis varies from 4%[9] to 88%[10] and from 9%[11] to 64%[12] in patients with viral meningitis. These differences suggest that the criteria used to define SIADH are not uniformly applied.

After the clinical observation that SIADH "was suggested by laboratory data in 88% of the patients studied,"[10] Kaplan and Feigin[3] went on to measure plasma AVP concentrations in 13 normal children, 21 patients with febrile illness (not meningitis), and 17 patients with bacterial meningitis. This study demonstrated that plasma AVP concentrations obtained within the first 48 hours of hospitalization for bacterial meningitis were significantly higher than those in either control group.[3] Kaplan and Feigin stated that none of the patients was dehydrated and that serum sodium and BUN concentrations did not differ between either control group and the patients with meningitis.[3] They then evaluated the relationship between the plasma AVP and $Na^+$ concentrations by calculating an AVP/$Na^+$ ratio; the AVP/$Na^+$ ratio was significantly higher in patients with bacterial meningitis than in control subjects, suggesting that the plasma AVP concentration was "inappropriately" elevated.[3] In our study, plasma AVP concentrations at the time of hospitalization were also elevated in most of the patients with either bacterial or aseptic meningitis. Furthermore, expressed as a function of serum osmolality, plasma AVP concentrations were "inappropri-

ately" elevated (Fig. 1). Although these data corroborate the findings of Kaplan and Feigin,[3] it should be emphasized than an abnormal AVP/$Na^+$ ratio does not constitute SIADH.

In our study, as well as Kaplan and Feigin's study,[3] at the time of admission the plasma AVP concentration was high relative to the concurrent serum osmolality or serum $Na^+$ concentration. However, in our study the plasma AVP concentration became normal in the fluid-replacement group without any significant change in serum sodium or osmolality. This finding supports the hypothesis that AVP release is being stimulated by nonosmotic factors.[13] Recognized, potent stimuli for AVP secretion include hypovolemia, hypotension, and nausea and vomiting.[13] Patients with meningitis have increased fluid losses from fever and vomiting and decreased fluid intake because of anorexia, so we hypothesized that AVP elevation might be secondary to hypovolemia.

In a previous study, history and physical examination were found to be no better than chance in detecting volume depletion in patients in whom measurement of the plasma renin and norepinephrine responses to administration of saline solution supported the presence of hypovolemia.[14] In our study, we attempted to obtain a better estimate of extracellular fluid volume by measuring the bromide space. Obtaining repeated weights on the same scale in acutely ill children was not achieved with consistency, and the accuracy of the calculated extracellular fluid volume was thought to be inaccurate and was therefore omitted.

Nevertheless, support for the hypothesis that hypovolemia is an important mechanism regulating the plasma AVP concentration in meningitis can be drawn from the finding that the change in the plasma AVP concentration during the first 24 hours was significantly correlated with the amount of sodium administered during that period, but not with the volume of fluid given. Sodium administration is an effective means of inducing fluid retention, and we suggest that the reduction in plasma AVP concentration reflected the degree of correction of the hypovolemia induced by the administered sodium. The hypothesis that the administered sodium was inducing fluid retention and thereby correcting the hypovolemia is supported by the observation that serum $Na^+$ concentration did not change in spite of the administration of 6.3 ± 1 mEq/kg of sodium in the maintenance-plus-replacement group.

Hypovolemia in meningitis may result from the associated vomiting and fever or from an increase in $Na^+$ excretion during the early stages of the disease.[15] Thus the hyponatremia observed in meningitis may reflect a negative sodium balance rather than dilutional hyponatremia secondary to water retention, as would occur with SIADH. The renal dysfunction responsible for the increased $Na^+$ excretion may be corrected by treating the infection; the administered sodium is then able to be effective in correcting the hypovolemia.

Another possible stimulus for increased AVP secretion in meningitis is vomiting. Although a history regarding vomiting was obtained for all patients, the degree of vomiting and the relationship between the most recent episode of vomiting and the time of measurement of the initial plasma AVP concentration were not documented. All patients who were vomiting received nothing by mouth during the first 24 hours of hospitalization, and only patients who received maintenance plus replacement fluid therapy had normalization of plasma AVP concentrations, so it is more likely that AVP elevations are secondary to hypovolemia.[13]

In an attempt to confirm the relationship between $Na^+$ administration and change in AVP concentration, the fluid balance, $Na^+$ retention, and urinary $Na^+$ excretion were calculated. None of the values obtained correlated with the measured changes in plasma AVP concentration. This finding probably reflects the inadequacies of performing balance studies in an open ward setting. Urinary catheters were not placed, so urine output was determined by weighing diapers, which often contained fecal material. Urine collection bags that were placed to obtain specimens for the measurement of urine osmolality frequently leaked, and urine specific gravity was measured on specimens squeezed out of diapers. Although orders were written to weigh infants daily on the same scale, this did not always occur, and it was not clear whether weights included arm boards or diapers. Thus, although routine procedures are usually satisfactory for managing ill children, they are inadequate to determine fluid and electrolyte balance accurately. Fortunately, fluid administration is carefully recorded and measurements of AVP and electrolyte levels are accurate, so the relationship between the amount of $Na^+$ given and the change in plasma AVP concentration can be considered reliable.

