D71

A medical report on the clinical events leading to the death of a young girl from cerebral oedema

Re: **Claire Roberts dob 10.1.87, died 23.10.96**

My Reference: 2008 / Roberts /N.48

Instructing Organisation:
Crime Operations Department
Serious Crime Branch
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I am a consultant paediatrician at Singleton Hospital, Swansea. I am a Fellow of both the Royal College of Physicians and the Royal College of Paediatrics and Child Health and have a Diploma in Obstetrics from the Royal College of Obstetrics and Gynaecology. I have been in consultant paediatric practice since 1980, and am currently clinical chair (head of department) of the Division of Women & Child Health. I lead the service for children with diabetes and endocrinological disorders, had an extensive neonatology practice until 2007, and deal with a wide range of clinical problems common to any large acute paediatric department.

I have prepared over 500 medico-legal reports over the past 20 years, and have given evidence in both the Civil and Criminal Court on issues of alleged clinical negligence and child protection matters.

Date: 1 March 2008

1. I have prepared this report at the request of the Crime Operations Department Serious Crime Branch, Gough Barracks, Barrack Hill, Armagh, BT60 I BW.

2. I have received the following documents

i. Letter of Instruction dated 23.1.08.
ii. The original clinical casefile of Claire Roberts.
iii. Verdict on Inquest.
iv. A letter from Dr Walby dated 16.12.04
v. Two Statements from Mr Alan Roberts, Claire's father.
vi. Statement of Dr Maconchie
vii. Statement of Dr Sands.
viii. Statement of Dr. Young.
ix. Statement of Dr Steane.
x. Statement of Dr. Webb.
xi. Autopsy report Dr Herron.
xii. Neuropathology report of Dr Harding.

3. My instruction is to review the clinical history and the enclosed Statements with regard to the death of Claire Roberts in October 1996.

Claire was a young girl of 9 years. She had long standing learning difficulties, and there was a query regarding attention deficit hyperactivity disorder (ADHD). She was otherwise in good physical health. She was admitted to the Royal Belfast Hospital For Sick Children on the evening of 21 Oct 96. Her condition deteriorated, and in the early hours of 23 Oct she collapsed and was found to have fixed dilated pupils. Resuscitation was unsuccessful and all treatment was withdrawn at 18:45 hr on the same day.

Post mortem findings concluded that the cause of death was cerebral oedema secondary to meningo-encephalitis. There was also a comment relating to the presence of both hyponatraemia and presumed inappropriate ADH secretion.

4. I have been asked to review her management, particularly with regard to fluid management and overall care. I have been asked to comment on any possible line of management that was below acceptable standards, and whether this contributes to a significant breach of clinical duty. The Letter of Instruction includes a list of questions, and I shall respond to these in my report.

Clinical History

5. The next few paragraphs summarise Claire's clinical history. There is a past medical history of interest, and I include a brief chronology of this history.

6. Claire was born at full term. Her birth weight was 7lb 9 oz. The labour and delivery were reported as normal. There were no known problems in relation to her birth and no significant family history. Her mother and father were noted to be 26 and 28 years old at the time.

7. I have seen a detailed letter relating to Claire's hospital admission of 4.9.87. The letter is from Dr M Hanlon, paediatric registrar. Claire was 8 months of age at the time. She presented with a history of seizure activity. Short lasting seizures were noted on a number of occasions, and these continued following her discharge from hospital.

8. Electroencephalogram (EEG) dated 10.9.87 showed results that were outside the norm, with indefinite spike and slow wave. A repeat EEG (14 Sept 87) also sowed some irregularities, although these were not consistent with any specific phenomenon. A whole range of other investigations carried out at the time, including CT scan of the brain, failed to confirm any specific cause for her seizure activity. Claire was placed on anticonvulsant medication, which continued for many years.

9. I have no detailed information of Claire's development over the next few years. A letter dated 2 August 96 confirms that she has both learning disability and behaviour difficulties. There was no record of any seizure activity from the age of 4 years. She had been off anticonvulsant therapy (sodium valproate, *Epilim*) for the past year.

At the 1 August 96 clinic the issue of placing Claire on a therapeutic trial involving either Ritalin (methylphenidate) or placebo was discussed. She was prescribed Ritalin 10 mg daily.

Index event

10. Claire was admitted via the Accident and Emergency (A & E) Department at 8 pm on Monday 21.10.96. The history was of vomiting at 3 pm and every hour since. There was also a history of *"slurred speech and drowsy"*. She had been unwell the previous day and there had been a history of loose motions three days earlier. Her father's Statement confirms that Claire had been at school that day (Monday).

The clinical entry confirms that under normal circumstances Claire's speech consisted of meaningful sentences and that her hearing and vision was normal. She was unable to dress herself. She could walk both up and downstairs. She favoured the left side of her body. She attended a local special school. The trial of Ritalin was noted and that it caused a dry mouth. It is not clear whether she was on Ritalin at this admission.

11. The initial clinical history is noted as follows. Her temperature was 37°C (normal). Pulse rate was 80 per minute. Examination of heart, chest and abdomen was normal. The neurological findings confirmed normal fundi. The discs were not blurred. She was noted to be sitting up and *"staring vacantly"*.

Reflexes were brisker on the right than the left. She was noted to be *"not responding to parents' voice / intermittently responding to deep pain."*

12. Claire was placed on a neurological monitoring system, and the results are noted here.

13. The diagnosis was suspected as being a viral illness. There was a second query regarding encephalitis, but this was crossed off. She was treated with intravenous fluids and diazepam, and a number of investigations were arranged.

14. The significant finding on admission was sodium of 132. The rest of the biochemistry was normal; in particular there was no evidence of significant dehydration.

15. Claire was maintained on 0.18% sodium chloride ("fifth normal saline"). The fluid chart confirms that she was written up for 64 ml / hour. I enclose a copy of the Fluid Chart with this report.

16. Claire received a total 536 ml over 9 hours on 21 Oct (equivalent to 60 ml / hour), between 22:00 hr and 07:00 hr the next day. From 08:00 hr on 22 Oct until 02:00 hr on 23 Oct (just before she collapsed) she received a total of 1,070 ml which works out at 53 ml/hr.

The chart records several episodes of vomiting and of her passing urine.

17. Claire received a neurology review at 4 pm on Tuesday 22 Oct. The clinical examination confirmed that she did not have a raised temperature and there was no evidence of meningism. The neurological findings were as follows.

"Rousable – eye opening to voice, non-verbal withdraws from painful stimulus. Reduced movement right side?
Antigravity all four limbs.
Mildly increased tone both arms.
Reflexes symmetrically brisk.
Clonus – sustained both ankles.
Tone increased.
Sits up – eyes open and looks vacantly.
Not obeying commands.
PEARL [pupils equal (to) accommodation (and) reactive (to) light] *5 mm*
Optic disc pale, no papilloedema.
Facial palatal and lingual movements appear normal"

The view was that the picture was of an acute encephalopathy, most probably post-ictal in nature. Treatment with phenytoin was suggested, with CT the following day if she does not wake up.

18. A further entry, written between 16:00 and 17:00 hr, notes *"still in status"* (presumably meaning '*status* epilepticus'). She was therefore given midazolam 0.5 mg / kg immediately, followed by midazolam infusion 2 ug / kg / min, (which works out at 69 mg/24 hrs).

I have seen a nursing entry in a sheet headed "Record of Attacks Observed". This notes: -

22/10	*"3.10 pm*	*Lasted frequently strong seizer (sic) at 3.25.*	*Duration 5 min*
	4.30	*Teeth tightened slightly*	*Few secs*
	7.15 pm	*Teeth clenched + groaned*	*1 min*
	9 pm	*Episode of screaming and drawing up of arms. Pulse rate 165 bpm. Pupils large but reacting to light. Dr informed"*	

I cannot find any other record of seizure activity in the file from this index event.

19. A further neurology review timed at 17:00 hr confirms that *"she continues to be largely unresponsive"*. A further history from her mother notes *"contact with cousin on Saturday who had a gastrointestinal upset. Claire had loose motions on Sunday and vomiting Monday. She had some focal signs on Monday with right sided stiffening"*.

Additional treatment with cefotaxime and acyclovir is advised. Viral cultures are checked and sodium valproate is prescribed; 20 mg/kg as IV bolus followed by 10 mg/kg over 12 hours.

The next entry is timed at 23:30 on 22 Oct. It notes sodium of 121, potassium 3.3, urea 2.9 and creatinine 33. There is a query regarding fluid overload with low sodium fluids and a further query regarding SIADH (syndrome of inappropriate antidiuretic hormone). Following discussions with the registrar her fluids are reduced to 2/3rds of their current volume; 41 ml/hr. Urine is checked for osmolality.

20. The entry timed at 3 am on 23 Oct notes;

"Had been stable when suddenly she had a respiratory arrest and developed fixed dilated pupils". When seen she was showing Cheynes Stokes (breathing) and receiving oxygen via face mask. The anaesthetist was called, intubated her orally with a 6.5 tube and transferred her to the PICU.

A review timed at 3 am (entry of 4 am) confirms that Claire is intubated and ventilated. Her pupils are noted to be fixed and dilated. There is bilateral papilloedema left more than right. Her blood pressure is 90/65, heart rate l00 / min. These values are acceptable.
Treatment was given with mannitol, dopamine infusion, and urgent CT scan arranged.

21. The entry timed at 05:30 hr is reported as showing results of the CT scan: there is severe diffuse hemispheric swelling with complete effacement of the basal systems, no focal abnormality is identified.

22. The entry timed at 6 am notes no response to stimulation. The clinical staff arrange brain stem tests. These are tests performed to check for brain viability in patients who are on life support, where recovery is deemed unlikely, and where life support may have to be discontinued.

23. There is an entry dated 23 Oct (untimed) noting that she now has polyuria, and that DDAVP (desmopressin, antidiuretic hormone, ADH) is required. Serum sodium is 129 (up from 121).

24. The entry timed at 18:25 hr notes that the diagnosis of brain death protocol is completed and that there is no spontaneous respiratory movement. Following discussion with the parents, ventilation is discontinued at 18:45 hr. Death is attributed to cerebral oedema secondary to status epilepticus.

25. I have seen the autopsy report from the RBHSC. It confirms that the time of death was 6.25 hr on 23.10.96. The report contains a clinical summary. The significant findings are as follows.

- Brain weight 1606 grams.
- Symmetrical brain swelling. On sectioning of the brain the presence of diffuse brain swelling is confirmed.
- Cortex and white matter sections show focal meningeal thickening and a cellular reaction in the meninges and perivascular space in the underlying cortex.
- There is no cortical necrosis but in the deep white matter focal collections of neurones are present arranged in a rather haphazard manner.
- Focal collection of neuroblasts in the subependymal zone suggestive of a migration problem.

The summary is as follows.

"The features are those of cerebral oedema with neuronal migrational defect and a low grade subacute meningo-encephalitis. No other discrete lesion has been identified to explain epileptic seizures. The reaction in the meninges and cortex is suggestive of a viral aetiology, though some viral studies were negative during life and on post mortem CSF.
With the clinical history of diarrhoea and vomiting this is a possibility though a metabolic cause cannot be entirely excluded. As this was a brain only autopsy it is not possible to comment on other systemic pathology in the general organs. No other structural lesion in the brain like corpus callosal or other malformations were identified."

