RESPONSE BY DR R MACFAUL TO COMMENTS RECEIVED ON MY REPORT BY PROF I YOUNG OCTOBER 2012

1) I accept Prof Young's criticism regarding undue reference I gave to the 3rd edition of Forfar and Arneil (1984) and concede that it would have been better to have included greater reference in my main report to the 4th edition Forfar Arneil (1992) which was current in 1996.

Action proposed

2) I suggest withdrawing the statement I made in various portions of the report from

> *" the textbook recommendation is to not to use 0.18 % saline "*

3) To another text:

> *"that continued use of IV fluids at normal rate was not in keeping with current guidance in acute encephalopathy with identified low blood sodium levels and that fluid restriction should have been used and also consideration given to change to a fluid with a higher sodium level than 0.18% saline e.g. at least 0.45% saline – in keeping with the principles set out in the textbook guidance in 1996 for management of hyponatraemia by fluid restriction and maintenance of homeostasis in acute encephalopathy with risk of cerebral oedema. "*

Reasoning

4) I acknowledge that the wording in respect of fluid management and acute encephalopathy in the 4th edition differs from the 3rd edition in no longer precisely and explicitly warning against the use of 0.18% saline. Instead wording is changed on intravenous fluid therapy which is implicit rather than explicit. Both editions include information about the risk of hyponatraemia in this condition and its potential contribution to or cause of cerebral oedema. The later edition confines its advice in the section on acute encephalopathy on fluid management to the maintenance of "homoeostasis" and to the use of fluid restriction in hyponatraemia. Maintenance of homoeostasis implies detection and management of hyponatraemia associated with water overload and/or SIADH by adjustment of the intravenous fluid regime and the guidance implicates inappropriate intravenous fluid management in the production of hyponatraemia by which is implied (but not stated in the later edition) change from the use of otherwise standard volumes of low solute/sodium intravenous fluid.

5) The guidance provided in both editions in respect of investigation, fluid management and other aspects is otherwise essentially the same. The later edition however requires the user to refer to separate Chapters (a) on fluid, electrolyte and acid-base disturbance – section on low sodium and water intoxication and SIADH (b) on endocrine disorders : syndrome of inappropriate secretion of antidiuretic hormone (c) on disorders of the central nervous system in the section dealing with raised intracranial pressure in focal

ischaemic brain insult and (d) on infections in the section advising on bacterial meningitis. The later edition expands the neurology section on management of raised intracranial pressure by pressure monitoring but removes the specific warning on usage of 0.18% saline.

6) In commenting on the care provided by the paediatric neurologist and the awareness by Dr Steen and Dr Webb of the potential role that hyponatraemia had in contributing to the cerebral oedema in Claire I highlighted the 1994 text because the caution about use of hypotonic solutions in encephalopathy is so clearly set out (and these cautions were still relevant in 1996). The 3rd Edition would thus have provided a source available to both clinicians and led to awareness of the risks of number 18 solution in acute encephalopathy. This text book, though 12 years, was in use until as late as and possibly beyond 1992 and thus was available over the period in which Drs Webb and Steen were in training. The wording in the later edition provides less directive guidance although in essence remains the same but has the disadvantage that it requires interpretation-a limitation for guidance used at the point of care. I provided the guidance from my own unit in Pinderfields Hospital which represented our practice at the time as an illustration of how the wording in a text book can be interpreted for use at the point of care. This guidance was based in part on the content of the 1984 text book as Prof Young suggests but to a greater extent on our own experience in the management of acute encephalopathy and there was no need to change this in the light of the content in the later editions.

7) By the guidance available in 1996 awareness of the risk of hyponatraemia in encephalopathy was such when detected, low solute fluid arguably should not have been continued in this condition. Many clinicians at the time would have anticipated the potential for this complication and advised intravenous fluid with higher sodium content than number 18 solution while awaiting results of the blood sodium. I am critical of the management by Dr Webb because when he saw Claire at 2 PM on 22 October a slight reduction in blood sodium had already been identified (although from the night before). In most general paediatric conditions such a degree of derangement is of little clinical significance but this is not the case in acute encephalopathy because it is a warning that the common and serious complication of hyponatraemia is emerging with its contribution to severity of cerebral oedema. Consequently I considered that Dr Webb at this consultation should have adjusted the intravenous fluid by reducing the volume (to treat possible SIADH) and increasing the sodium content (to maintain homoeostasis and avoid water overload) in keeping with current guidance in both these widely available texts (and others) and, to have ordered further blood investigation which would on balance of probability have identified a further derangement of blood sodium. It is the case that greater emphasis is given in publications around 1996 to use of fluid restriction in treating identified hyponatraemia rather than avoidance of 0.18% saline although in practice many clinicians would change to a fluid with a higher sodium content such as 0.45% or normal saline as means of preventing further water overload.

8) This approach was suggested in the following publications in use in UK paediatric practice at the time:

9) <u>FROM THE 1990 VADE-MECUM Insley et al (Birmingham Childrens' Hospital)</u>

a. Hyponatraemia is usually due to haemodilution because of water retention (inappropriate ADH secretion) or inappropriate use of IV fluids (mentions cerebral oedema as a cause in an older child). If not dehydrated and is asymptomatic use 0 .9% saline. If symptomatic and sodium is less than 120 advises use of 30% saline.