The data from our study therefore suggest that hypovolemia is responsible for the elevated plasma AVP concentration in patients with meningitis. Furthermore, the results of this study suggest that the administration of $Na^+$ in replacement fluids results in a more rapid normalization of the plasma AVP concentration than does the restriction of fluid and, thereby, of $Na^+$.

Clinical estimates of dehydration are grossly inaccurate. Replacement fluids should be estimated conservatively and should contain 0.9% saline solution. Maintenance fluids should be hypotonic. Although this study demonstrates that an elevated AVP concentration in the patient with meningitis does not mean that the patient has SIADH, the syndrome can occur in patients with meningitis. Thus, although it is appropriate to give maintenance plus replacement fluids

to patients with meningitis, it is essential to monitor the serum sodium concentration and urine specific gravity so that if there is evidence of SIADH, it can be treated appropriately by restricting fluids.

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REVIEW

# Renal salt-wasting syndrome in children with intracranial disorders

**Alberto Bettinelli · Laura Longoni · Fabiana Tammaro · Pietro B. Faré · Luca Garzoni · Mario G. Bianchetti**

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**Abstract** Hypotonic hyponatremia, a serious and recognized complication of any intracranial disorder, results from extra-cellular fluid volume depletion, inappropriate anti-diuresis or renal salt-wasting. The putative mechanisms by which intracranial disorders might lead to renal salt-wasting are either a disrupted neural input to the kidney or the elaboration of a circulating natriuretic factor. The key to diagnosis of renal salt-wasting lies in the assessment of extra-cellular volume status: the central venous pressure is currently considered the yardstick for measuring fluid volume status in subjects with intracranial disorders and hyponatremia. Approximately 110 cases have been reported so far in subjects ≤18 years of age (male: 63%; female: 37%): intracranial surgery, meningo-encephalitis (most frequently tuberculous) or head injury were the most common underlying disorders. Volume and sodium repletion are the goals of treatment, and this can be performed using some combination of isotonic saline, hypertonic saline, and mineralocorticoids (fludrocortisone). It is worthy of a mention, however, that some authorities contend that cerebral salt wasting syndrome does not exist, since this diagnosis requires evidence of a reduced arterial blood volume, a concept but not a measurable variable.

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**Keywords** Cerebral salt-wasting syndrome · Hyponatremia · Renal salt-wasting syndrome · Syndrome of inappropriate anti-diuresis

## Introduction

Hypotonic hyponatremia, subsequently referred to as hyponatremia, results either from a negative balance for sodium (= depletional hyponatremia) or from a positive balance for water (= dilutional hyponatremia) [1–3]. Vasopressin, the anti-diuretic hormone, plays a crucial role in this dyselectrolytemia. This hormone is present and active both in depletional as well as in dilutional hyponatremia, since it is secreted not only with circulating levels of sodium in excess, but also with extra-cellular fluid volume in deficit [1, 2]. Since hyponatremia implies expansion of the intracellular fluid, the danger is the swelling of brain cells [1–3].

Hyponatremia, along with elevated vasopressin levels, is a serious complication of any intracranial disorder, including infection, trauma, surgery, hemorrhage, and stroke [4–9]. The purpose of the present report is to discuss the underlying causes, focusing on renal salt-wasting syndrome, and to rapidly review the corresponding pediatric literature.

## Mechanisms underlying hyponatremia

In intracranial disorders, hyponatremia results from extracellular fluid volume depletion (= appropriate anti-diuresis), from inappropriate anti-diuresis, or from renal salt-wasting (Fig. 1; Table 1).