26. I have seen the report of Dr Brian Harding consultant neuropathogist at Great Ormond Street Hospital, London (dated 22.8.07). He reports on the autopsy report of Dr Herron and on 32 H & E stained sections, 23 immunostained slides 4 semi thin slides and a further 13 H & E stained sections from various parts of the brain. His conclusions are as follows.

- There is no evidence of acquired infection (meningitis or encephalitis)
- The cause of death on the Death Certificate and in the Inquest verdict is not concordant with his observations.
- The brain weight is excessive (1606 grams). The normal weight is about 1200 grams (there is no record of Claire's head circumference to indicate whether head circumference was normal).

[Note: I cannot find a record of head circumference from the clinical notes. DRE]

- "Effacement of gyri" and "uncal prominence" are rather weak indicators (of brain swelling). This is not supported by *"major downward shift of the brain and cerebellum which is common in severe swollen brain and by the microscopy (lack of vacuolation of white matter)."*

- He considers meningo-encephalitis excluded both by microbiology and the post mortem neuropathology.
- Hyponatraemia is known to cause brain swelling. But there is no other specific neuropathological indicator for hyponatraemia.
- Seizures were not witnessed prior to hospital admission, and certainly not status epilepticus.
- The neuropathological sequelea of status were not present.
- There was no damage to the hippocampus which may be seen in children with chronic epilepsy.

In Dr Harding's opinion the cause of death was brain swelling and hyponatraemia is the only causative factor that has been positively identified.

27. Other investigations were carried out either following the death or where the results were obtained after Claire's death.

Cerebro-spinal fluid (CSF) analysis was obtained on 25.10.96. The results were received on 4.11.96. Clearly this fluid would have been obtained at post mortem. CSF is described as being blood stained and straw coloured. The protein content is 95.0 g/L. The normal reference range is 0.15 – 0.45. CSF is noted to contain 300,000 red cells per ul and 4,000 leucocytes per ul. The leucocytes are described as being *"mostly lymphocytes"*. Subsequent CSF culture is reported as showing no growth in 48 hours (report of 28.10.96).

28. Serum samples looking for viruses, obtained on 21.10.96, is reported on 30.10.96 as showing negative findings for the following; mumps, measles, herpes simplex, herpes zoster (chicken pox) CMV, adenovirus, Q fever, PLGEV, mycoplasma pneumoniae and influenzae A and B. There is no record of any samples being sent off for viral culture, and no samples were sent off for PCR estimations.

29. The CT scan of the brain dated 23.10.96 is reported as follows.
"There is generalised cerebral swelling with effacement of the cortical sulci as well as the basal cisterns and the third ventricle. No focal lesion has been identied".

A chest x-ray of the same date is reported as showing "*patchy consolidation in the mid and upper zones on both sides, slightly more extensive in examination 2. An ETT* (endotracheal tube) *is in position with the tip at the thoracic inlet and in film 3 an IV line is present with the tip in the SVC* (superior vena cava)."
The presence of the ETT confirms that this chest x-ray was carried out following Claire's respiratory arrest.
I have not seen the original CT and chest x-ray.

30. For completion, I note the CSF findings from Claire's admission in September 1987. There were two samples dated 12.9.87. One sample was described as *"blood stained"*. Protein was 1.7 g/L.

There were 8,400 red cells and less than I white cell. The second sample was described as being *"faintly blood stained"*. There were 1,140 red cells and less than I white cell. CSF culture was reported as showing no growth in 48 hours.

Opinion

31. My opinion is based on my experience as a consultant paediatrician in Swansea since 1980. The management of children who present with an altered level of consciousness is one that should be common to all practicing hospital based paediatricians. The presentation is one that should always be taken seriously. The cause is often not obvious, and one is always faced with the risk of the child deteriorating, falling into a coma, and sustaining a respiratory or cardio-respiratory arrest.

I have been involved with hospital based acute paediatrics throughout my career, from 1973 until the present day. The management of children with an altered level of consciousness is a clinical scenario I have encountered on numerous occasions during this time.

32. My first involvement with this case was following a consultation with two officers of the Northern Ireland Police Service on 24 Jan 08. This report is a first completed draft, and I will add or amend to this report on receipt of any additional information.

33. My preliminary view is as follows. There does not appear to be any significant history relating to the pregnancy or birth. Claire was born at term. It looks as if her early development was appropriate.

34. Claire sustained a significant neurological illness at the age of 8 months. Tonic clonic convulsions were recorded on numerous occasions. The convulsions continued beyond her discharge, and she remained on anticonvulsant therapy until the age of 4 years. The cause of this encephalopathic illness has never been ascertained. Investigations available at the time were not particularly helpful. Normal CSF would tend to rule out an infective cause. A normal CT scan of the brain does not help to establish a diagnosis. Electroencephalography (EEG) carried out at the time showed non-specific findings, not diagnostic of any specific disorder.

35. It looks as if the acute encephalopathic illness burnt itself out but left Claire with a residual permanent neuro-disability. A letter dated 9.2.88 from the consultant paediatrician at the Ulster Hospital records that Claire has had no convulsions since September (1987 presumably). She was on Epilim (sodium valproate) 2.7 ml twice daily at that time. The consultant notes that her speech is *"undoubtedly slow"*. She was also noted to grind her teeth, was able to sit well and get into the crawling position but doesn't really move forwards, but may go backwards. She is not standing with support. Claire was 13 months at that time.

There is a discrepancy in the documentation regarding the time that Claire had been seizure free and the date that her anticonvulsant therapy was discontinued. The letter from Dr Gaston of 30 May 96 notes that she has a history of seizures from 6 months to 4 years of age, and had been off Epilim for

the past year (presumably 1995). The entry from her index event suggests that the sodium valproate was discontinued at 4 years of age.

She experienced seizure activity for some time afterwards, but she had been free of seizures for many years prior to her index and final clinical presentation. She was left with learning difficulties. This is summarised in the letter of 30 May 96 when she was noted to have a short attention span, and features consistent with attention deficit disorder. All the documents suggest that Claire has had no history of seizures after 4 years of age.

Claire's index event

36. Claire was unwell for a very short period of time prior to her hospital admission on the evening of 21 Oct 1996. Her father's Statement notes that she attended school that day and that she had been sick before returning home at approximately 15:00 hr. The vomiting continued at home on 2 or 3 occasions. She also had one loose bowel movement. Hospital admission was arranged following a visit from the GP at 18:00 hr.

37. There is nothing in Mr Roberts's Statement or in the medical notes to suggest that Claire has had any kind of convulsive episode. Right from the outset, the clinical entry describes very significant findings consistent with an altered level of consciousness. The initial entry of 8 pm records *"not responding to parents' voice / intermittently responding to deep pain"*. There is therefore compelling evidence consistent with Claire having some kind of encephalopathic illness at presentation.

It is reasonable at this time to outline the likely cause of such a presentation, and the steps that would be taken by any medical practitioner to confirm or rule out any specific disorder, with the emphasis on confirming or ruling out any disorder that is treatable, and where early treatment can make a difference, and / or confirming or ruling out any disorder that is likely to lead to a deterioration.

38.

- There is no evidence of trauma; no head injury.

- Whilst one will get an altered level of consciousness following a seizure (and I used the word seizure, fit, convulsion or epileptic fit interchangeably) there is no evidence whatsoever of Claire having had a convulsion. She was under the supervision of adults; school teacher, parents, GP, continually in the hours leading to her hospital admission. The likelihood of her sustaining a convulsion without any one noticing is unrealistic in my opinion. Moreover, if her lack of response was a post-ictal phenomenon, one would not expect the post-ictal phase to last several hours in the absence of a significant tonic clonic seizure (also known as a *grand mal* fit).

- There is no history of her having taken any medication or inappropriate drug. I am not quite certain whether she was on methylphenidate (Ritalin) at this time, but I would not expect methylphenidate to cause an event of this nature anyway.

39. Claire was not systemically ill, i.e. she did not have symptoms consistent with, for example, severe gastroenteritis sufficient to cause fluid loss and dehydration. She was not febrile. There was no clinical evidence to suggest a condition such as pneumonia or severe urinary tract infection. There was no clinical evidence of meningitis.

40. All the above conditions would have been ruled out as a matter of course during Claire's initial assessment. One is therefore left with a very worrying scenario, a child who has an altered level of consciousness and where the cause is not obvious. Whilst I would not be critical of anyone for not reaching a specific diagnosis at this time, her clinical presentation was sufficient to cause significant concern.

41. Having ruled out the above one is left with the very non-specific diagnosis, which is that of encephalopathy.

Encephalopathic illness is not uncommon in children. It frequently occurs as a complication of one of the viral illness such as measles, chickenpox or mumps. When associated with a specific infection the diagnosis is relatively straightforward, as one can find more common features of the disease. I suspect that my primary diagnosis would have been an encephalopathy secondary to an unknown viral infection. There was a history of vomiting and a mild tummy upset, and whilst one cannot explain the mechanism, certain viruses can cause this kind of presentation. Herpes simplex (which is the organism that causes cold sores) can cause encephalitis, so can enteroviruses. On admission therefore such an option would be at the top of my differential diagnosis.

42. Another diagnostic issue to consider is a so-called metabolic encephalopathy. I am responsible for the management of children with diabetes. A child who develops severe and protracted hypoglycaemia as a result of taking too much insulin or failure to take sufficient calories can develop a seizure, which would be followed by a period of altered consciousness. In serious cases this is associated with a degree of cerebral oedema. Indeed it may cause permanent neuronal damage. There is of course no evidence of such an event in Claire's case; I am using this example for illustrative purposes only.

Another disorder, more common during the 1970s and 80s, is Reye's syndrome. This is a very poorly understood disorder, which is thought to be linked to the prescribing of aspirin and / or some link with chickenpox. There are plenty of reports of Reye's Syndrome where there is no known aspirin or chicken pox contact. Children develop a liver disorder with an accompanying encephalopathy. It is disappointing that this disorder was not considered, and that there was a failure to arrange the necessary investigations, especially to check her liver enzymes and her serum ammonia level. Reye's syndrome is a serious disorder with a high mortality. Careful supportive therapy can make a significant difference.

43. I do not think that Claire had any of the rare inborn errors of metabolism, and which can create diagnostic confusion. Any such consideration is purely speculative, and I do not think that there is any purpose in exploring the matter in any detail.

44. I now turn to an interesting finding from the post mortem.

At post mortem the pathologist arranged analysis of the cerebral spinal fluid (CSF). The findings are interesting. The sample of CSF was unfortunately blood stained which makes interpretation more difficult. However the number of white cells (leucocytes) in the sample is far greater than what one would expect if the leucocytes reflected the normal "mix" of blood cells that had leaked into the CSF during the process of obtaining the CSF sample.

The CSF contained 300,000 RBCs and 4,000 leucocytes. This is a ratio of 1 : 75. I have looked at the results of Claire's blood tests during her admission. There were three, as follows.