> Note : The updated later edition of this guide edited by Barratt et al 2003 lists as a cause of hyponatraemia "water retention (iatrogenic due to excess IV fluid), inappropriate antidiuretic hormone pulmonary disease ,cerebral oedema.
>
> "In an acutely ill child with plasma sodium levels of < 125 mmol per litre and inappropriate antidiuretic hormone secretion restrict fluids. "
>
> ....."Hypertonic saline is only used in exceptional circumstances. "
>
> Comment: Does not specifically mention management in acute encephalopathy/cerebral oedema.
>
> "If the child is dehydrated 0.9% saline is usually appropriate. Infuse saline to correct dehydration plus the amount needed for continuing needs and losses."
>
> "The following formula gives an approximation of the amount required to correct deficit repletion. The amount is replaced over a period of 24-48 hours.
>
> Mmol /l Na required = 0.6x (target sodium level -presenting serum sodium level) x weight in kg "

10) <u>FROM HOSPITAL PAEDIATRICS Milner & Hull 2nd EDITION 1992</u>

In the section dealing with Stupor and Coma Page 347 et seq

a. " Most stuporose and comatose children require admission to the intensive care unit"

b. "… regular measurements of blood electrolytes and gases"

c. " Give intravenous dextrose-saline at maintenance requirement rate unless fluid and electrolyte derangements are to be corrected."

d. " deterioration in level of consciousness ….(+ other features listed)….. may all be signs of increasing intracranial pressure …….Where raised intracranial pressure is not due to a neurosurgically treatable disorder attempts should be made to reduce intracranial pressure by other means.The child should be nursed with the head elevated at 30 degrees. Serum osmolality should be kept at around 300 mOmol/l by moderate fluid restriction if necessary."

In the section dealing with hyponatraemia Page 211

e. "This is usually due to fluid overload. Central nervous system signs are not likely to be present unless the plasma sodium is less than 120 mm/l or the hyponatraemia develops in less than 24 hours"

f. "The problem can be generally managed by fluid restriction"

g. If the patient is symptomatic use 3 % sodium chloride (0.5mmol/ml) ….

MY COMMENTS ON PROFESSOR YOUNG'S ROLE:

11) I reported that the advice given to parents by Prof Young in 2004 was incorrect. It is noted that he stated that

    a. " *treatment today differs from that used 8 years ago.*"

12) I repeat my assertion here that guidance and practice in 2004 in acute encephalopathy management did not differ from that in 1996 save for advice on less stringent (or even no) fluid restriction in management of acute encephalopathy unless hyponatraemia was identified when restriction was used both in 1996 and 2004.

13) And that

    a. "*the doctor gave her standard fluid intravenously-which is the text book recommendation*."

14) Number 18 solution was the standard intravenous maintenance IV fluid used in children in 1996 in UK and in 2004 (save its withdrawl from 2002 in Northern Ireland and in some other hospitals in UK) until later in the 2000s. Thus I agree with this statement in respect of IV fluid maintenance in general management of paediatric conditions and considered that its use overnight on 21 October was not inappropriate. But textbook guidance offered for fluid management in acute encephalopathy required a change from standard management - especially when hyponatraemia has been identified with the need to maintain homeostasis and to avoid excessive water administration e.g. from IV fluids with low sodium content. Paediatric neurology texts address this issue also. The guidance was to restrict fluid and to give consideration to change to an IV fluid with higher sodium content although the latter point in 1996 is not well set out and not universally adopted in practice as there was and still is a range of views on this point..

15) Professor Young also refers to my comment on the advice incorporated in the medical reports provided for the coroner and that I considered that they did not properly address the specific fluid requirements in acute encephalopathy in which hyponatraemia had been identified and I made reference again to the stark warning about 0.18% saline in the 1984 edition which drew attention to the risks in the use of this and other low solute IV fluids in encephalopathy care.

16) There remains a range of opinion on this matter and I drew attention (as Prof Young notes) to the 2006 published guideline on management of reduced conscious level in children endorsed by the Royal College of Paediatrics which did not specifically advise low solute fluid in the initial management of acute encephalopathy but does advise avoidance of hypotonic fluid in the presence of symptoms or signs of raised intracranial pressure (present in Claire).

17) Thus I do not consider that there are major factual errors in my report and can justify the critical comments I made as set out in my report. I do however accept that the warnings and guidance about use of hypotonic IV fluid in acute encephalopathy are not clearly stated in the later text. Greater emphasis is given to fluid restriction in management in the later text and guidance on specific choice of fluid to be used is not set out after the 1984 3rd Edition. The wording in the later edition of the major text requires an individual clinician to make a judgment on how to " maintain homeostasis" and to correct and prevent electrolyte disturbance. But in 1996 , based on the guidance of the time arguably this should have led to a choice of at least 0.45% saline for Claire from at latest mid-afternoon 22 October together with fluid restriction.

18) Although I have proposed replacement of my reference to the 1984 guidance regarding 1996 current advice I consider in the context of the events related to Claire that attention should be drawn to the 3rd Edition 1984 warning on 0.18 % because it is relevant to the level of awareness in the consultants involved in her care of the potential contribution which the IV regime used may have made to her deterioration.

PROFESSOR YOUNG RESPONSE

19) I have not otherwise dealt with Prof Young's criticisms point by point but do challenge his assertion regarding use of fluid restriction in 1996. In his paper the following comments are made:

- *"It is therefore crucial that there is no suggestion from 1992 onwards that fluid should be restricted to 60% of daily requirements or that 0.18% saline in 5% dextrose in contraindicated in this setting. Sections of Dr MacFaul's report which state this and the criticisms which flow from his incorrect citation of an out of date textbook are simply wrong and should be corrected or withdrawn.*

- *"Dr MacFaul addresses his error in a very incomplete way in his supplementary report: "wording as specific and direct as in the 1984 textbook has not appeared in publications since then". However, this correction is totally inadequate. The truth is that words to this effect are completely absent from the 1996 contemporary edition of Forfar & Arneil. They have been removed and nothing comparable is included. "*
- *"In reality, in 1996 there simply was not any general or widespread understanding that there was a routine need to restrict fluid intake in encephalopathy and to use fluid with a higher sodium content than 0.18%."*
- *"I include as an attachment the relevant pages from the fourth edition of the textbook (1996 reprint) which was the current edition at the time of Claire's admission (page 771-778). These pages are completely different to the 1984 edition pages cited and used by Dr.MacFaul. The 1996 edition (valid since 1992) makes no reference to the need to restrict intravenous fluids in the management of encephalopathy or to the need to avoid 0.18% saline."*
- *"In addition I attach a key section from earlier in the textbook (479-480) dealing with the syndrome of low sodium and water intoxication, including the syndrome of inappropriate antidiuretic hormone secretion, which does not mention encephalopathy at all*."