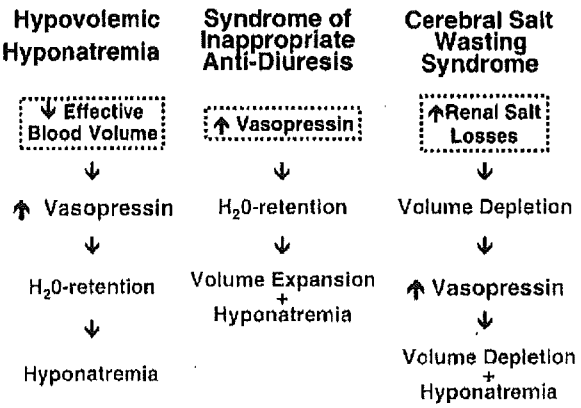


**Fig. 1** Mechanisms underlying the tendency toward hypotonic hyponatremia in intracranial disorders. In most cases (*left panel*) hyponatremia results from a low effective arterial blood volume and is termed hypovolemic hyponatremia. The term appropriate anti-diuresis has also been used to denote this condition. In patients with hypovolemic hyponatremia release of vasopressin is due to extra-cellular fluid volume depletion. The syndrome of inappropriate anti-diuresis results from persistently high levels of vasopressin or, more rarely, up-regulation of its renal receptor (*middle panel*). Cerebral salt-wasting syndrome is a further form of hyponatremia that sometimes develops in patients with intracranial disorders (*right panel*). In this condition renal salt-wasting is the primary defect, which is followed by volume depletion leading to a secondary rise in vasopressin

## Extra-cellular fluid volume and blood volume depletion (= appropriate anti-diuresis)

Release of vasopressin secondary to a decrease in extra-cellular fluid volume and effective arterial blood volume is an important cause of hyponatremia in acute intracranial conditions [1, 2, 8].

**Table 1** Clinical and laboratory characteristics of extra-cellular fluid volume depletion, inappropriate anti-diuresis, and renal salt wasting in patients with intracranial disorders complicated by hyponatremia. The central venous pressure is currently considered the yardstick for measuring fluid volume status in patients with intracranial disease and hyponatremia

| | Extra-cellular fluid volume depletion | Syndrome of inappropriate anti-diuresis | Renal salt wasting |
|---|---|---|---|
| Body fluid status | ⇓ | ⇑ | ⇓ |
| Central venous pressure | ⇓ | ⇔ ⇑ | ⇓ |
| Circulating potassium | ⇔ ⇓ | ⇔ | ⇔ |
| Acid-base balance | ⇔ ⇓ ⇑ | ⇔ | ⇔ |
| Circulating uric acid | ⇑ | ⇓ | ⇓ |
| Circulating urea/creatine ratio | ⇑ | ⇔ ⇓ | ⇔ ⇓ |
| Circulating aldosterone | ⇑ | ⇓ | ⇔ ⇓ |
| Circulating renin level | ⇑ | ⇓ | ⇔ ⇓ |
| Natriuretic peptides[a] | ⇓ | ⇑ | ⇑ |

[a] B-type natriuretic peptide

⇓ reduced, ⇑ increased, ⇔ unmodified

## Syndrome of inappropriate anti-diuresis

In 1957, Schwartz et al. observed patients with chronic hyponatremia and urinary wasting of sodium and speculated that the cause was release of vasopressin in amounts inappropriate to the prevailing low circulating sodium level [10]. The primary pathophysiology underlying the syndrome of inappropriate anti-diuresis is persistently high levels of vasopressin or, more rarely, up-regulation of its renal receptor. Until recently, the original term of inappropriate release of vasopressin was used. Because not all patients with this form of hyponatremia have elevated circulating levels of vasopressin, the term inappropriate anti-diuresis was proposed as a more accurate description [4–9]. This is especially true for subjects affected by the nephrogenic syndrome of inappropriate anti-diuresis, a recently described genetic disorder characterized by a gain-of-function mutation in the renal vasopressin receptor type 2 [4–9].

The syndrome of inappropriate anti-diuresis has until recently been thought to be responsible for the majority of cases of hyponatremia developing during or after acute intracranial conditions. It has become evident, however, that inappropriate anti-diuresis is less common than assumed from previous studies [1, 2, 4–9]. Investigations performed >10 years ago indicate that in children with meningitis hyponatremia is often associated with extra-cellular fluid volume depletion [11–15].

Inappropriate anti-diuresis can be induced by administration of vasopressin and water, which leads to accumulation of solute-free water, which is distributed in intra- and extra-cellular fluid compartments, and thus to dilutional hyponatremia. When blood volume exceeds 5–10% of normal, natriuresis develops, which is explained by a reduction in proximal sodium reabsorption, by a decrease in aldosterone level and by an increase in natriuretic peptides [1, 2].

## Renal salt-wasting syndrome

Seven years before the identification of the syndrome of inappropriate anti-diuresis, Peters et al. coined the term cerebral salt-wasting to denote patients with intracranial disease, who develop extra-cellular fluid volume depletion due to a renal sodium transport abnormality [16].