21.10.96	RBC	3,760,000	white cells	16,520	ratio	1 : 228
23.10.96	RBC	3,660,000	white cells	9,350	ratio	1 : 391
23.10.96	RBC	3,860,000	white cells	5,540	ratio	1 : 696

Conventional teaching suggests that one should expect a ratio of 1 white cell (leucocyte) per 500 red cells if the blood found in a CSF sample has got there as a result of the sampling process. In Claire's case, the red cell : white cell ratio ***in the blood*** ranges from 1:228 to 1 : 696, consistent with conventional teaching.

The CSF analysis in Claire's case contain disproportionate number of leucocytes, giving this low ratio; 1:75. This suggests that Claire's CSF contained a genuine increase in white cells, which is what one would find in a patient with meningo-encephalitis. It is also important to note that these white cells were *"mostly lymphocytes"*. This is what one would expect in a patient with a meningo-encephalitis of viral cause.

Normally, in the blood stream, there are two major types of white cell, neutrophils and lymphocytes. In an acute infection one gets a rapid rise in the neutrophil count. In a viral infection one may get an early increase in neutrophil count, but it is not uncommon to have a normal total number of white cells, or indeed a relative increase in lymphocyte count.

Unfortunately, there is no information regarding the type of white cell found in Claire's blood. The figure relates to the total white count only. I would predict that her first result (16,520 white cells) would have contained mainly neutrophils. The figure had dropped to 5,540 by 24 Oct. It is likely that by this time the numbers of neutrophils and lymphocytes would have been similar. This is the result where the red cell : white cell ratio is highest (1 : 696) . Whilst interpreting these findings is far from being an exact science, the difference in ratios between the blood sample of 24 Oct (1 : 696) and the ratio on the CSF sample obtained the following day (1:75) makes it quite probable that there were

lymphocytes present in Claire's CSF, and that this is consistent with a diagnosis of viral meningo-encephalitis.

Observations on management

45. I have expressed my disappointment at the relative lack of investigations carried out early, particularly the failure to check Claire's plasma ammonia and her liver enzymes. Also, the medical care did not appear to have a "working diagnosis" or a "differential diagnosis" where one would list all possible options, if only to rule them out.

A "differential diagnosis" is a standard format used by all clinicians when working out the cause of a clinical disorder when the diagnosis is not immediately obvious. Interestingly, the handwritten entry comments on "viral infection". Encephalitis is also written down and is then crossed out. Clinically, I would be approaching the clinical management of Claire as a case of encephalopathy (and would not be particularly concerned if the term encephalopathy and encephalitis were used interchangeably. The former is a more generic descriptive term, whilst the term encephalitis suggests an infective disorder.)

46. The only investigations carried out soon after her admission were the basic ones, and my observations are as follows. Claire's haemoglobin was slightly low, and that is of no diagnostic help. Her white cell value (16,000) is raised. This is typical of an infection, but it does not distinguish the cause of the infection. I am rather surprised that a major children's hospital did not carry out a differential white count as a matter of course, providing information on the neutrophil count and lymphocyte count.

The medical officer queried the option of a lumbar puncture. This is the procedure carried out to obtain CSF, and is essential if one suspects meningitis. In the event, a lumbar puncture was not performed.

The only other investigation performed was the basic biochemistry. The key result is the sodium of 132. The laboratory's own reference range is 135 – 145. This range is quite wide. The key finding is that the sodium is low. Moreover the sodium is low in the presence of a normal potassium. The urea is normal at 4.5 (normal range 3.3 – 8.8). A normal urea suggests that Claire is not suffering any significant dehydration. I also note that the creatinine is at the lower end of the normal range at 36 (normal 40 – 110) but I am not sure that this is particularly useful as a pointer to confirming or ruling out any diagnosis.

The key result is the sodium of 132. It is low. Whilst a sodium of 132 is unlikely to cause any harm to a young child, within the context of Claire's clinical presentation it is of important **diagnostic** significance. It is not clear when the blood test was taken; I assume the test was taken soon after she was admitted to hospital (see also below). The sodium of 132 is therefore indicative of her biochemical balance **prior to the introduction of any intravenous fluids.**

There was no evidence of significant dehydration, for the reasons I have described above. Her pulse rate was a satisfactory 80. One would expect a pulse rate of 100 or more in any child who was significantly dehydrated.

47. In my opinion, a sodium of 132 at or soon after hospital admission is evidence that Claire was already showing signs of retaining fluid. The lowish creatinine value probably indicates the same thing. Within the context of her clinical condition; which is that she has an encephalopathy, one needs to consider seriously the possibility of her already experiencing the syndrome of inappropriate ADH (SIADH) secretion.

48. I enclose a summary of the pathophysiology and diagnosis of SIADH (Oski's Paediatrics, 2,206 – 7). Its consideration is essential to the safe management of any significantly ill child. The enclosed article contains a large list of disorders associated with this phenomenon. In clinical practice SIADH is most commonly associated with any severe systemic illness or a number of intracranial disorders such as head trauma, encephalitis or brain hypoxia. I shall comment on Claire's neurological observations later.

Intravenous fluid therapy

49. Claire weighed 24.1 kg. One calculates a child's fluid replacement as follows. One gives 100 ml / kg / 24 hours for the first 10 kg body weight, 50 ml / kg per 24 hours for the next 10 kg body weight and 20 ml / kg per 24 hours for every subsequent kg body weight. A girl of 24 kg would therefore require a total of 1,000 + 500 + 80 ml per 24 hours, a total of 1,580 ml per 24 hr, or 65 ml / hr. One would give additional fluid in a patient who was dehydrated, but this was not relevant here.

Claire's fluid chart confirms that the fluid replacement therapy *was "5/N saline at 64 ml/hr"*. The rate of fluid is therefore correct. The intravenous fluid prescription chart notes 0.18% NaCl plus 4% Dextrose. Between 23:00 hr on 21 Oct and 07:00 hr the following morning Claire receives 536 ml. This averages 60 ml / hr over 9 hours. The fluid chart also records seven separate episodes of vomit during this time.

50. I enclose a copy of the chapter on Fluid and Electrolyte Management from the "Advanced Paediatric Life Support" manual. The second edition was published in 1997. Whilst there is no controversy regarding the volume of fluid required, there is concern in paediatric circles regarding the type of fluid that should be prescribed. 0.18% sodium chloride with added glucose has been a commonly used fluid in paediatric practice and the 1997 edition continues to recommend it as a standard regime (page 249). It has been my practice to insist on the use of 0.45% NaCl as the standard fluid therapy for sick children, and cannot recall a time when I was comfortable with using 0.18% solution. I have always been concerned about the risk "waterlogging" a patient by giving too dilute a solution. That is, running the risk of a patient becoming oedematous (fluid overload) and sustaining a consequent drop in serum sodium. Whilst I would have prescribed 0.45% Dextrose from

the onset I have to acknowledge that, by 1996 standards, 0.18% solution remained a recommended regime in the published literature.

51. This takes me to my next observation, which is whether prescribing 0.18% NaCl was appropriate ***in this patient at this time***. In my opinion once it was known that Claire's sodium was 132 her fluid regime should have changed immediately to 0.45% NaCl. The fluid chart notes that intravenous therapy was only commenced at about 23:00 hr, so it is virtually certain that the value of 132 pre dates intravenous therapy i.e. Claire is showing evidence of fluid retention ***prior to receiving intravenous fluids***. In conjunction with her clinical encephalopathy, there is compelling grounds for considering a diagnosis of SIADH already.

I have commented earlier on the possibility of Reye's syndrome, and whilst there is insufficient evidence to confirm the diagnosis, the continued history of vomit is not atypical. The vomiting could also of course be a reflection of Claire now developing a gradual increase in intracranial pressure.

52. The fluid chart does not record Claire receiving any oral fluid from the time of admission, other than sips of water. One would therefore expect any history of vomiting to reduce both in volume and in frequency. The chart for the following day, from 08:00 onwards, does not record any further vomiting until two separate entries at midnight and 01:00 hr (a couple of hours before she collapsed) where she is noted to have brought up *"small mouthfuls"*.

53. The fluid chart notes that Claire has passed urine (PU) at 03:00 hr, 11:00 hr, 19:00 hr and 21:00 hr during Tuesday 22 Oct. The volume of urine is not recorded. The nursing entry records *"urinary catheter inserted 22.10.96"*. Time of insertion is not recorded. The entry is from the paediatric intensive care unit so I presume this occurred following her respiratory arrest (in the early hours of 23 Oct.

54. The nursing entry timed at 10 pm on the night of admission confirms *"two small bile stained vomits"*. A further bile stained vomit is recorded at 7 am.

55. There is no record of urinary volume and there is no evidence of any urine analysis (apart from one test looking for evidence of infection). There is therefore no information regarding urine concentration or urinary sodium or osmolality. These investigations can be carried out routinely, and results obtained quickly.

If Claire was passing urine voluntarily, measuring urine volume is straight forward, and assessing its concentration (osmolality) and sodium output should be a routine procedure. This is noted in the APLS protocol. If Claire's level of consciousness was associated with incontinence urinary catheterisation should have been performed as a routine procedure. Failure to conduct these measurements is indicative of unsatisfactory clinical practice. It was also unsatisfactory not to carry out a repeat blood electrolyte investigation (to monitor sodium, potassium , urea, creatinine and serum osmolality) on the morning following her admission. It is virtually certain that her sodium value would have fallen below

132, and any results below 130 would have alerted any medical practitioner to the possibility indeed probability of inappropriate fluid retention irrespective of whether this was part of the phenomenon of SIADH. The lower sodium would also have alerted any reasonable medical practitioner to the need to monitor urinary output obsessionally, and arrange the investigations described above.

In the event Claire's fluid management was not changed at all. I have already noted that she should have been placed on 0.45% NaCl as of midnight on the night of admission (when the sodium result returned at 132). I would have added potassium chloride (KCl) to her fluid regime from the outset. Her potassium level fell, although the failure to use KCl probably did not influence outcome, and I won't comment on this aspect of her care any further.

Claire was maintained on the same volume of fluid replacement throughout Tuesday 22 Oct. If the medical staff had repeated the blood serum sodium and monitored urinary sodium they would have had the option of adjusting fluid regime carefully and accurately. Increased sodium in the urine would have confirmed the diagnosis of SIADH, allowing treatment with a combination of adjusting fluid volume and prescribing a more concentrated sodium chloride solution. Getting the fluid balance right can be extremely tricky, and it would not be possible to describe in detail Claire's ideal fluid replacement; it would depend on regular monitoring of both serum and urinary sodium levels, and of course on her overall condition.

The other advantage of course of considering SIADH as part of Claire's condition is that it would strengthen the clinical impression of an encephalopathy.

56. I have seen the central nervous system (CNS) observation chart. It was only commenced at 1 pm on the day following admission. For the record, she should have been on a CNS observation chart (on "neuro obs") from her admission. *"Not responding to parents' voice"* and *"intermittently responding to deep pain"* are both indicators of a serious neurological disorder. Failure to place Claire on a CNS observation chart is indicative of unsatisfactory care.