20) My response is that fluid restriction was recommended management at the time for identified hyponatraemia in acute encephalopathy the latter is mentioned in other parts of the Textbook related to SIADH (P 1111-2) in terms of listing relevant brain illnesses– see Annex.

21) I agree to some extent on his comment on the relevance of the Arieff et al 1992 paper to Claire when Prof Young states

    a. They concluded that "*The hyponatraemia in these children seems to have been caused by extensive extrarenal loss of electrolyte containing fluids and intravenous replacement with hypotonic fluids in the presence of antidiuretic hormone activity*". This was undoubtedly a key observation, though not of direct relevance to the management of Claire Roberts, but a considerable period elapsed before this significantly influenced routine practice, as demonstrated below.

22) My comment: this paper mainly focused on causation of encephalopathy with IV fluid use rather than management of an existing encephalopathy but knowledge of its content should have influenced fluid choice had the clinicians been aware of it.

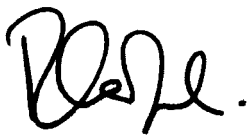
REFERENCE SOURCES FOR MY RESPONSE

23) In the next section I provide more detail in support of my response and

(a) attempt in the following Table to summarise the guidance and advice in the textbooks at the dates in question

and

(b) In the Annex to provide content from sources both in general paediatrics and paediatric neurology which highlight the contemporary awareness of the need to manage hyponatraemia in acute encephalopathy to reduce its contribution to the development of cerebral oedema.



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7 NOVEMBER 2012

	Forfar & Arneil 1984 3rd Edition	***Forfar & Arneil 1992 4rd Edition***	***Forfar & Arneil 2003 6th Edition***	***Kirkham 2001***
Twice daily electrolyte monitoring	Y	Y	"monitor"	6 hourly
Warning re cerebral oedema	Y	Y	Y (fluid restrict 75%)	Y
Text advising risk of and management of raised intracranial pressure	Y	Y	Y	Y
Warning re SIADH	Y	Y	Y	Y
Risk of hyponatraemia related to IV fluid therapy	Y	Y	Y	Y
Risk with use of hypoosmolar/hypotonic IV fluid	Y	not specifically mentioned	not specifically mentioned. "Maintain homeostasis"	Y
Fluid restriction for hyponatraemia from SIADH	Y	Y (60 % in bacterial meningitis & between 50-66% in SIADH p 1112) Note [2]	Y (70-50% of maintenance and replace Na). May be due to inappropriate IV fluid therapy P502	Y
Management of IV fluid	0.18% contraindicated	Maintain homeostasis and fluid restrict 0.18% not specifically mentioned Refers to IV fluid potentially causing hyponatraemia	"Maintain homeostasis"	"Essential that..large volumes of hypo-osmolar fluids are not given "see note [1]
Full range of investigation	Y	Y	Y	Y
ICP monitoring	Y	Y	Y	Y
Other treatments including :Mannitol frusemide elective ventilation	Y	Y	Y	Y

Note [1] *Kirkham FJ. Non-traumatic coma in children. Arch Dis Child 2001;85:303-312*

It was conventional in 1996 (and 2004) for fluid restriction to be used in the management of acute encephalopathy with hyponatraemia although there was increasing debate in regard to the severity of this restriction. An important study published in 2000 (Yu et al) which has been referred to by others including Dr Kirkham, advises the use of fluid restriction but limited to mild dehydration and cautions against excessive fluid restriction in which a higher mortality was found. Less stringent fluid restriction became part of practice in the early 2000s.

In regard to specific advice on the fluid to be used, the Yu study advocates a high sodium content although largely because the authors were addressing the need to correct acidosis with sodium bicarbonate.

In her review of management of non-traumatic coma in the Archives paper in 2001 Dr Kirkham cautions against the use of hypo-osmolar fluid mentioning 5% or 10% dextrose as follows

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

It is noteworthy that Dr Kirkham does not specifically mention avoidance of hypotonic intravenous fluid such as number 18 solution. But the advice given in the text is confusing because of the examples mentioned 5% dextrose is only slightly hypo-osmolar (with an osmolality of 277 – plasma is 290) and it is classified as iso-osmolar in the Table in the NPSA Alert); and, 10% dextrose is hyperosmolar. On the other hand both are hypotonic.

Note [2]

I have referred to meningitis here for two reasons:

(a) It is an inflammatory condition as is encephalitis (which was part of the diagnostic consideration in Claire) and similar mechanisms apply in cerebral oedema. Up to 1/3 of all cases of acute encephalopathy in paediatric practice are infective in origin.

(b) Management of bacterial meningitis forms part of general paediatric practice and thus specialists would be aware of the hyponatraemia complication (30% or more) and its management

ANNEX

GENERAL PAEDIATRIC GUIDANCE

FORFAR & ARNEIL TEXTBOOK OF PAEDIATRICS. FOURTH EDITION. 1992. (THE THIRD EDITION WAS 1984)

Relevant guidance appears in different chapters and sections of this edition of the textbook

In the sections on **low sodium and water intoxication and SIADH included in the chapter on fluid, electrolyte and acid-base disturbance.** Page 479/480 .Refers to water intoxication occurring in conditions associated with increased ADH secretion (only mentioning head injury and tumours) and "when parenteral hypotonic fluid is given in excess of requirements." It advises fluid restriction for treatment.

In the **chapter on endocrine disorders** page 1111-syndrome of inappropriate secretion of antidiuretic hormone. The causes of SIADH including CNS disease/disorder : meningitis/encephalitis etc.are listed **in table 18 .10** (see below) and mentions "excessive AVP secretion resulting in water retention, hypo osmolality and dilutional hyponatraemia."

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

Causes are listed in Table 18.10. Excessive AVP secretion results in water retention, hypo-osmolality and dilutional hyponatraemia. Inhibition of aldosterone with continuing AVP secretion leads to paradoxically high urinary sodium levels and concentrated urine. AVP levels may not be above the normal range but are inappropriately high for the expanded extracellular volume and hypo-osmolality.