Cerebral salt-wasting as a cause of hyponatremia was abandoned after 1957 in favor of the newly described syndrome of inappropriate anti-diuresis. Multiple reports published over the last 30 years prompted a reconsideration of renal salt-wasting syndrome as a distinct entity, in particular because excessive urine output (and natriuresis) and dehydration occur in some patients with intracranial disorders [4–9].

## Renal salt-wasting in intracranial disorders

The diagnosis of cerebral salt-wasting requires an intracranial disorder and renal salt-wasting. Regardless of the underlying mechanisms, the brain injury results in renal salt losses, polyuria, fluid volume contraction with secondary release of vasopressin, and a tendency toward hyponatremia [4–9].

## Renal function

With respect to its pathophysiology, three issues will be addressed in this section of the manuscript: the site of the defective sodium transport, the release of vasopressin (with the tendency toward hyponatremia), and the activity of the renin–angiotensin II–aldosterone system in cerebral salt-wasting.

### Defective sodium transport in the proximal tubule

In fluid volume depletion, urinary urate and urea excretion are blunted. Surprisingly, in renal salt-wasting syndrome, a peculiar form of extra-cellular fluid volume depletion, urinary urate and urea excretion are normal or high. Consequently, hypouricemia, hypouremia, and a normal or even low urea-to-creatinine ratio in blood characteristically occur in renal salt-wasting [4–9, 17]. Taken together, these observations favor the proximal tubule as the major site of defective sodium transport in this condition (Fig. 2).

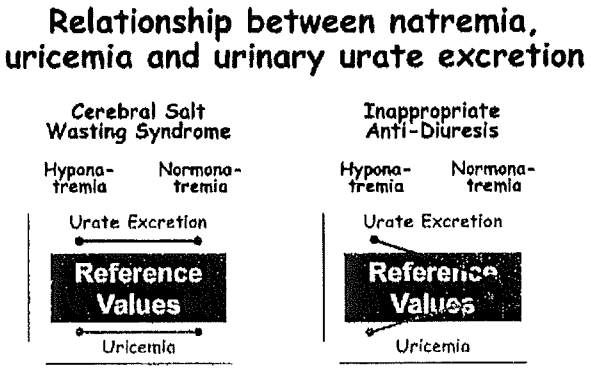


Fig. 2 Relationship among natremia, uricemia, and urinary urate excretion before (= hyponatremia) and after correction of hyponatremia (= normonatremia) in intracranial disorders associated with renal salt-wasting (*left panel*) or inappropriate anti-diuresis (*right panel*). Hypouricemia and increased urinary urate excretion coexist with hyponatremia in both cerebral salt-wasting and inappropriate anti-diuresis before correction of hyponatremia and persist after correction in cerebral salt-wasting syndrome. Hypouricemia and increased urinary urate excretion return to normal after correction of hyponatremia (= normonatremia) in the syndrome of inappropriate anti-diuresis

### Release of vasopressin (and hyponatremia)

The abnormalities in the proximal tubule result in excessive sodium losses, which lead to decreased effective circulating volume and activate the release of vasopressin (vasopressin levels have rarely been assessed in this setting.) This results in some water conservation.

Almost every patient with renal salt-wasting syndrome has hyponatremia. Nonetheless, it has been suggested that development of hyponatremia may be prevented if a parenteral solution containing the same amount of sodium as in the urine and a volume equal to the urine output are infused [4–9].

### Renin–angiotensin II–aldosterone system

Some reports demonstrate suppressed renin and aldosterone levels in spite of volume contraction in subjects affected with cerebral salt-wasting.

## Mechanisms causing salt-wasting

The mechanisms by which intracranial disorders lead to renal salt-wasting are poorly understood. Two putative mechanisms will be discussed: disruption of neural input to the kidney and elaboration of a circulating natriuretic factor [4–9]. First, the sympathetic nervous system promotes sodium, uric acid, and water reabsorption in the proximal tubule, as well as renin release. Thus, impaired sympathetic neural input could explain the reduction in proximal sodium and urate reabsorption and the impaired release of renin and aldosterone. The second theory is the release of a circulating factor that impairs renal tubular sodium re-absorption in patients with brain injury. The primary candidate is B-type natriuretic peptide, once known as "brain natriuretic peptide", which decreases sodium reabsorption, inhibits renin release and also decreases autonomic outflow at the level of the brainstem. More recent observations suggest that adrenomedullin, a further natriuretic factor, might mediate renal salt wasting [6].

## Diagnosis

### Distinguishing renal salt-wasting from inappropriate and appropriate anti-diuresis

In patients with intracranial disorders and hyponatremia, the distinction between on the one side inappropriate anti-diuresis, and on the other side the two forms of depletional hyponatremia, i.e., appropriate anti-diuresis and renal salt-wasting, is critically important. In fact, the three conditions are managed differently, with possible adverse consequences if the incorrect therapeutic strategy is administered.