The chart records the Glasgow Coma Scale (GCS). The results are extremely disturbing, more or less from 1 pm, where the score is 9. From 4 pm her response is limited to the ability to localise pain. Her pulse rate, blood pressure and respiratory rate remained pretty stable throughout.

The only information regarding possible seizure activity is the nursing entry timed at 3.15 pm on 22 Oct. In my opinion these symptoms reflect her worsening condition. Her Coma Chart was getting worse about the same time. The presumed seizure was a reflection, probably, of increased intracranial pressure, ie, a reflection of (relatively) early cerebral oedema. Given the absence of obvious seizure activity at admission, and during the next few hours, I do not think that this episode reflects primary epilepsy (or status epilepticus).

57. In my opinion Claire should have had an urgent CT scan on the day following her admission. Indeed there were grounds for demanding a scan first thing in the morning. She had shown

significant altered level of consciousness of nearly 12 hours by 9 am the following day; she was showing no sign of improvement, there was no obvious evidence of infection, and there were minor but significant biochemical abnormalities (sodium of 132) recorded from the previous evening. In my opinion failing to demand CT scan during Tuesday 22nd October is indicative of unsatisfactory care. The result is likely to have shown some evidence of cerebral oedema, allowing intervention with mannitol, plus accurate manipulation of intravenous fluid. One would also have the option of considering transfer to a high dependency area. I suspect that the hospital has a neurosurgery department, and there would be the option of considering intracranial pressure monitoring as well. Effective and frequent monitoring of both fluid intake and urinary output, plus intervention with mannitol if there was evidence of cerebral oedema on an earlier CT scan, could have led to a reversal of her symptoms, avoiding the catastrophe that she experienced in the early hours of the following day.

The issue of status epilepticus

58. The working diagnosis, at least from the 22nd Oct was "*non fitting status*", meaning status epilepticus. I disagree. The concept of "*non fitting status epilepticus*" is rather nebulous anyway, although I would recognise that such a phenomenon may occur, but typically in children who have a well documented history of epilepsy, usually difficult to control. Claire had experienced no seizures for years, and there is nothing in her history to suggest that she had any kind of seizure prior to admission or later. I would not have prescribed phenytoin, although I do not think that the phenytoin contributed to her demise in any way. I would not have prescribed midazolam. The problem with this drug is that it would have significantly altered her level of consciousness, confusing the natural picture.

If one makes the **hypothetical** assumption that Claire was experiencing status epilepticus it does not detract from the concerns and criticisms that I have regarding the failure to monitor her blood and urine frequently and the failure to organise CT scanning. After all, if Claire was experiencing status epilepticus (and I don't think she was) her condition was even more serious, and the need to arrange the above investigations was even more pressing.

The post mortem findings

59. I cannot possibly comment where two pathologists have prepared reports that have different conclusions. Neither has commented on the results of the post mortem CSF, and whilst I am comfortable with the interpretation described above, I need to add the caveat which is that I am not familiar with commenting on CSF analysis carried out after death. As far as I know, there would be no significant post mortem changes, although I would defer to a pathology or neuropathology opinion on this particular aspect of the case.

Summary

60. Claire was a young girl of 9 years who had a history of learning difficulties, probably following a serious neurological illness at the age of 8 months.

61. Claire presented to hospital with a relatively short history of vomiting and loose stools. She had been well enough to go to school on the day of her admission.

62. Her clinical condition showed a significant altered level of consciousness from her arrival in hospital. In the absence of a history of seizure activity, head trauma, or accidental drug ingestion, an encephalopathic illness should have been considered on the night of admission. I would not be critical of the failure to identify the specific cause of the encephalopathy.

63. Given her altered level of consciousness and a history of vomiting in a previously physically well child, investigations should have included tests to rule out Reye's syndrome. These would have included checking her liver enzymes, blood ammonia and prothrombin time. Reye's syndrome is a possible diagnosis, but it cannot be confirmed, given the failure to carry out the above tests, and the unavailability of liver tissue for post mortem examination.

64. The initial volume of intravenous fluid prescribed is consistent with current protocols. Whilst the use of 0.18% NaCl as fluid replacement therapy is one of the options available in the protocols of the time, the fluid should have been replaced by stronger concentration, in the form of 0.45% NaCl, as of midnight (when the biochemistry results showed a sodium value of 132).

65. A combination of clinical encephalopathy and low serum sodium should alert any medical practitioner to the possibility of SAIDH as an additional complication.

66. Irrespective of the significance of SAIDH, failure to change fluid to 0.45%, and the failure to monitor both the urine volume and also urine concentration and urinary sodium is indicative of a level of care that is below acceptable standards in a modern children's department in the British Isles during the 1990s. Accurate and frequent measurement of both serum and urine sodium values would have allowed careful attention to Claire's fluid balance, minimising the risk of cerebral oedema.

67. Failure to arrange CT scan at any time on the day following her admission is indicative of a level of care that falls significantly below acceptable standards in a modern children's department in the British Isles. There was compelling evidence of an encephalopathic illness for which there was no clear explanation. Her condition showed no sign of improving during the day; the CNS observation chart showed deterioration throughout the day.

Failure to place Claire on a CNS observation chart from her time of admission is also indicative of an unsatisfactory level of care by the standards of a modern children's department in the British Isles during the 1990s.

68. Careful monitoring of Claire's fluid balance, and arranging earlier CT scan, would have alerted medical staff to the earlier diagnosis of cerebral oedema. Earlier intervention, by means of mannitol, supported by the option of intensive monitoring in a children's intensive care unit, could have held up the progression of the cerebral oedema, reversed its effect, and prevented the respiratory arrest.

69. The cause of Claire's encephalopathy must remain speculative, in view of the difference of opinion of the two pathologists. The prodomal history of vomiting and loose stool, in association with the raised blood white cells at presentation, and the presence of an apparent increased number of lymphocytes in the post mortem CSF is consistent with a clinical diagnosis of meningo-encephalitis. The histological findings of the local pathologist are consistent with the clinical impression. The findings of the second pathologist do not support that diagnosis. I cannot possibly comment on the different interpretation of the two pathologists. I would advise that one obtains an additional opinion from Drs Herron and Harding, seeking their views on the post-mortem CSF findings, and whether the presence of 5,000 leucocytes (in a sample containing 300,000 red cells) is sufficient to warrant a diagnosis of meningo-encephalitis. The findings of "negative viral tests" does not rule out a viral cause for her encephalopathy.

70. There is no evidence in my opinion of Claire having had a seizure or that her condition was due to status epilepticus. The episode described at 3.15 pm on 22 Oct (my paragraph 18) was an indication of her worsening neurological condition, not the cause of it.

71. I am certain that the direct cause of death was cerebral oedema, and that the hyponatraemia was due initially to the syndrome of inappropriate ADH. The progression of the hyponatraemia was due to the failure to prescribe the appropriate fluid and the failure to take adequate measures to monitor sodium balance and the consequent failure to change both the type of fluid given and its volume. The failure was exacerbated by the delay in organising CT scanning, which led to the delay in identifying cerebral oedema.

72. There was no reasonable hope of recovery once Claire experienced her respiratory arrest during the early hours of Wednesday 23 Oct, when she sustained her respiratory arrest and was found to have fixed dilated pupils.

Specific questions from the Letter of Instruction of 23 Jan 2008

73. Whilst most of the queries have been answered, I include these responses separately, for completion. There may be some duplication.

73.1 Did cerebral oedema cause Claire's death?

Yes

73.2 Was hyponatraemia a factor?

Yes

73.3 What was the cause of the hyponatraemia?

See main report and paragraph 71

73.4 How sudden was the hyponatraemia...?

It was there from the time of the first blood test, and worsened during her admission.

73.5 Comments on care

This is detailed in the report.

73.6 Should we get a paediatric neurology opinion?

I think we should, but they are difficult to get. I enclose some names separately.

73.7 Was there a breach of duty of care?

In my opinion there was, and it's detailed in the report.

73.8 Did the breach of duty of care lead to her death, or contribute to it?

The breach of duty was significant. Unfortunately there is no way of knowing the cause of her encephalopathy. Encephalopathic illness in a child may take a very fulminant course despite optimal care. The presence of SIADH from early on in her illness is rather worrying, suggesting that there was something very serious going on right from the beginning. Her hyponatraemia become more significant, contributing to the eventual cerebral oedema.

73.9 Was the breach of duty gross?

There was a failure to plan the basics. The failures include lack of regular blood tests, lack of careful neurological observations, and a delay in getting neuro-imaging (CT or MRI) sorted. The staff failed to work out why Claire suffered an altered level of consciousness.

73.10 Other issues

The coroner should have been informed as a routine procedure. A child had died within a short time of hospital admission, and the cause was not obvious. The lack of agreement between the two pathology consultants is indicative of the complexity of this very tragic case.

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APPENDIX

B

Fluid and electrolyte management

INTRODUCTION

Fluid and electrolyte management is an essential part of both the immediate and the ongoing care of all sick children. In this Appendix we will look at the following:

- Normal requirements
- Dehydration
- Diabetic ketoacidosis
- Hypervolaemia
- Specific electrolyte problems

NORMAL REQUIREMENTS

Volume

Blood volume is about 100 ml/kg at birth, falling to about 80 ml/kg at one year. Total body water varies from just under 800 ml/kg in the neonate to about 600 ml/kg at one year, after this it varies little. Of this about two-thirds (400 ml/kg) is intracellular fluid, the rest being extracellular fluid. Thus initial expansion of vascular volume in a state of shock can be achieved with relatively small volumes of fluid: 20 ml/kg will usually suffice. However, this volume is only a fraction of that required to correct dehydration if the fluid has been lost from all body compartments: 20 ml/kg is 2% of body weight. Clinically, dehydration which is distributed across the fluid compartments rather than being restricted to the vascular compartment is not detectable until it is greater than 5% (50 ml/kg).

Much is spoken about normal fluid requirements, although in truth there is no such thing. We are all aware as adults that if we drink little we do not get dehydrated and if we drink lots we merely diurese. Healthy children's kidneys are just as capable of maintaining fluid balance. Fluids in neonates are often prescribed upon the basis of 150 ml/kg/day but this is not related to fluid needs but is merely the volume of standard formula milk required to give an adequate protein and calorie intake. What is required clinically is a simple means of prescribing fluid such that patients are maintained well hydrated and passing reasonable quantities of urine. This formula then has to be modifiable to take account of the need for rehydration of dry patients, and prevention of overhydration in patients in whom renal function is impaired or there is a reason to keep the patient underhydrated (for example, meningitis, cerebral oedema). Fluid requirement can be divided into four types:

1. For replacement of *insensible losses* through sweat, respiration, gastrointestinal loss etc.
2. For replacement of *essential urine output*, the minimal urine output to allow excretion of urea etc.
3. Extra fluid to maintain a *modest state of diuresis*.
4. Fluid to replace *abnormal losses* such as blood loss, severe diarrhoea, diabetic polyuria losses etc.

A formula for calculating normal fluid requirement is given in Table B.1 below. It is useful because it is simple, can be applied to all age ranges and is easily subdivided. The formula gives total fluid requirements, that is, types 1+2+3 above.