Table 18.10 Causes of inappropriate ADH secretion

CNS disease/disorder
Meningitis/encephalitis
Trauma
Tumour
Haemorrhage
Hypoxia
Ischaemia
Malformation
Guillain–Barré syndrome
Obstructed ventriculoatrial shunt
Lung disease
Pneumonia
Tuberculosis
Pneumothorax*
Asthma*
Cystic fibrosis*
Ventilation
Postoperative (including mitral valvotomy*, ductus arteriosus ligation*)
Drugs (e.g. analgesics, sedatives, anaesthetics)
Malignancy
Trauma/burns
Endocrine/metabolic
Hypothyroidism
Adrenocortical failure
Hypoglycaemia
Idiopathic

*May be secondary to reduced left atrial filling.

And P 1112:

> "in paediatric practice SIADH is usually seen either in newborn infants in association with birth asphyxia and hyaline membrane disease or intraventricular haemorrhage or, in the older child in association with meningitis, encephalitis or CNS tumours…."
>
> "Diagnosis depends on a high clinical index of suspicion and the finding of the abnormalities in blood and urine described above. Treatment is by water restriction to

between 1/3 and one half maintenance and sodium replacement to compensate for the secondary sodium losses. Correction should be gradual (over several days)."

Refers the reader then to the chapter on salt and water metabolism.

In the chapter on diseases of the central nervous system on the management of acute encephalopathy page 771 "infection accounts for approximately one third of cases presenting with acute encephalopathy and coma."

On page 772 refers to cerebral oedema complicating status epilepticus.

On page 773 in the table numbered 14.18 lists endogenous causes of acute encephalopathy resulting from fluid balance including water intoxication and hyponatraemia.

Page 774 on management "the philosophy of management of treating the treatable which includes: Treatment of infection; control of seizures; detection and treatment of raised intracranial pressure (maintenance of cerebral metabolism and blood flow); maintenance of homoeostasis and removal of circulating toxins.

In the table on the same page the investigations are listed advising amongst others : osmolality 8 hourly, urea and electrolytes twice daily.

On page 776 reference is made to cerebral oedema as a common factor in children's encephalopathy

In the section on treatment of raised intracranial pressure on page 777 there is no reference to fluid management other than the use of mannitol.

On page 781 in **a section dealing with raised intracranial pressure in focal ischaemic brain insult** the following is stated

" The three common types of cerebral oedema,i.e vasogenic, toxic and osmotic, may all be present together in the same patient. The area infarcted from ischaemia is associated opening of tight endothelial junctions which allows fluid and protein into the intercellular space. "

"Steroids are now back in favour in the management of **meningitis**….. Fluid should be restricted to 50-60% of calculated requirement to prevent water intoxication from inappropriate antidiuretic hormone secretion. If there is hyper osmolality and hyper viscosity which require fluids the circulation must be maintained by use of plasma expander is and extra cellular dehydration treated with normal saline so that there is no change in osmolality. If the child has any impairment of consciousness or change a neurological state intracranial pressure should be monitored. If it is found to be raised treatment with mannitol, hyperventilation, frusemide and colloid may be given appropriately."

In the section on **maintain homoeostasis** on page 782 the following text appears

“The sick child may show the syndrome of inappropriate antidiuretic hormone secretion inability to excrete water overload. Water intoxication with oedema and hyponatraemia may result if intravenous fluids are given at the normal rate.”

In the chapter on infections Page 1347 which addresses management of bacterial meningitis the following is stated

“Although vomiting may be a presenting symptom of meningitis, dehydration is unusual and fluid overload associated with inappropriate ADH secretion is a more frequent occurrence. Plasma and urine electrolytes should be carefully monitored and fluids restricted until there are clear signs of recovery.”

Advises hyperventilation should not be used prophylactically.

Comment-*there is no specific warning here in relation to hypotonic/hyposmolar fluid administration as appeared in the Third edition 1984.*

F&A 6TH Edition 2003

In section on Acute Encephalopathy similar advice to 1996 Edition but with changes in layout and text. Maintain homeostasis advised. The following advice from the section on fluids supports the need to anticipate SIADH.

“SIADH is well recognized but it is frequently a misnomer. ADH secretion can be considered an appropriate evolutionary physiological response to injuries/illnesses which are of sufficient severity to preclude drinking for several days. The most common causes are CNS injury and bacterial pneumonia. The retained water however often does not come from a physiological source but from a prescription to administer fluid in quantities that did not anticipate the ADH secretion. In any case the clinical picture of water intoxication (hyponatremia) develops. The diagnosis is made by proving that urine osmolality exceeds that of a hypo-osmolar plasma (i.e. inappropriate retention of water by the kidney) and the treatment is usually fluid restriction. “

FROM THE TEXTBOOK OF PAEDIATRICS. NELSON. 14TH EDITION. 1992

Acute coma Page 1519.

“The principles of treatment include maintenance of the respiratory status, normalisation of cardiovascular function, and correction of acid base, fluid and electrolyte abnormalities. Seizures, increased intracranial pressure, and hyperthermia (or hypothermia are managed appropriately…….”

Hyponatraemia page 209

“the serum sodium level is most commonly reduced as a result of either sodium depletion or water “intoxication” or a combination of both…..”

“Treatment of asymptomatic hyponatraemia depends on its cause. With water overload, fluid restriction is the appropriate measure; the serum sodium level may return rapidly to normal if there is good renal function but may take several days or weeks with the inappropriate ADH secretion.”

Points out that the wrong treatment does not correct the deficit and may be detrimental for example, administering sodium to a patient with hyponatraemia resulting from water excess, such as that seen in the chronic oedema of heart failure, nephrotic syndrome, or cirrhosis may result only in further expanding the extra cellular fluid without correcting the serum sodium level.”

Then (Page 210) refers to the use of hyper tonic saline in symptomatic hyponatraemia but cautions on the risk of correcting a sodium level too rapidly.