Renal salt-wasting is suspected in patients with the following characteristics: hyponatremia, salt-wasting, polyuria, and hypouricemia due to urinary urate wasting. However, evidence of fluid volume depletion is crucial, since all of these laboratory findings are also seen in inappropriate anti-diuresis. In children with renal salt-wasting (and appropriate anti-diuresis), the pulse rate is expected to be increased, the blood pressure low (in children with minimal to mild (or even moderate) fluid volume depletion blood pressure is normal or sometimes slightly increased), the capillary refill time prolonged, the mucous membranes dry, the eyeballs receded, the skin elasticity decreased, the neck veins not distended and, in infants, the fontanel sunken. On the contrary, the findings mentioned are expected to be absent in the context of inappropriate anti-diuresis. Unfortunately, the assessment of the fluid volume status by history and physical examination in hyponatremia is quite inaccurate. Hence, the central venous pressure is currently considered the yardstick for measuring fluid volume status in patients with intracranial disease and hyponatremia [4–9, 18]. In renal salt-wasting, fluid volume depletion leads to a decrease in central venous pressure. This parameter is essentially available non-invasively in every patient through physical examination of the external jugular veins. The invasive determination of central venous pressure by a central venous catheter in the intensive care unit setting is obviously the established standard.

## Further differential diagnosis

In intracranial disorders the diagnosis of renal salt-wasting cannot be established with complete confidence from examination or testing. This diagnosis is therefore made by elimination of other reasonable causes [4–9, 18, 19]. Hence, before making the diagnosis, some further causes of excessive urinary sodium excretion should be ruled out (Table 2), including the development of a salt-wasting state by prior expansion of the fluid volume state. This unusual condition develops in a patient hydrated over a period of many days with a large parenteral volume of normal saline and therefore develops a sustained stimulus to excrete sodium. In this setting an abrupt decrease in the rate of hydration is followed by a persistent excessive sodium excretion and one should not make a diagnosis of cerebral salt-wasting [20]. It has been suggested [20] that a prolonged period of expanded fluid volume state causes transporters of sodium to be removed from the membranes of individual proximal tubular cells and therefore they become less able to reabsorb sodium (Fig. 3).

Finally, a combination of both central diabetes insipidus and renal salt-wasting syndrome can occur simultaneously in the same child. Concurrent occurrence of the two diseases has been reported subsequent to neurosurgery, with brain tumors, with severe infection of the central nervous system, and with hypoxic ischemic events [4].

**Table 2** Conditions that may mimic renal salt-wasting in intracranial disorders [4–9, 20]

| |
|---|
| Development of salt-wasting state following prior chronic expansion of the fluid volume |
| Use of diuretics |
| Hypercalcemia |
| Tubular damage (interstitial nephritis, acute tubular necrosis, obstructive uropathy) |
| Congenital salt-losing renal tubular disorders (Gitelman or Bartter syndrome) |
| Adrenocortical insufficiency |
| High effective arterial blood volume despite a contracted fluid volume status (high adrenergic tone that constricts venous capacitance vessels or increases myocardial contractility) |

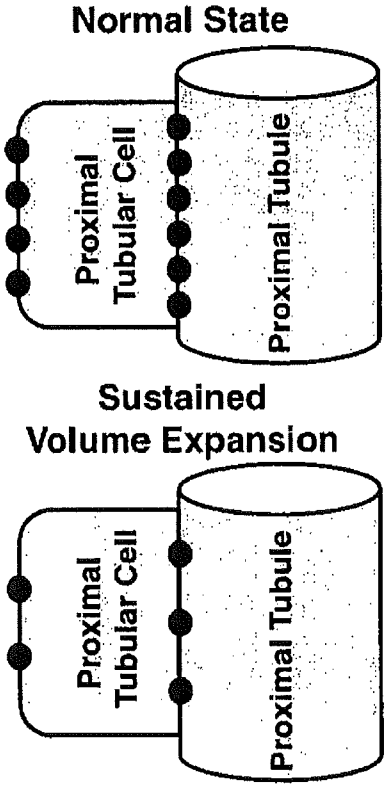


Fig. 3 Salt-wasting state following prior expansion of the fluid volume state. The *upper panel* depicts the normal state with a luminal sodium transport system and basolateral sodium pump that constitute the process by which filtered sodium is reabsorbed in the proximal tubule. The *lower panel* depicts the suggested response to a prolonged period of expanded fluid volume state: the luminal sodium transport system and the basolateral sodium pump are removed from the membranes of individual proximal tubular cells, which become less able to reabsorb filtered sodium. The *red circles* denote the luminal sodium transport systems and the *blue circles* the baso-lateral sodium pump

### Causes of renal salt-wasting syndrome associated with intracranial disorders in childhood

Among adult patients with intracranial disorders, renal salt-wasting has been most often described (60–70% of the cases) in patients with subarachnoid hemorrhage. Renal salt-wasting has also been reported in patients with carcinomatous or infectious meningitis or encephalitis, and following surgery [5–9].