Table B.1. Normal fluid requirements

Body weight	Fluid requirement per day	Fluid requirement per hour
First 10 kg	100 ml/kg	4 ml/kg
Second 10 kg	50 ml/kg	2 ml/kg
Subsequent kg	20 ml/kg	1 ml/kg

For example: a 6 kg infant would require 600 ml per day
a 14 kg child would require 1000+200=1200 ml per day
a 25 kg child would require 1000+500+100=1600 ml per day

Electrolytes

To speak of normal electrolyte requirements is as artificial as speaking of normal fluid requirements. There are obligatory losses of electrolytes in stools, urine, and sweat, and these require replacement. Any excess is simply excreted in the urine. Table B.2 shows the electrolyte content of various body fluids and Table B.3 gives electrolyte "requirements" if there are not excessive losses from any compartment. In truth these "requirements" represent quantities that if given maintain homeostasis without recourse to the various hormonal and renal tubular mechanisms for maintaining the extracellular fluid composition.

Table B.2. Electrolyte contents of body fluids

Fluid	Na (mmol/l)	K (mmol/l)	Cl (mmol/l)	HCO_3 (mmol/l)
Plasma	135–141	3·5–5·5	100–105	24–28
Gastric	20–80	5–20	100–150	0
Intestinal	100–140	5–15	90–130	15–65
Diarrhoea	7–96	34–150	17–164	0–75
Sweat	<40	6–15	<40	0–10

Table B.3. Normal water, electrolyte, energy and protein requirements

Body weight	Water (ml/kg/day)	Sodium (mmol/kg/day)	Potassium (mmol/kg/day)	Energy (kcal/day)	Protein (g/day)
First 10 kg	100	2–4	1·5–2·5	110	3·00
Second 10 kg	50	1–2	0·5–1·5	75	1·50
Subsequent kg	20	0·5–1	0·2–0·7	30	0·75

Intravenous fluids are available in a variety of electrolyte compositions. In particular, there are a number of different strengths of dextrose and saline (often as a mixture in the same bag) – the concentration of sodium being expressed in mmol/l on the side of the infusion bag, as well as a percentage. Always check the sodium concentration in mmol/l is actually what you require and take great care to specify the concentration of both the dextrose and the saline (if a dextrose/saline solution is being used) when writing the prescription to avoid ambiguity. Tables B.4 and B.5 show the composition of commonly available fluids.

Table B.4. Commonly available crystalloid fluids

Fluid	Na^+ (mmol/l)	K^+ (mmol/l)	Cl^- (mmol/l)	Energy (kcal/l)	Other
Isotonic crystalloid fluids					
Saline 0·9%	150	0	150	0	0
Saline 0·45%, dextrose 2·5%	75	0	75	100	0
Saline 0·18%, dextrose 4%	30	0	30	160	0
Dextrose 5%	0	0	0	200	0
Saline 0·18%, dextrose 4%, 10 mmol KCl/500 ml	30	20	50	160	0
Hartmann's solution	131	5	111	0	Lactate
Hypertonic crystalloid solutions					
Saline 0·45%, dextrose 5%	75	0	75	200	0
Dextrose 10%	0	0	0	400	0
Saline 0·18%, dextrose 10%	30	0	30	400	0
Dextrose 20%	0	0	0	800	0

Table B.5. Commonly available colloid fluids

Colloid solutions	Na^+ (mmol/l)	K^+ (mmol/l)	Ca^{2+} (mmol/l)	Duration of actions (hours)	Comments
Albumin 4·5%	150	1	0	6	Protein buffers H^+
Gelofusine	154	<1	<1	3	Gelatine
Haemaccel	145	5	12·5	3	Gelatine
Pentastarch	154	0	0	7	Hydroxyethyl starch

DEHYDRATION

Dehydration is the result of abnormal fluid losses from the body which are greater than the amount for which the kidneys can compensate. The natural mechanisms for compensation have the primary aim of maintaining circulating volume and blood pressure at all cost. Thus the majority of patients with dehydration maintain their central circulation satisfactorily. Loss of central circulatory homeostasis constitutes *hypovolaemic shock* and is dealt with in Chapter 10.

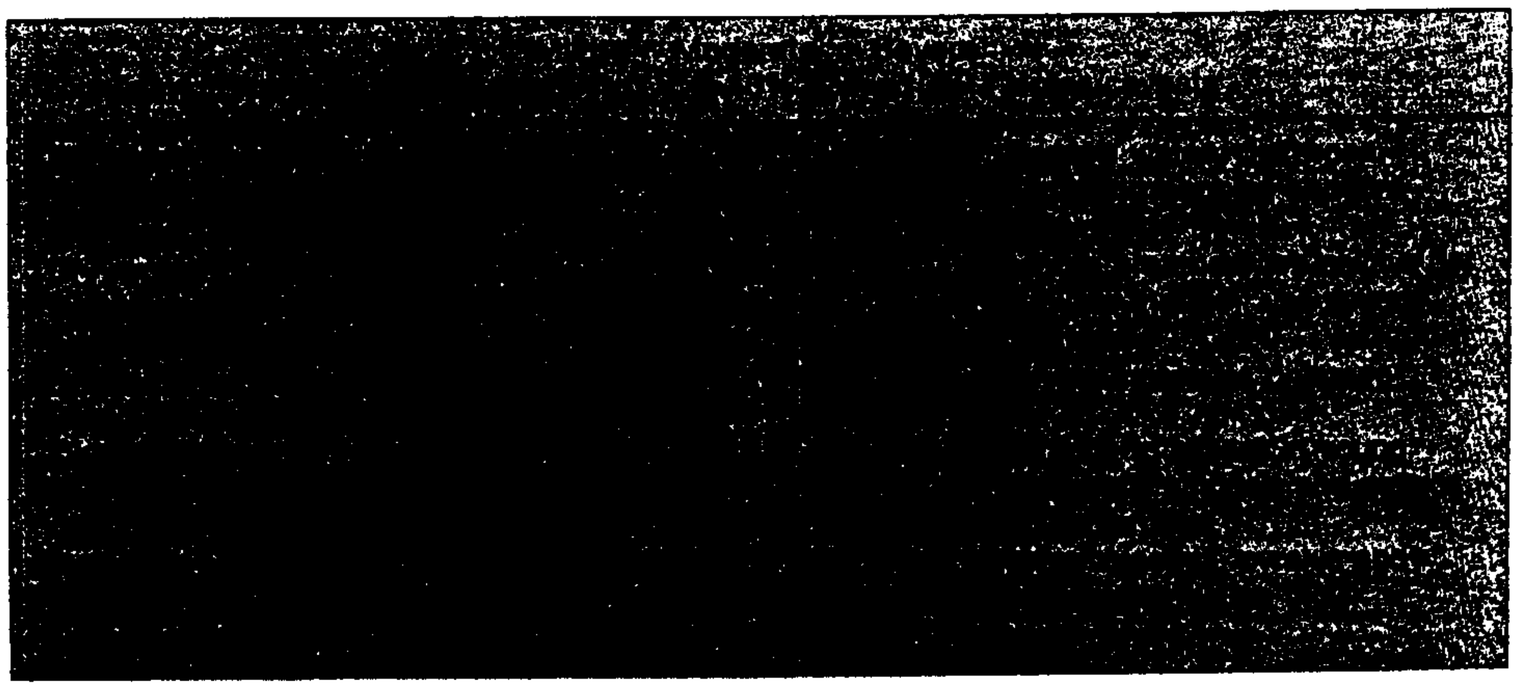
The major causes of dehydration in children are gastrointestinal disorders and diabetic ketoacidosis. Some renal disorders (polyuric tubulopathy with urinary tract infection, polyuric chronic renal failure and diabetes insipidus) might also present in this way. Depending on the source of fluid losses and the quantities of electrolytes lost (Table B.3), dehydration can be divided into three types:

1. Isotonic dehydration – sodium and water lost in proportion to each other.

2. Hyponatraemic dehydration – more sodium lost than water proportionately.
3. Hypernatraemic dehydration – more water lost than sodium proportionately.

In all three types there is usually a total body deficit of *salt and water.* Between the three types the relative amounts of salt and water loss vary. Table B.6 shows the symptoms and signs of dehydration and gives a guide towards the assessment of the degree of dehydration. On the whole, the more severe the dehydration the more likely that hypovolaemia will be a problem; most patients with more than 10% dehydration are hypovolaemic at presentation. However, speed of fluid loss is important. Slow, prolonged losses can give rise to massive dehydration without hypovolaemia, similarly acute, severe loss can present as hypovolaemia without apparent significant dehydration. The latter is not infrequently the case in acute gastroenteritis in infants where acute fluid loss into the bowel causes hypovolaemia and the patient can present even before any diarrhoea has occurred.

Table B.6. Symptoms and signs of dehydration



Management of dehydration

Mild dehydration (<5%) can usually be managed with oral rehydration if vomiting is not a major problem. Oral rehydration fluids are better absorbed if they contain a small amount of sodium and glucose in addition to water. Commercial preparations contain, for example, 35–50 mmol of sodium per litre when made up as instructed.

Moderate and severe dehydration will require more accurate replacement of fluid loss and although oral rehydration may sometimes be possible, intravenous therapy may be needed.

For fluid balance purposes, as the body is mostly water, a weight loss of 1 kg equals a fluid loss of 1 litre, as one millilitre of water weighs one gramme. Thus fluid loss or gain can be measured easily by weighing the patient. The child's fluid deficit can be worked out from the child's weight and a clinical assessment of the percentage dehydration. For example, a 10 kg child is 7·5% dehydrated. How much fluid will the child need for rehydration and what sodium concentration will be required?

The child will need maintenance + replacement of deficit. Calculate them separately and add them up.

Step 1

What is the fluid deficit?

7·5% of 10 kg = 0·75 kg = 750 g
750 g is the weight of 750 ml fluid

A convenient formula to remember is:

Percentage dehydration × Weight in kg × 10 = Fluid deficit (ml)

Thus the fluid deficit is 750 ml. The fluid deficit is essentially made up from (roughly) 0·9% saline (which has 150 mmol/l) since it is mainly extracellular fluid that has been lost which has a sodium concentration of approximately 140 mmol/l.

Step 2

The child also needs maintenance fluids. These can be worked out in the normal way. A 10 kg child will need 10 × 100 ml/day for normal maintenance (Table B.1) = 1000 ml. The sodium required for maintenance (Table B.3) will be approximately 3 mmol/kg × 10 kg = 30 mmol/day.

In total, then, the child needs 1000 ml maintenance plus 750 ml replacement of losses, totalling 1750 ml, for adequate rehydration.

If we were following the sums exactly we should put up two drips – one of 750 ml with sodium of 140 mmol/l and another of 1000 ml with 30 mmol of sodium. As fluid balance is not often an exact science (ongoing losses, clinical estimations etc.), it is usually more convenient to pick one intravenous fluid with a sodium concentration somewhere between the two and give the total volume using this. The fluid which fits this specification best in this case is 0·45% saline, which has 75 mmol/l. This can be changed to fluid containing more or less sodium depending on subsequent serum sodium results. To make it isotonic 0·45% saline is usually made up with 2·5% dextrose. Beware of using IV fluids with no dextrose in small children as they may become hypoglycaemic.