Inappropriate secretion of antidiuretic hormone. Page 1405

“The syndrome is being recognised in an increasing number of clinical conditions, particularly those involving a central nervous system, including meningitis, and encephalopathy, brain tumour and abscesses, subarachnoid haemorrhage, Guillain Barre syndrome, head trauma and after trans-sphenoidal surgery for pituitary tumours. Pneumonia tuberculosis acute intermittent porphyria, cystic fibrosis, infant botulism, perinatal asphyxia, use of positive pressure respirators, and certain drugs such as vincristine or vinblastine also produce the syndrome. The mechanism of disturbed regulation vasopressin in these conditions is not fully understood but in many instances there is direct involvement of the hypothalamus….”

“Clinical manifestations: the syndrome is probably most often latent and asymptomatic and forms the basis for the long known observation that serum sodium levels may be unexpectedly low in conditions such as pneumonia, tuberculosis and meningitis. Careful attention to fluid replacement in patients with conditions known to be associated with the syndrome may prevent the development of symptoms. The clinical manifestations are attributable to hypotonicity of body fluids and those of water intoxication. If the serum sodium is not below 120 mEq per litre there may be no symptoms…..”

“*Treatment:* successful treatment of the underlying disorder (meningitis, pneumonia) is followed by spontaneous remission immediate management of the hyponatraemia simply consists of restriction of fluids. Sodium should be made available to replace the sodium loss; hypotonic saline solution is usually of little benefit however since even large sodium loads are excreted in the urine.”

(Then continues with management of severe water intoxication including use of furosemide.)

Page 686. Management of bacterial meningitis.

"The syndrome of inappropriate secretion of antidiuretic hormone occurs in 30% to 50% of cases of meningitis. The resulting hyponatraemia and reduced serum osmolality may exacerbate cerebral oedema or independently produce hypernatraemic seizures."

Page 688 continuing on management of bacterial meningitis "initially the patient should receive nothing by mouth. Intravenous fluid administration should be restricted to one half to 1/3 of maintenance until it can be established that increased intracranial pressure or SIADH is not present. Fluid administration may be returned to normal when serum sodium levels are normal. Fluid restriction needs to be balanced against the need to treat systemic hypotension….."

FROM THE TEXTBOOK OF PAEDIATRICS. NELSON. 16TH EDITION. 1999

Chapter 64.7 on acute neurological deterioration. page 273

"Circulation should be stabilised with the aim of optimising perfusion to all tissue. If after appropriate fluid resuscitation, a patient is still without adequate perfusion, inotropic agents may be indicated to enhance cardiac output. Once a patient has been stabilised, modest fluid restriction is beneficial to avoid fluid overload without producing oliguria. Urine output and serum sodium levels should be monitored…….

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is frequently associated with CNS injury or infection; it can also occur with pulmonary disease. SIADH usually responds to fluid restriction……."

Chapter 46. Sodium. Page 196.

"Hyponatraemia (serum sodium<130 mEq per litre) is caused by conditions that create primary sodium deficits resulting in the depletion of sodium; produce a gain in total body water; or combine sodium and water abnormalities. Refers to table.

"Of the disorders resulting in a primary water excess, the most common is the syndrome of inappropriate ADH secretion (SIADH). This disorder which has many potential causes, is marked by the secretion of ADH in the absence of a physiologic stimulus for its secretion. The increased ADH secretion increases collecting duct water reabsorption and dilutes the ECF producing hyponatraemia . In children, of the many conditions associated with SIADH , the most common is acute meningitis.

The hyponatraemia of water excess involve the addition of excess water from an exogenous source such as the use of dilute or sodium-poor intravenous fluids for the treatment of dehydration….."

Chapter 174 central nervous system infections. Page 755 regarding treatment of bacterial meningitis.

"patients should initially receive nothing by mouth. If a patient is judged to be normovolemic with normal blood pressure, intravenous fluid administration should be restricted to one half to 2/3 of maintenance until it can be established that increased ICP or SIADH is not present. Fluid administration may be returned to normal when serum sodium levels are normal……."

Page 756 regarding treatment of bacterial meningitis.

"SIADH occurs in the majority of patients with meningitis resulting in hyponatraemia and reduced serum osmolality in 30-50%. This may exacerbate cerebral oedema or incidentally produce hyponatraemic seizures."

Page 758 regarding treatment of acute viral meningoencephalitis.

"It is important to anticipate and be prepared for convulsions, cerebral oedema, hyperpyrexia, inadequate respiratory exchange, disturbed fluid and electrolyte balance, aspiration and asphyxia , cardiac or respiratory arrest of central origin……..

All fluids and medications are initially given parenterally. SIADH is quite common in acute CNS disorders thus constant evaluation is required for its early detection. Normal blood levels of glucose magnesium and calcium must be maintained to minimise the threat of convulsions. If cerebral oedema or seizures become evident vigorous treatment should be instituted."

Page 1684. Chapter 569 on abnormalities of Arginine vasopressin metabolism.

"Treatment of SIADH consists of simultaneously treating the underlying disorder causing SIADH and restricting fluids. Sodium replacement for urinary losses of sodium should be provided but both intravenous and oral water administration should be reduced significantly based on careful calculation of actual and insensible and body water losses. Serum as well as urine electrolytes and osmolality should be closely monitored and the patient's status re-evaluated on a frequent basis…….

FROM HOSPITAL PAEDIATRICS Milner & Hull 3RD EDITION 1998

In the section dealing with altered consciousness. (Page 420 et seq)

Two third fluid restriction is advised with monitoring of urea and electrolytes (without explanation of the reason why) the text does not mention SIADH but does state "careful attention to fluid balance is necessary".

There is no mention of hyponatraemia specifically in this section or edition separately (or in the index).