The presumed diagnosis of renal salt-wasting associated with intracranial disorders has been so far made (Fig. 4) in approximately 110 subjects (male: 63%; female: 37%) ≤18 years of age reported in the literature [21–62]. Not surprisingly, no clear-cut diagnostic criteria were used for most cases. Intracranial surgery, meningo-encephalitis (most frequently tuberculous) or head injury were the most common underlying intracranial disorders (Table 3). Like in adults [5–9], the typical onset was within the first 8 days (82% of the cases) following the intracranial event irrespective of the neurosurgical procedure (Fig. 4).

### Management

Replacement of the sodium and water that is lost as a result of pathological natriuresis and diuresis is the mainstay of therapy for renal salt-wasting in intracranial disorders. This

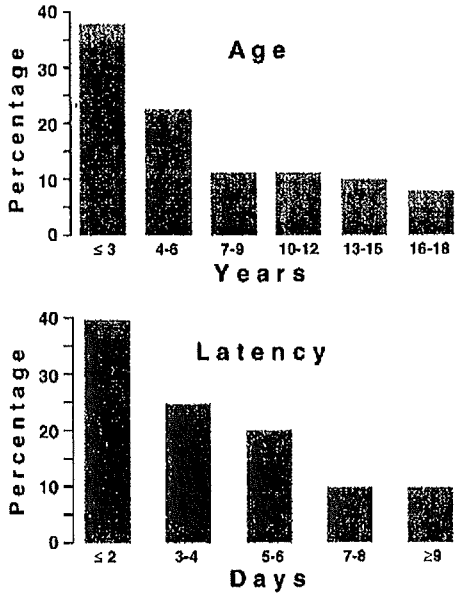


Fig. 4 The *upper panel* depicts the age distribution in patients ≤18 years of age with the presumed diagnosis of renal salt-wasting syndrome in the context of intracranial disorders. The *lower panel* depicts the time elapsed between onset of renal salt-wasting syndrome and the intracranial event, irrespective of the neurosurgical procedure

Table 3 Causes of cerebral salt-wasting in subjects ≤18 years of age

| Intracranial disorder | Frequency (percentage) |
|---|---|
| Intracranial surgery | 42 |
| Meningo-encephalitis | 23[a] |
| Head injury | 15 |
| Intracranial bleeding | 5 |
| Hydrocephalus | 4 |
| Other causes | 11 |

[a] Meningoencephalitis was tubercolous in 69% of the cases

is in direct contrast to the treatment of inappropriate antidiuresis, the crux of which is free water restriction [4–9, 19].

A practical initial management approach is administration of normal saline with the intent of restoring fluid volume status. Most authors currently recommend that fluid and salt replacement is guided, at least in severe cases, by the patients' fluid volume status as determined by the central venous pressure. Once normal fluid volume status is achieved, attention should be directed to the correction of hyponatremia. In patients with sodium levels approaching dangerously low levels of ≤125 mmol/L or when large volumes of intravenous fluid are required to maintain normal fluid volume status, intravenous hypertonic saline is a useful adjunctive therapy. A dose of 1.5% ($Na^+$ 258 mmol/L) sodium chloride can be administered through peripheral veins, and can safely and effectively restore and maintain intravascular volume and sodium concentration when administered at rates that are titrated to achieve a normal to slightly positive fluid balance. Some authors routinely use 1.5% sodium chloride in adult patients at rates between 50 and 150 mL per hour. The use of 3.0% ($Na^+$ 517 mmol/L) sodium chloride (often through a central vein) should be reserved for severe hyponatremia (≤120 mmol/L) [6].

Another approach is the prescription of the mineralocorticoid fludrocortisone: most authors typically prescribe 0.1 to 0.2 mg orally twice a day, starting once the diagnosis of renal salt-wasting is made and continuing until sodium concentrations and fluid volume remain stably normal, typically 3 to 5 days later.

Since in renal salt-wasting the renal concentrating ability is preserved and the vasopressin level high, the concentration of sodium in the urine may rise to close to 300 mmol/L; hence, a patient given a large amount of normal saline ($Na^+$ 155 mmol/L) may sometimes further decrease the blood level of sodium [4–9, 19].