In patients with a low or normal sodium lost fluid can be replaced over 24 hours. In hypernatraemic patients it must be replaced over at least 48 hours and sometimes longer depending on the severity – the higher the sodium the slower the rehydration must be. If the sodium and water are corrected too rapidly in the extracellular space, water will pour into cells, and if this happens in the brain, cerebral oedema and even death may occur. Aim to bring down the serum Na in a hypernatraemic patient by no more than 5 mmol per day, for example, in an infant who presents with a Na of 170 mmol/l, the Na should be no less than 165 mmol/l by the next day. In these patients, the electrolytes should be checked 4-hourly, at least initially.

The very sick child

In the very sick child it may be uncertain whether normal homeostatic mechanisms will work. The patient may be progressing into renal failure and be oliguric or inappropriately polyuric. In such cases the best management is to:

- Catheterise the patient.
- Calculate and replace deficit, over 24 hours, with normal saline.
- Calculate insensible losses and replace with 0·18% saline, 4% dextrose.
- Measure urine output and replace ml for ml on an hourly basis with 0·18% or 0·45% saline with dextrose according to the plasma electrolytes.

This technique is applicable to all patients with all conditions in all states of hydration. Moreover, subsequent measurement of urinary electrolytes can allow exact tailoring of IV fluids to maintain normal serum electrolytes.

DIABETIC KETOACIDOSIS (DKA)

DKA is a special case in which a relative or absolute lack of insulin leads to an inability to metabolise glucose. This leads to hyperglycaemia and an osmotic diuresis.

Once urine output exceeds the ability of the patient to drink, dehydration sets in. In addition, without insulin, fat is used as a source of energy leading to the production of large quantities of ketones and metabolic acidosis. The latter is initially compensated for by hyperventilation and a respiratory alkalosis but, as the condition progresses, the combination of acidosis, hyperosmolality, and dehydration leads to coma. DKA is often the first presentation of diabetes; it can also be a problem in known diabetics who have decompensated through illness, infection or non-adherence to their treatment regimes.

History

The history is usually of weight loss, abdominal pain, vomiting, polyuria, and polydipsia, though symptoms may be much less specific in under-5 year olds who also have an increased tendency to ketoacidosis.

Examination

Children are usually severely dehydrated with deep and rapid (Kussmaul) respiration. They have the smell of ketones on their breath. Salicylate poisoning and uraemia are differential diagnoses to be excluded. Infection often precipitates decompensation in both new and known diabetics, and must be sought.

Management

Assess

- Airway.
- Breathing.
- Circulation.

Give 100% oxygen and place on a cardiac monitor. Hypokalaemia can cause dysrhythmias.

Site IV infusion and begin fluid replacement. If shock is present, treat as discussed in Chapter 10.

Take blood for:

- Bicarbonate/blood gases.
- Urea and electrolytes, creatinine, calcium, albumin.
- Glucose.
- Culture.
- Haemoglobin and differential white cell count.

Take urine for:

- Culture.
- Sugar.
- Ketones.

Fluids

Children with DKA will have lost a great deal of sodium, whatever their initial measured plasma sodium. Normal saline is the correct initial fluid. The principles of fluid management outlined above work as well for DKA as for any other cause of dehydration. However, because of the hyperglycaemia it is often best not to give dextrose initially. Thus, having calculated deficit, maintenance, and 24-hour requirement, this can initially be given all as normal saline, switching to 0·45% saline or 0·18% saline with dextrose once the blood sugar has fallen. With the osmotic diuresis, which will

persist until the blood sugar falls, calculated fluid requirements will be an underestimate and ongoing fluid replacement should be recalculated 4 hourly to take into account excess fluid losses. Potassium should be added to the fluids (20–40 mmol/l initially) once a urine output has been confirmed. There is a loss of potassium in DKA and, additionally, the use of insulin will drive potassium into cells, further lowering the plasma potassium.

Insulin

Insulin ought to be given by continuous infusion. The initial dose is 0·1 units/kg/hour. Once the blood sugar falls to less than 10 mmol/l, glucose must be added to the IV. *Do not stop using insulin. This is the child's prime requirement.* Administer the insulin by separate line. Add 50 units of soluble insulin to 50 ml saline. This solution is 1 unit/ml: 0·1 units/kg/hour is equal to 0·1 × weight in kg, as ml/hour. Thus a 20 kg child would have 2 ml/hour, a 35 kg child 3·5 ml/hour. This often needs decreasing to 0·05 units/kg/hour when blood sugar starts to fall. In a very young diabetic (under 5 years), start with the smaller dose.

Acidosis

The acidosis of DKA is initially compensated for by hyperventilation. Once the blood pH falls below 7·1, CNS depression can occur and this can prevent compensation. Almost always acidosis will correct with correction of fluid balance and cessation of ketosis following insulin therapy. Bicarbonate should be avoided unless the blood pH is less than 7·0, or less than 7·1 and not improving after the first few hours of fluid and insulin therapy. Many formulas exist relating the base excess to the child's weight and the bicarbonate requirement. However, because of the logarithmic relationship between $[H^+]$ and pH a dose of 2·5 ml/kg of 8·4% $NaHCO_3$ will correct the pH to 7·2 or 7·3 in all cases. This should be administered slowly over 2 hours by infusion. Recheck the pH after the first hour and stop the infusion if the pH is above 7·15 as the rest will correct naturally.

Other treatments

A nasogastric tube is essential as acute gastric dilatation is a complication. Depending on the level of consciousness, bladder catheterisation may be required. Antibiotics may be indicated.

Monitoring progress

Use a flow sheet to record vital signs, neurological status, input and output of fluids, blood results and insulin infusion rates. Record urine ketones and glucose. Initially, whilst IV insulin is in use, check blood sugar, biochemistry and acid–base status 2-hourly.

Regular, frequent (i.e. initially half-hourly) assessment of conscious level by the Glasgow Coma Score is required to recognise early cerebral oedema. This complication of diabetic ketoacidosis is uncommon but may be devastating. It is not confined to children with severe illness. Early recognition of reduced conscious level should lead to measures to reduce raised intra cranial pressure, and transfer to intensive care for intra cranial pressure monitoring.

Complications

Major complications of diabetic ketoacidosis

Cerebral oedema	Prevent by slow normalisation of sugar and hydration over 36–48 hours; monitor GCS; treat with mannitol and hyperventilation. Inform neurosurgeons. ?CT scan. ?Monitor ICP
Cardiac dysrhythmias	Usually secondary to electrolyte disturbances, particularly potassium
Acute renal failure	Uncommon because of high osmotic urine flow

All of these complications require intensive monitoring on an intensive care unit.

HYPERVOLAEMIA

Hypervolaemia in children is uncommon and is usually due to either cardiac or renal failure. Occasionally water intoxication due to deliberate ingestion of water or excessive administration of desmopressin (DDAVP) may be the cause.

Signs of hypervolaemia include raised venous pressure, a triple rhythm on auscultation of the heart, and pulmonary crackles. Hypertension may be present, particularly in fluid overload of renal origin. Treatment of hypervolaemia is initially with diuretics. These may be ineffective, particularly in renal failure, in which case urgent dialysis may be needed. Oxygen may be required and in severe cases positive pressure ventilation may be needed to maintain adequate oxygenation because of pulmonary oedema.

β-blockers are contraindicated in hypervolaemia, because of the risk of cardiac failure.

Water intoxication will usually present as convulsions from cerebral oedema and hyponatraemia. Treatment is along the usual lines for patients with convulsions and coma (Chapters 12 and 13). Severe fluid restriction will be necessary, and if hyponatraemia is severe (<120 mmol/l), fluids ought to be given as 0·9% saline. Diuretics, particularly mannitol, which causes a free water diuresis and reduces cerebral oedema, are sometimes of value.

Mild oedema may occur in any of these conditions. Severe oedema does not, and when present, is usually a manifestation of nephrotic syndrome. This is important as patients with nephrotic syndrome are intravascularly fluid depleted and diuretics are contraindicated.

SPECIFIC ELECTROLYTE PROBLEMS

Sodium

Sodium is the major extracellular cation. Its movement is inextricably linked to that of water. Disorders of sodium balance are, therefore, those of over- and under-hydration, and are dealt with in the section on fluid and electrolyte problems.

Potassium

Unlike sodium, potassium is mainly an intracellular ion and the small quantities measurable in the serum and extracellular fluid represent only a fraction of the total body potassium. However, the exact value of the serum potassium is important as cardiac arrhythmias can occur at values outside of the normal range. As the majority of potassium is stored intracellularly this acts as a large buffer to maintain the serum value within its normal narrow range. Thus hypokalaemia is usually only manifest

after significant total body depletion has occurred. Similarly, hyperkalaemia represents significant total body overload, beyond the ability of the kidney to compensate. The exception to both these statements is the situation in which the cell wall pumping mechanism is breached. A breakdown of the causes of hyper- and hypokalaemia is given in Table B.7.

Table B.7. Causes of hypo- and hyperkalaemia

Hypokalaemia	Hyperkalaemia
Diarrhoea	Renal failure
Alkalosis	Acidosis
Volume depletion	Adrenal insufficiency
Primary hyperaldosteronism	Cell lysis
Diuretic abuse	Excessive potassium intake

Hypokalaemia

Hypokalaemia is rarely a great emergency. It is usually the result of excessive potassium losses from acute diarrhoeal illnesses. As total body depletion will have occurred, large amounts are required to return the serum potassium to normal. The fastest way of giving this is with oral supplementation. In cases where this is unlikely to be tolerated, IV supplements are required. However, strong potassium solutions are dangerous and can precipitate arrhythmias, thus the concentration of potassium in IV solutions ought not to exceed 80 mmol/l. Fortunately this is not usually a problem as renal conservation of potassium aids restoration of normal serum levels.

Patients who are alkalotic, hyperglycaemic (but not diabetic), or are receiving insulin from exogenous sources will have high intracellular potassium stores. Thus hypokalaemia in these cases is the result of a redistribution of potassium rather than potassium deficiency and treatment of the underlying causes is indicated.

Hyperaldosteronism is a cause of hypokalaemic alkalosis. Patients with this condition will have salt and water retention and will be hypertensive on presentation. Isolated primary hyperaldosteronism is the body's natural response to hypovolaemia and salt deficiency. Thus secondary hyperaldosteronism is a common cause of hypokalaemic alkalosis. As there is primary salt and water deficiency the patient is not usually hypertensive. The most common causes are diarrhoeal illness and salt-losing conditions such as cystic fibrosis. External loss of fluid from intestinal ostomies or drains are other causes. Although potassium replacement is required in this condition the main thrust of therapy has to be with salt and water replacement to re-expand the circulation and cut down on aldosterone production.

Hyperkalaemia

Hyperkalaemia is a dangerous condition. Although the normal range extends up to 5·5 mmol/l it is rare to get arrhythmias below 7·5 mmol/l. The most common cause of hyperkalaemia is renal failure – either acute or chronic. Hyperkalaemia can also result from potassium overload, loss of potassium from cells due to acidosis or cell lysis, hypoaldosteronism and hypoadrenalism.