PAEDIATRIC NEUROLOGY GUIDANCE

MENKES TEXTBOOK OF CHILD NEUROLOGY 5th Edition 1995

Hyponatraemia: "low sodium syndromes can result from an increasing body water with retention of a normal sodium store, or can occur following reduction of sodium stores. “

The clinical conditions associated with hyponatraemia are outlined in table 14.3. (including the administration of salt poor solutions) – see next page:

commonly associated with hyper- or hypokalemia. The effect of potassium on muscular function is reviewed in Chapter 13. The reader is also referred to a review by Katzman and Pappius (68) for a full discussion of the pathogenesis of cerebral symptoms in electrolyte disorders, and to a review by Strange on disorders of osmotic balance (69).

Hyponatremia

Low-sodium syndromes can result from an increase in body water with retention of a normal sodium store, or can occur following reduction of sodium stores. The clinical conditions associated with hyponatremia are outlined in Table 14.3.

Neurologic symptoms of hyponatremia include headache, nausea, incoordination, delirium, and, ultimately, generalized or focal seizures with apnea and opisthotonus (70, 71).

Generally, severe neurologic symptoms with permanent residua do not develop at sodium levels above 110 mEq/l, unless plasma sodium has dropped rapidly. Some have advocated rapid correction of hyponatremia in a patient with neurologic symptoms using urea in conjunction with salt supplements and water restriction (72). However, too rapid correction of hyponatremia has been thought to play a role in the development of central pontine myelinolysis (73), a frequently fatal disorder characterized clinically by confusion, cranial nerve dysfunction, and, in larger lesions, a "locked in" syndrome and quadriparesis. Pathologically, central pontine myelinolysis is characterized by symmetric destruction of myelin at the center of the pons. The pontile demyelination can be visualized by MRI (74). Although other investigators have challenged the concept that this condition is related to the rate of correction of hyponatremia, the optimum rate for correcting hyponatremia is still controversial (75). It appears, however, that central pontine myelinolysis is more likely to develop when the initial sodium level is less than 105 mEq/l, when hyponatremia has developed acutely, and when sodium levels are corrected more rapidly than 0.7 mEq/l/hr (76).

Table 14.3
Clinical Conditions Producing Abnormalities of Sodium Concentration

Hyponatremia
1. Administration of salt-poor solutions in the presence of impaired function, acute overload of solute-free water in infants.
2. Water retention (congestive heart failure, hepatic cirrhosis)
3. Depletion of intracellular solutes (diuretics, protein energy malnutrition, cystic fibrosis, adrenogenital syndrome)
4. Postoperative hyponatremia, associated with nonosmotic release of antidiuretic hormone
5. Inappropriate secretion of antidiuretic hormone in diseases involving the central and peripheral nervous systems (anatomic isolation of supraoptic nucleus of hypothalamus resulting in released firing of osmoreceptors)
6. Encephalitis, poliomyelitis, meningitis, polyneuritis, diffuse cerebral damage in infancy, cerebral infarction, supratentorial and infratentorial brain tumors, subarachnoid hemorrhage.

Hypernatremia
1. Limited water intake
2. Excessive evaporative losses (hyperpnea, increased environmental temperature)
3. Excessive excretory losses (diarrhea, diabetes insipidus)
4. Salt loading (often accompanied by excessive water loss)
5. Sodium retention (hyperaldosteronism and Cushing syndrome)

Hypernatremia

Increased concentration of sodium in body fluids elevates fluid osmolality and induces severe cerebral manifestations. Major causes for hypernatremia are outlined in Table 14.3.

Luttrell and Finberg have delineated the factors responsible for neurologic symptoms. These are subdural hematomas, venous and capillary congestion, and hemorrhages, the last produced by shrinkage of the brain during dehydration (77).

Neurologic symptoms can also occur in the absence of any structural alteration and are probably the direct result of hyperosmolality. Guisado and Arieff have suggested that hyperosmolality inhibits the activity of the cerebral Krebs cycle and induces an increased utilization of neuronal γ-aminobutyric acid (GABA) (78). Additionally, and perhaps most commonly, symptoms are due to cerebral edema, which is particularly likely to occur with rapid rehydration and is caused by an elevated content of chloride and potassium in the brain (79, 80).

Hypernatremia is generally seen in infants under 6 months of age. All have clear evidence of dehydration. Patients have varying

FROM SWAIMAN TEXTBOOK OF PEDIATRIC NEUROLOGY Second edition volume 1 1994.

In the chapter on viral diseases of the nervous system.

In regard to treatment of aseptic meningitis. Page 657.

"Supportive or palliative treatments depend on the needs of the patient but generally include proper fluid and electrolyte balance, control of hyperthermia, proper supportive body care, control of pain, maintenance of nutrition, and sedation for hyperkinesis and delirium. Seizures may occur in aseptic meningitis. Antiepileptic medication is usually indicated when Seizures strongly indicate that a more serious and extensive encephalitis is probably developing. Additionally, control of brain oedema is seldom the consideration in the typical aseptic meningitis patient. If coma and more severe neurological symptoms and signs were to develop, reflecting severe brain oedema, the diagnosis should be re-evaluated."

In regard to treatment of viral encephalitis. Page 661.

"In all cases of all viral encephalitis, general supportive treatment is imperative and includes all modalities used to treat patients with severe illness. Respiratory and cardiovascular support is required, as well as proper fluid maintenance and electrolyte balance. Hydration must be restricted because over hydration worsens cerebral oedema

……. Cerebral oedema is the rule rather than the exception and must be treated appropriately. Oedema is believed to result from toxins liberated by the destruction of this years and from vasculitis and may be treated by inducing hyperventilation, continuing mild depletion of intravascular volume, and using controlled quantities of anti-oedema agents such as mannitol……."

In regard to management of bacterial infections of the central nervous system-meningitis. Page 617.

"Major complications include increased intracranial pressure, seizures, extra axial collections, shock, brain infarction or necrosis, ventriculomegaly, cranial nerve involvement, and inappropriate secretion of anti-diuretic hormone…….