### Criticism

Some authorities contend that the condition cerebral salt-wasting syndrome does not exist, since a convincing diagnosis requires evidence of a reduced effective arterial blood

volume, a concept but not a measurable variable [4–9]. As a consequence, the literature regarding renal salt-wasting in intracranial disorders relies on clinical impressions, direct determinations of plasma volume, negative sodium balance, levels of vasopressin and natriuretic peptides, and responses to therapy. However, the aforementioned authorities believe that none of these measures is up to the task. Furthermore, the central venous pressure, which is currently considered the yardstick for measuring fluid volume status in patients with intracranial disease and hyponatremia, might be a poor marker of cardiac filling pressure.

## Conclusion

Extra-cellular fluid volume depletion due to inappropriate urinary sodium-wasting sometimes occurs in the setting of central nervous system disorders. The pathophysiology is related to impaired sodium reabsorption, possibly because of either altered sympathetic activity or the release of B-type natriuretic peptide. Regardless of the mechanism, sodium-wasting can lead sequentially to volume depletion, increased vasopressin release, hyponatremia due to the associated water retention, and possibly increased neurological injury. Although some authorities contend that the condition does not exist, most authorities feel that the condition is a distinct entity. Specific findings include polyuria, hypotonic hyponatremia, an inappropriately elevated urine osmolality, a rather high urine sodium concentration, a low uric acid concentration due to urate-wasting in the urine and, in particular, reduced central venous pressure.

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# Harmonisation of Reference Intervals

In recent times it has become clear to the users and commissioners of hospital diagnostic services that there are differences in reference intervals and units of measurement between laboratories. We, in the profession, recognise that there are sometimes genuine scientific reasons for these differences, for example differences in local populations or analytical methodology. However, it is important to differentiate those analytes for which there is no clearly identifiable reason for a difference. It is these analytes that have been considered by the Pathology Harmony group. This is a professionally led group supported by a grant from the Department of Health.

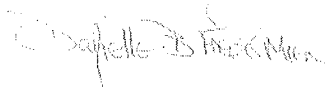
The identification of harmonisable analytes has been achieved through a process of consensus involving a large number of laboratory scientists supported by professional bodies. Clearly many analytes, particularly those measured by immunoassay, cannot be easily harmonised. This has been recognised by Pathology Harmony and further work will be necessary. In addition, this group has made recommendations on units of measurement that should be used to minimise possibility of confusion.

The Association for Clinical Biochemistry, the Institute of Biomedical Science and Royal College of Pathologists support this process and believe that the introduction of common reference ranges and units of measurement will improve patient safety.

We recommend that our members should introduce these changes and would hope that this can be achieved by April 2011.

**Julian Barth**
**President, Association for Clinical Biochemistry**

**James Kenneth Rae**
**President, Institute of Biomedical Science**



**Danielle Freedman**
**Chair, SAC Clinical Biochemistry and Vice-President, Royal College of Pathologists**

The Association for Clinical Biochemistry

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# Agreed Adult Clinical Biochemistry Reference Intervals

| Test Name | Units | Range low | Range high | Comments |
|---|---|---|---|---|
| Sodium | mmol/L | 133 | 146 | |
| Potassium | mmol/L | 3.5 | 5.3 | |
| Urea | mmol/L | 2.5 | 7.8 | |
| Chloride | mmol/L | 95 | 108 | |
| Bicarbonate | mmol/L | 22 | 29 | |
| Phosphate | mmol/L | 0.8 | 1.5 | |
| Magnesium | mmol/L | 0.7 | 1.0 | |
| Albumin | g/L | 35 | 50 | |
| Total Protein | g/L | 60 | 80 | |
| Osmolality | mmol/kg | 275 | 295 | |
| Alkaline Phosphatase (ALP) | U/L | 30 | 130 | IFCC candidate method p-NPP using AMP buffer |
| Creatine Kinase (CK) | U/L | 40 | 320 (M) | Ranges are for white Caucasian only; |
| | | 25 | 200 (F) | other ethnic groups may have higher values |
| Bilirubin (total) | µmol/L | | <21 | |
| Adjusted Calcium | mmol/L | 2.2 | 2.6 | Use adjustment equations normalised to mean calcium of 2.4 mmol/L |
| Urate | µmol/L | 200 | 430(M) | |
| | | 140 | 360(F) | |
| Carbamazepine | mg/L | 4 | 12 | |
| Phenobarbitone | mg/L | 10 | 40 | |
| Phenytoin | mg/L | 5 | 20 | |
| Theophylline | mg/L | 10 | 20 | |
| Valproate | mg/L | | | No range should be quoted |
| Paracetamol | mg/L | | | |
| Salicylate | mg/L | | | |
| Methotrexate | µmol/L | | | |
| Lithium | mmol/L | 0.4 | 1.0 | Complies with NPSA guidance |
| Digoxin | µg/L | 0.5 | 1.0 | |
| Tacrolimus | µg/L | | | |
| 25OH Vitamin D (including separately measured D2 & D3) | nmol/L | | | No ranges recommended |
| PTH | pmol/L | | | Method dependent |
| BNP/NTproBNP | ng/L | | | |
| Troponin I | ng/L | | | Method dependent |
| Troponin T | ng/L | | | |
| 24 h Urine Calcium | mmol/24h | 2.5 | 7.5 | |
| 24 h Urine Urate | mmol/24h | 1.5 | 4.5 | |
| 24 h Urine Phosphate | mmol/24h | 15 | 50 | |
| 24 h Urine Magnesium | mmol/24h | 2.4 | 6.5 | |