The immediate treatment of hyperkalaemia is shown schematically in Figure B.1. If there is no immediate threat to the patient's life because of an arrhythmia then a logical sequence of investigation and treatment can be followed. β_2 stimulants, such as salbutamol, are the immediate treatment of choice. They act by stimulating the cell wall pumping mechanism and promoting cellular potassium uptake. They are best administered by nebuliser. The dose to be given is shown in Table B.8. The serum potassium will fall by about 1 mmol/l with these dosages.

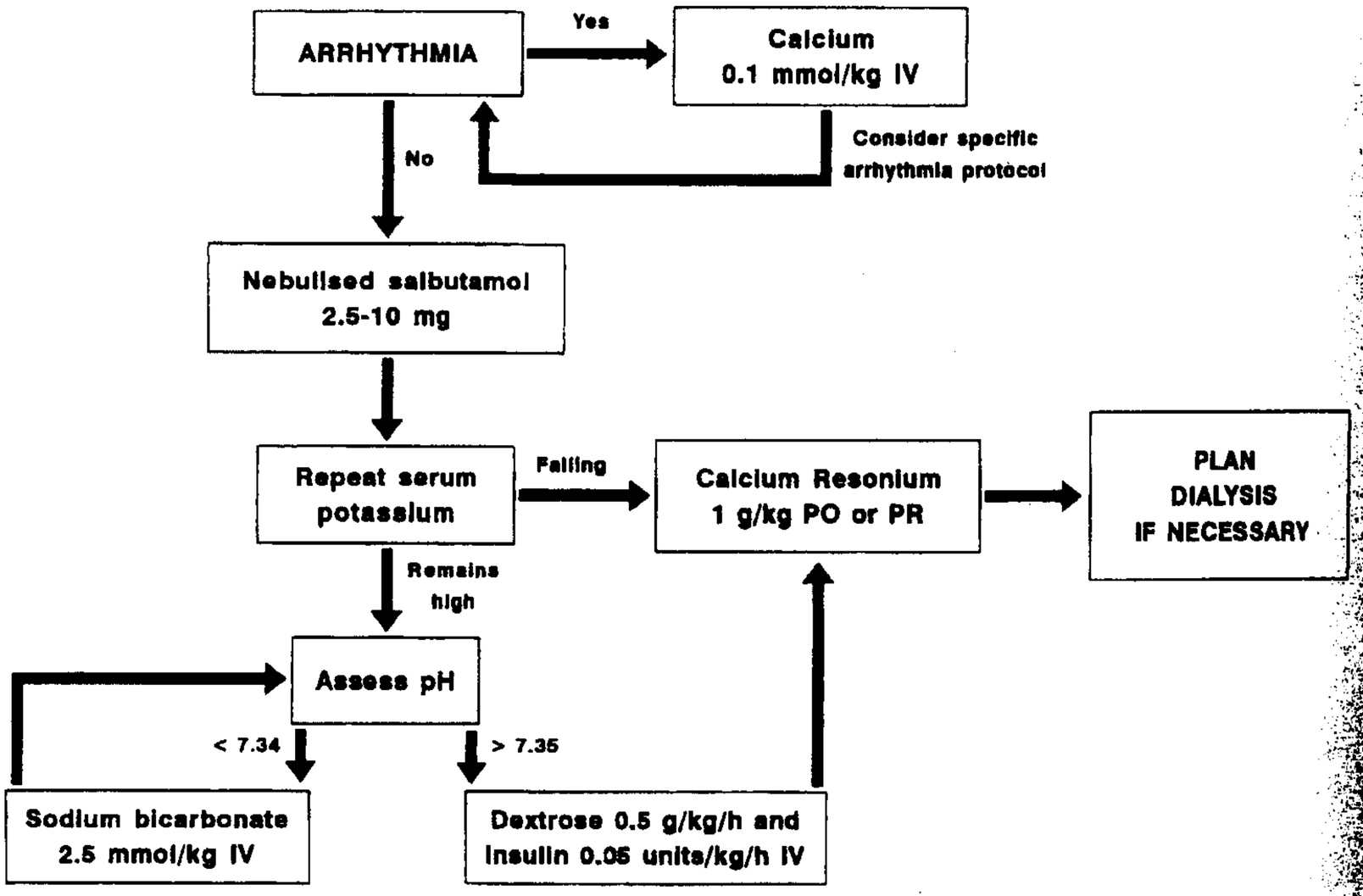


Figure B.1. Algorithm for the management of hyperkalaemia

Table B.8. Salbutamol dose by age

Age (years)	Salbutamol dose (mg)
≤2·5	2·5
2·5–7·5	5
>7·5	10

Sodium bicarbonate is also effective at rapidly promoting intracellular potassium uptake. The effect is much greater in the acidotic patient (in whom the hyperkalaemia is likely to be secondary to movement of potassium out of the cells). The dosage is the same as that used for treating acidosis and 2·5 ml/kg of 8·4% $NaHCO_3$ is usually effective. It is mandatory to also check the serum calcium, since particularly in patients with profound sepsis or renal failure, hyperkalaemia can be accompanied by marked hypocalcaemia. The use of bicarbonate in these situations can provoke a crisis by lowering the ionised calcium fraction, precipitating tetany, convulsions or hypotension and arrhythmias.

Insulin and dextrose are the classic treatment for hyperkalaemia. They are not, however, without risks. It is very easy to precipitate hypoglycaemia if monitoring is inadequate. Large volumes of fluid are often used as a medium for the dextrose and particularly in the patient with renal failure, hypervolaemia and dilutional hyponatraemia can then be a problem. Many patients are quite capable of significantly increasing endogenous insulin production in response to a glucose load and this endogenous insulin is just as capable of promoting intracellular potassium uptake. It thus makes sense to start treatment with just an intravenous glucose load and then to add insulin as the blood sugar rises. The initial dosage of glucose ought to be 0·5 g/kg/hour, i.e. 2·5 ml/kg/hour of 20% dextrose. Once the blood sugar is above 10 mmol/l, insulin can be added if the potassium is not falling. The dosage of insulin is initially half that used in diabetic ketoacidosis, i.e. 0·05 units/kg/hour. This can then be titrated according to the blood sugar.

The above treatments are the fastest means of securing a fall in the serum potassium but all work through a redistribution of the potassium into cells. Thus the problem is merely delayed rather than treated in the patient with potassium overload. The only ways of removing potassium from the body are with dialysis or ion exchange resins such as calcium resonium. If it is anticipated that the problem of hyperkalaemia is going to persist then the use of these treatments ought not to be delayed. Dialysis can only be started when the patient is in an appropriate environment. Ion exchange resins can be used at the outset. The dosage of calcium resonium is 1 g/kg as an initial dose either orally or rectally, followed by 1 g/kg/day in divided doses.

In an emergency situation where there is an arrhythmia (heart block or ventricular arrhythmia) the treatment of choice is intravenous calcium. This will stabilise the myocardium but will have no effect on the serum potassium. Thus the treatments discussed above will still be necessary. The dosage is 0·5 ml/kg of 10% Ca gluconate (i.e. 0·1 mmol/kg Ca). This dose can be repeated twice.

Calcium

Some mention of disorders of calcium metabolism is relevant as both hyper- and hypocalcaemia can produce profound clinical pictures.

Hypocalcaemia

Hypocalcaemia can be a part of any severe illness, particularly septicaemia. Other specific conditions that may give rise to hypocalcaemia are severe rickets, hypoparathyroidism, pancreatitis, or rhabdomyolysis, and citrate infusion (in massive blood transfusions). Acute and chronic renal failure can also present with severe hypocalcaemia. In all cases hypocalcaemia can produce weakness, tetany, convulsions, hypotension, and arrhythmias. Treatment is that of the underlying condition. In the emergency situation, however, intravenous calcium can be administered. As most of the above conditions are associated with a total body depletion of calcium and as the total body pool is so large, acute doses will often only have a transient effect on the serum calcium. Continuous infusions will also often be required, and must be given through a central venous line as calcium is so irritant in peripheral veins. In renal failure, high serum phosphate levels may prevent the serum calcium from rising. The use of oral phosphate binders or dialysis may be necessary in these circumstances.

Hypercalcaemia

Hypercalcaemia usually presents as long-standing anorexia, malaise, weight loss, failure to thrive and vomiting. Causes include hyperparathyroidism, hypervitaminosis D or A, idiopathic hypercalcaemia of infancy, malignancy, thiazide diuretic abuse and skeletal disorders. Initial treatment is with volume expansion with normal saline. Following this, investigation and specific treatment are indicated.

ADVANCED PAEDIATRIC LIFE SUPPORT

The Practical Approach

Fourth edition

Advanced Life Support Group

Edited by
Kevin Mackway-Jones
Elizabeth Molyneux
Barbara Phillips
Susan Wieteska

BMJ Books

Blackwell Publishing

CR - PSNI

096-022-153

APPENDIX

B

Fluid and electrolyte management

B.1 INTRODUCTION

Between 70 and 80% of a child's body is made up of water. That water is distributed between the intracellular, interstitial and intravascular spaces. Fluid moves from one compartment to another depending on various pressure and osmotic gradients. In illness and injury these fluid shifts may be rapid, with significant clinical consequences.

B.2 FLUID BALANCE

In health, fluid balance is tightly controlled by thirst, hormonal responses and renal function. In this context the formulae in Table B.1 provide a guideline to appropriate fluid intake. These formulae are based on an assumption of 100 kcal/kg/day of caloric intake, 3 ml/kg/day of urine output and normal stool output.

Table B.1. Normal fluid requirements

Body weight	Fluid requirement per day (ml/kg)	Fluid requirement per hour (ml/kg)
First 10 kg	100	4
Second 10 kg	50	2
Subsequent kilograms	20	1

For example, a 6-kg infant would require 600 ml/day,

a 14-kg child would require $1000 + 200 = 1200$ ml/day and
a 25-kg child would require $1000 + 500 + 100 = 1600$ ml/day.

In critical illness or injury some or all of these mechanisms may be profoundly disrupted, and fluid therapy has to be tailored to the needs of the specific child. In the presence of acute respiratory or CNS pathology, fluid requirements may be as low as 30 ml/kg/day, while in diarrhoea requirements may be as high as 300–400 ml/kg/day.

Fluid intake is required to replace fluid losses, and to enable the excretion of various waste products through the urine. Insensible losses (via respiration, sweat) generally

amount to between 10 and 30 ml/kg/day. The actual volume of insensible fluid loss is related to the caloric content of the feeds, the ambient temperature, humidity of inspired air, presence of pyrexia and the quality of the skin. Insensible losses from a child on a ventilator in a cool environment and with minimal caloric intake may be minimal. Usually between 0 and 10 ml/kg/day are lost in stool (obviously this will increase markedly in diarrhoea, where losses in excess of 300 ml/kg/day are not uncommon). Urinary losses are between 1 and 2 ml/kg/hour (i.e. approximately 30 ml/kg/day).