(page 621) “Over hydration with intravenous fluids may predispose patients to or exaggerate existing cerebral oedema; therefore fluids should be carefully administered to minimise the risk of developing cerebral oedema. In the absence of hypertension and with normal serum sodium content, administering two thirds of the calculated daily maintenance fluids intravenously during the first 24 hours of illness is usual practice. Usually the fluid is administered as ¼ to 1/3 saline in 5% dextrose. Fluid restriction has a theoretic disadvantage because many patients are dehydrated on arrival at a medical facility……

“In bacterial meningitis maintaining a state of fluid balance as close to physiologically normal as possible is advisable. About 20% of children with bacterial meningitis developed hyponatraemia.

The frequency of hyponatraemia related to inappropriate hypothalamic release of antidiuretic hormone and secondary fluid retention is controversial. In hyponatraemia the symptoms are those of water intoxication (e.g. restlessness, irritability, lethargy, seizures and coma) with inappropriate secretion of antidiuretic hormone serum sodium level is low, the serum hypoosmolar, and the urine excessively concentrated with elevated urine sodium concentration. Treatment for inappropriate release of antidiuretic hormone is fluid restriction. The recommendation has been made to institute fluid restriction only when serum sodium concentration decreases to less than 125 mEq per litre……."

Refers to :

Powell KR, Sugarman LI, Eskenazi AE, et al. Normalization of plasma arginine vasopressin concentrations when children with meningitis are given maintenance plus replacement fluid therapy. J Pediatr 1990;117:515–22. Which includes :

"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) recelved 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 fluidrestricted 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 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 facilltate 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.

From Family Physician. September 1, 1993 : author Hector James.. Emergency management of acute coma in children.

"Administration of fluids to support the circulation is critical. Hypotonic fluids should be avoided because excessive free water may augment existing brain oedema."

PUBLICATIONS FOLLOWING CLAIRE'S ILLNESS

2000

Yu PL, Jin LM, Seaman H, *et al*. Fluid therapy of acute brain edema in children. *Pediatr Neurol* 2000;22:298–301.

Various relevant text :

….. we proposed a new fluid therapy, based on the patient's condition, for maintaining children with acute brain edema in a mild state of dehydration by means of both dehydration and fluid replenishment. "

…"……In this report, our clinical experience in treating acute brain edema in children using this fluid therapy is summarized and compared with the old method of therapy, in which fluid intake was limited to less than 60 mL/kg daily. "

…"…… The fluids administered included several group solutions. NaHCO3, 2-4% or 1.4% was administered to correct the acidosis and blood pH to within the normal range. Because more than 80% of the children with brain edema had acidosis [4,9], which might increase the permeability of the blood-brain barrier and in turn increase the brain water content, Bruce [10] and Bruce et al. [11] also proposed that the blood pH of children with brain edema should be slightly alkalinized. The rest of the fluid was 10% glucose; blood glucose was maintained in a normal range. Some patients with low blood sodium or chloride were given a normal saline solution because the use of NaHCO3 in this situation was often enough to replenish the sodium. Normal saline was given to only a few patients. For patients with severe brain edema, 10% low–molecular-weight dextran- 40 (10 mL/kg) was given 1-2 times daily to improve the microcirculation of the brain. Albumin or fresh frozen plasma was given 1-2 times daily 8-12 hours after fluid therapy to maintain the colloid osmotic pressure; packed erythrocytes were given to the patients with anemia. As the urinary excretion of potassium increased and a large amount of potassium entered the cells after the correction of acidosis, the blood potassium of patients with brain edema frequently decreased rapidly within a few hours of fluid therapy. Blood potassium was measured promptly and 0.1-0.3% of potassium chloride was administered intravenously in varying amounts to most patients. Calcium and magnesium were given to children with polyuria because hypocalcemia and hypomagnesia frequently occurred in these patients. Multivitamins were also given to patients with polyuria. Using the aforementioned diagnostic criteria, all patients in both the prospective and retrospective groups were diagnosed as having acute brain edema **complicated by infectious disease ."**

2001

Acute symptomatic hyponatraemia and cerebral salt wasting after head injury: an important clinical entity. Journal Paediatric Surgery. 2001; 36:1094.

"Hyponatraemia is a well-known complication of traumatic and non-traumatic cerebral injury, often related to the syndrome of inappropriate antidiuretic hormone secretion."

Management of hyponatraemia in patients with acute cerebral insults. Albanese a Archives Disease In Childhood. 2001; 85:246-251

"hyponatraemia is a common finding in patients with acute cerebral insults, especially after a neurosurgical procedures…."

Then refers to the combination of cerebral salt wasting and inappropriate ADH

"Many conditions affecting the brain (post-neurosurgery, head injury, haemorrhage, infections, etc) can cause SIADH."

Comment In an otherwise detailed review about mechanisms, there is no attention given to prevention by the avoidance of hypotonic fluid intravenously. But the text confirms the awareness of the risk over previous years.

Kirkham FJ. Non-traumatic coma in children. Arch Dis Child 2001;85:303-312

This review includes the following text:

"……but salt wasting is an important association with conditions such as meningitis; initial fluid therapy should aim to slowly replace salt and water losses as well as maintain adequate nutrition. Resuscitation and maintenance of systemic homoeostasis are the priorities in the acute situation and there is no case for fluid restriction; however hypo-osmolar fluids such as 5 or 10% dextrose are contraindicated because of the risk of delayed cerebral oedema. "

In Table warns against possibility of low sodium and if present advises " appropriate fluids" Text follows as:

"Fluid management can be very difficult and should be tailored for the individual patient's needs. There is considerable controversy over fluid restriction, which has been shown to be potentially harmful in patients with subarachnoid haemorrhage and meningitis. The syndrome of inappropriate secretion of ADH, for which fluid restriction is indicated, is relatively rare; instead cranial diabetes insipidus may require careful management. It is essential that the systemic circulation is well filled and that large volumes of hypo-osmolar fluids are not given. To manage these patients properly it is essential to monitor blood pressure, central venous pressure, urine output, weight, core and peripheral temperature, plasma and urine electrolytes, and osmolality at least six hourly and to make appropriate management decisions with the same frequency. Mannitol may reduce spikes of ICP very rapidly and acts either as an osmotic

diuretic or by reducing cerebral blood volume. As with hyperventilation, there is no evidence that regular prophylactic mannitol is of benefit. A few years ago there was a vogue for using anaesthetic agents which reduce ICP by reducing cerebral metabolic demand and therefore cerebral blood flow and blood volume. There is no evidence that barbiturates and other sedatives are of any benefit in global cerebral ischaemia. Although there may be an intermediate group of patients in coma from other causes who might benefit from barbiturate therapy, the risk of hypotension probably outweighs any useful effect in reducing ICP. In addition, drug levels may remain high several days after the drug has been discontinued, making the diagnosis of brain death impossible. "

2003

Intravenous Fluids For Seriously Ill Children: Time To Reconsider. Duke T Lancet 2003; 362:1320.