## Agreed Paediatric Clinical Biochemistry Reference Intervals

| Test Name | Age | Units | Range low | Range high | Comments |
|---|---|---|---|---|---|
| Sodium | No age-related differences | mmol/L | 133 | 146 | |
| Plasma Potassium | Neonate | mmol/L | 3.4 | 6.0 | |
| | Infant | mmol/L | 3.5 | 5.7 | |
| | 1-16 yrs | mmol/L | 3.5 | 5.0 | |
| Urea | Neonate | mmol/L | 0.8 | 5.5 | |
| | Infant | mmol/L | 1.0 | 5.5 | |
| | 1-16 yrs | mmol/L | 2.5 | 6.5 | |
| Magnesium | Neonate | mmol/L | 0.6 | 1.0 | |
| | Infant - 16 yrs | mmol/L | 0.7 | 1.0 | |
| Plasma lactate | No age-related differences | mmol/L | 0.6 | 2.5 | Enzymatic method only |
| Bilirubin (total) | 14 days - 16 yrs | µmol/L | | <21 | |
| Albumin | Neonate | g/L | 30 | 45 | |
| | Infant | g/L | 30 | 45 | |
| | 1-16 yrs | g/L | 30 | 50 | |
| Calcium | Neonate | mmol/L | 2.0 | 2.7 | Actual not adjusted |
| | Infant - 16 yrs | mmol/L | 2.2 | 2.7 | |
| Phosphate | Neonate | mmol/L | 1.3 | 2.6 | |
| | Infant | mmol/L | 1.3 | 2.4 | |
| | 1-16 yrs | mmol/L | 0.9 | 1.8 | |
| Alkaline Phosphatase (ALP) | Neonate | U/L | 70 | 380 | p-NPP using AMP buffer |
| | Infant - 16 yrs | U/L | 60 | 425 | |
| Ammonia | Sick or premature | µmol/L | | <150 | Follow metbio.net guidance |
| | Neonate | µmol/L | | <100 | |
| | Infant - 16 yrs | µmol/L | | <50 | |
| Plasma Bicarbonate | No age-related differences | mmol/L | 19 | 28 | |

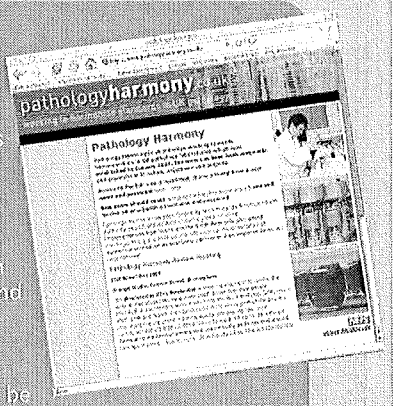
Definitions Neonate 0 weeks - 1 month

# What Happens Next . . .

The Pathology Harmony project was conceived as an action learning set in the West Midlands SHA and more recently has received support from Dr Ian Barnes and the Department of Health. In Phase II of the project laboratory staff were joined by representatives from the Royal College of Pathologists, Association for Clinical Biochemistry and Institute of Biomedical Science.

The results of Phase I and II of the project have culminated in recommendations that have been widely consulted on, including consideration by professional groups. Phase II of this work included studies in Immunology and Haematology but here we present just the harmonised reference intervals and units in Clinical Biochemistry.

Details of the members of Pathology Harmony group and approaches taken and background information behind the decisions that are presented here can be found on the Pathology Harmony website.




## What Next?

Early in 2011 the Pathology Harmony group will be meeting to consider how to take forward new areas of activity. If you have comments or suggestions then you can contact Pathology Harmony by emailing secretary@pathologyharmony.co.uk

Pathology Harmony Group, Clinical Biochemistry Outcomes, January 2011