> "Intravenous (iv) fluids are used for many sick and injured children. Such fluids generally used are 0·18% or 0·2% saline with 5% dextrose. These fluids are often given at maintenance rates—100 mL/kg for the first 10 kg of bodyweight, 50 mlL/kg for the next 10 kg, and 20 mL/kg for bodyweight exceeding 20 kg. Some standard paediatric texts caution the need to modify maintenance requirements according to disease states, but this specification has been lost in some recent empirical recommendations: for example, WHO now suggests full maintenance fluids for the routine treatment of bacterial meningitis (albeit with a caution about cerebral oedema), with an emphasis on glucose but not sodium content. This is partly based on concerns about dehydration, but there is no strong evidence that this advice is ideal. Hypotonic iv fluids given at maintenance rates might be unsafe, especially in hospitals in developing countries where serum sodium concentration often cannot be measured. "
>
> "Children with serious infections share similar pathophysiological mechanisms and risks of adverse neurological outcomes if given hypotonic IV solution."

Refers to hyponatraemia arising in between 20% and 45% of children with meningitis referring to papers published in 1987 and 2000, pneumonia dated 1992, and encephalitis dated 2001.

Considers that the pathophysiological basis is not fully understood.

> "Many case reports have described acute neurological deterioration in children with serious infections, associated with progressive hyponatraemia and hypotonic intravenous fluid administration (table 2). Researchers who examined the aetiology of extreme hyponatraemia (<115 mmol/L) in a tertiary children's hospital, reported iatrogenic administration of excessive free water as the most common cause.31 "
>
> "Avoidance of hyponatraemia is essential, but not sufficient, to prevent adverse events associated with IV fluid in all children. Fluid overload occurs in children with impaired free water clearance who receive 100% or more of maintenance fluid."

"Potential pitfalls

Use of an isotonic, rather than hypotonic, solution does not mean that progressive hyponatraemia would not take place, but that it is much less likely. Although use of high-sodium-containing solutions in children with meningitis in the first 24 h was not associated with development of hypernatraemia, during the later phases of illness there is a theoretical risk of hypernatraemia if isotonic saline is used. ……

Possible solution

We postulate that 0·9% saline (with 5% dextrose) at less than standard maintenance volumes results in a lower frequency of hyponatraemia, seizures, and adverse neurological events than do hypotonic solutions (0·18%–0·3% saline), in acutely unwell children with brain injury of any type (meningitis, encephalitis, cerebral malaria, febrile seizures); serum sodium less than 138 mmol/L;30 or severe infection associated with greatly impaired free-water excretion. Ideal testing of this hypothesis would be done in a large randomised controlled trial of hypotonic versus isotonic saline in children with severe infections, stratified for types of infections. However, we think it would be unethical to include some infections, particularly encephalitis and meningitis, because there is already substantial experience of harm from hypotonic solutions and pathophysiological plausibility of the cause of such harm. Such infections also have a much higher risk than do other infections of cerebral oedema and adverse outcomes if hyponatraemia occurs. ……."

In referring to the 1990 Powell paper (quoted in Swaiman textbook and Kirkham review)

"Administration of sodium results in a more rapid return to normal of antidiuretic hormone concentrations than does use of low sodium-containing fluid."

2004

Hypotonic intravenous solutions in children. Playfor SD. Expert Opin Drug Saf. 2004 Jan;3(1):67-73. Paediatric Intensive Care Unit, Royal Manchester Children's Hospital, Hospital Road, Pendlebury, Manchester M27 4HA, UK.

Abstract

"The use of hypotonic intravenous solutions, especially 4% dextrose/0.18% saline, remains standard practice in many paediatric units in the UK. The practice of prescribing hypotonic intravenous fluids derives from the work of investigators in the 1950s, who produced arbitrarily-derived formulae for calculating the maintenance requirements for water and electrolytes in hospitalised patients. Combining these values led to the widespread acceptance of hypotonic solutions such as 4% dextrose/0.18% saline as 'standard maintenance' parenteral fluids. Unfortunately, these calculations do not

account for the effects of antidiuretic hormone, the secretion of which is stimulated by many factors encountered during acute illness and especially in the perioperative period. In this setting, the administration of hypotonic intravenous fluids results in the retention of free water and the development of hyponatraemia. The routine administration of hypotonic intravenous fluids has been shown to be associated with severe morbidity and the deaths of many previously healthy children. The problem is compounded by the fact that 4% dextrose/0.18% saline is labelled as 'isotonic'. Whilst this solution is isosmolar compared to plasma, lack of osmotically-effective solutes means that it is hypotonic with reference to the cell membrane. There is no justification for the routine administration of hypotonic intravenous fluids."

BEFORE CLAIRES ILLNESS

Hyponatraemia and death or permanent brain damage in healthy children. Arieff a et al BMJ 1992; 304:1218

Prevention and Treatment of Hyponatraemic Encephalopathy

> **"**symptomatic hyponatraemia can best be prevented by not infusing hypotonic fluids to hospitalised children unless there is a clear-cut indication for their use."

Comment: this is the paper which was referred to in the press statement from the Royal Hospitals Belfast following Adam Strain's death and is not specifically addressing management of an existing acute encephalopathy.