Dehydration and shock

Concepts

1) Dehydration does not cause death, shock does. Shock may occur with the loss of 20 ml/kg, while clinical dehydration is only evident after losses of >25 ml/kg.
2) The treatment of shock requires rapid administration of intravascular volume of fluid that approximates in electrolyte content to plasma.
3) The treatment of dehydration requires gradual replacement of fluids, with electrolyte content that relates to the electrolyte losses, or to the total body electrolyte content.
4) Damage from electrolyte changes is related to either extreme levels, or rapid rates of change.
5) Administration of sodium bicarbonate is rarely indicated.
6) Overhydration is potentially much more dangerous than dehydration.

The intravascular volume is approximately 80 ml/kg. Rapid loss of 25% of this volume (i.e. 20 ml/kg) will cause shock unless that volume is replaced from the interstitial fluid at a similar rate. Clinical signs of dehydration (see table) only occur when the patient is 2.5–5% dehydrated. Five percent dehydration implies that the body has lost 5 g/100 g body weight, i.e. 50 ml/kg. Clearly, shock may occur in the absence of dehydration, dehydration may occur in the absence of shock or both may occur together – all dependent on the rate of fluid loss and the rate of fluid shifts.

Fluid and electrolyte losses occur in a number of situations:

Abnormal renal losses

- abnormal renal function (both high and low urine output may occur)
- endocrine problems: both high (e.g. diabetes mellitus, diabetes insipidus) and low urine output (syndrome of inappropriate ADH secretion) may occur

Abnormal GIT losses

- Mostly high output, with vomiting, diarrhoea or both.
- Abnormal intake: excessive intake may be iatrogenic, with excessive fluid administration; accidental excessive intake of electrolytes such as sodium may occur, and occasionally this may be given deliberately (a form of child abuse).

The priorities of management are to identify shock and treat it effectively and rapidly (see chapter 9), identify dehydration and devise a treatment programme that will enable effective rehydration over 24–48 hours, identify the presence and aetiology of acid–base problems and correct these where necessary, identify the presence and aetiology of electrolyte abnormalities and correct these gradually without precipitating complications.

One factor remains unknown at the initiation of therapy, namely the ongoing fluid losses that will occur during therapy. Thus any plan of fluid management represents a starting point, and this will have to be modified in the light of data from constant monitoring.

The critical clinical questions are therefore:

Is the patient shocked?
Is the patient dehydrated?
Does the patient have a significant acid–base abnormality?
Are there significant electrolyte problems?

Shock

The clinical signs of shock from fluid loss are:

Cardiovascular signs	Tachycardia usually associated with poor volume peripheral pulses Poor peripheral perfusion with prolonged capillary refill time and cool peripheries Low blood pressure as a pre-terminal sign
Consequences of poor perfusion	Alteration of mental status Development of metabolic acidosis with compensatory tachypnoea Poor urine output

The treatment of hypovolaemic shock secondary to fluid loss (after securing the airway and providing high-flow oxygen) is the rapid administration of crystalloid. The starting volume is 20 ml/kg, and this can be repeated if there is inadequate clinical response (with no evidence of intravascular overload). The fluids used should approximate in electrolyte concentrations to those of serum (options include 0.9% saline, Hartmann's solution). The presence of hyper- or hyponatraemia does not affect the choice of fluids during this phase of resuscitation.

Occasionally, shock may be precipitated by cardiac dysrhythmia secondary to electrolyte abnormalities (most commonly of potassium). In this situation rapid correction of the electrolyte anomaly may be essential. Usually electrolyte abnormalities should be corrected gradually.

Once shock has been adequately treated, attention can turn to management of hydration. Frequent reassessment is however necessary, as the patient may well become shocked again if the basic cause of the fluid shifts (e.g. gastro-enteritis) is ongoing.

Dehydration

The clinical signs of dehydration are:

Sign	Comment
Drop in weight	Only objective measure of acute change in hydration Unfortunately the child's pre-illness weight is usually not available, and so this is rarely useful in the initial evaluation of the child
Depressed fontanelle	Only useful if fontanelle well-patent, and in absence of disorders such as meningitis
Sunken eyes	Mothers may well recognize this sign, but it is poorly reproducible among clinical staff, especially if brief contact with the patient

(Continued)

Sign	Comment
Dry mouth	Mouth breathers tend to have dry mouths, and mouth will be wet if fluids have just been administered orally.
Decreased skin turgor	Difficult to interpret in malnourished children. Particularly unreliable in fat children and in children with hypernatraemic dehydration.
Decreased urine output	In renal disorders, patient may be dehydrated in association with inappropriately high urine output (same happens in diabetes). In the presence of gastroenteritis it is very difficult to establish urine output accurately, particularly in girls.

The clinical signs of dehydration are individually unreliable (see table) and have poor inter-observer reproducibility, but taken together they provide a reasonable estimate of total body fluid losses. Weight is the only objective measure of total body fluid shifts, and enables an accurate assessment of fluid balance over time (unfortunately initial fluid therapy must usually be based on a clinical assessment of hydration because the pre-sickness weight is usually not available).

The weight loss or percentage dehydration (5% dehydration = loss of 5 ml of fluid per 100 g body weight, or 50 ml per kg) provides an estimate of the volume of fluid required to replace the dehydration.

Management of dehydration consists of administration of calculated daily maintenance fluids in addition to calculated replacement fluids over a 24-hour period. The patient should thus achieve normal body weight over a 24-hour period (this may increase to 48 hours if there are electrolyte problems). Therapy must be monitored at 3–4-hourly intervals using weight as an objective measure, to ensure that the patient is gaining weight at an appropriate rate. If the calculated fluid administration rate is too slow or too fast, then the rate should be modified appropriately.

Table B.2. Commonly available crystalloid fluids

Fluid	Na^+ (mmol/l)	K^+ (mmol/l)	Cl^- (mmol/l)	Energy (kcal/l)	Other
Isotonic crystalloid fluids					
Saline 0·9%	150	0	150	0	0
Saline 0·45%, dextrose 2·5%	75	0	75	100	0
Saline 0·18%, dextrose 4%	30	0	30	160	0
Dextrose 5%	0	0	0	200	0
Hartmann's solution	131	5	111	0	Lactate
Hypertonic crystalloid solutions					
Saline 0·45%, dextrose 5%	75	0	75	200	0
Dextrose 10%	0	0	0	400	0
Saline 0·18%, dextrose 10%	30	0	30	400	0
Dextrose 20%	0	0	0	800	0

When there is excessive vomiting or there are signs of damaged bowel, fluid therapy should be given intravenously.

Example

A 6-kg child is clinically shocked and 5% dehydrated as a result of gastroenteritis.

Initial therapy

20 ml/kg for shock = 6 × 20 = 120 ml of 0.9% saline given as a rapid intravenous bolus

Estimated fluid therapy

50 ml/kg for 5% dehydration = 50 × 6 = 300 ml
100 ml/kg for daily maintenance fluid = 100 × 6 = 600 ml
Rehydration + maintenance = 900 ml
∴ Start with infusion of 900/24 = 37 ml/h

Application of fluid therapy

Reassess clinical status and weight at 4–6 hours, and if satisfactory continue. If the child is losing weight increase the fluid rate, and if the weight gain is excessive decrease the fluid rate. Start giving more of the maintenance fluid as oral feeds if the child is tolerating the fluids.

When the gut is functioning, oral rehydration using standard solutions is ideal (WHO formulation provides 75 mmol Na, 20 mmol K, 65 mmol Cl, 10 mmol citrate and 75 mmol glucose per litre. The formulations generally used in the UK have lower Na concentrations of 50–60 mmol/l). This fluid should be administered frequently in small volumes (cup and spoon works very well for this process). Generally normal feeds should be administered in addition to the rehydration fluid, particularly if the infant is breast-fed.

Fluid overload and overhydration

In the same way that fluid losses may cause shock, dehydration or both, excessive fluid administration can cause intravascular fluid overload, overhydration or both.

In the patient with nephrotic syndrome, fluid has leaked out of the intravascular space and into the tissues because of a low serum albumin. Such children may be grossly overhydrated, with diffuse severe oedema (see table). However, many patients with nephrotic syndrome have a contracted intravascular space, and attempts to diurese these patients without first expanding the intravascular space with albumin may result in shock.

By contrast the patient with myocardial dysfunction may have an intravascular compartment that is grossly overfilled. The clinical signs of intravascular overload (see table) may be present, and yet the patient (particularly if they have been on diuretics) may actually be total body fluid depleted and may appear dehydrated.

Children with other renal conditions may often have a combination of intravascular and total body fluid overload. They are then oedematous, but this is combined with features of intravascular fluid overload, and administering albumin would be dangerous.

Signs of intravascular fluid overload

Raised jugular venous pressure	May be difficult to elicit in young child
Enlarged (and often tender) liver	Difficult to assess in the patient who already has a large liver. May also be difficult to assess if the patient has ascites
Cardiac gallop, usually together with cardiomegaly	May be difficult to assess in the patient with severe tachycardia, and particularly if pulmonary oedema or other signs are present

(Continued)

Hypertension	An important clinical feature of excessive intravascular fluid, particularly in patients with renal problems.
Pulmonary signs	Diffuse fine crepitations in the bases of the lungs, together with other clinical signs of fluid in the lungs.

Signs of overhydration

Oedema	Usually in dependent areas. In the infant or child who is either lying or sitting, this may not affect areas such as the buttocks or lower legs. Marked facial puffiness may be a feature.
Weight gain	Sudden increases in weight are often markers of excessive fluid intake.

Therapy is critically dependent on an understanding of the fluid balance.

The patient with nephrotic syndrome who is overhydrated should not be treated by diuresis alone. The management consists of fluid restriction, and in some cases diuresis following the prior administration of albumin, so that fluid is brought into the intravascular compartment, prior to initiation of diuresis and thus preventing shock.

The patient with intravascular overload as well as overhydration requires fluid restriction and administration of diuretics. It is inappropriate (and potentially dangerous) to try and treat the resultant hypertension with agents such as β-blockers because this may precipitate heart failure.

In patients with cardiac failure, which has led to intravascular overload because of pump failure, a situation may be reached where treatment with diuretics of intravascular overload is causing dehydration. Attention must then be focused on a way of increasing cardiac output (using measures such as afterload reduction, or in the acute phase inotropic support) – in other words, treating the underlying cause.

The treatment of fluid overload is complex and the non-specialist should seek help.

Electrolyte abnormalities

Table B.3. Normal water, electrolyte, energy

Body weight	Water (ml/kg/day)	Sodium (mmol/kg/day)	Potassium (mmol/kg/day)	Energy (kcal/day)	Protein (g/day)
First 10 kg	100	2–4	1·5–2·5	110	3·00
Second 10 kg	50	1–2	0·5–1·5	75	1·5
Subsequent kilograms	20	0·5–1	0·2–0·7	30	0·75

Sodium

In situations of critical illness or major fluid and electrolyte abnormality, very variable fluid and electrolyte intake may be required.

Both low and high sodium levels are potentially dangerous to the patient. Severe hypernatraemia may be associated with severe brain damage, because brain tissue shrinks as a result of intracellular dehydration and blood vessels may tear or clot up. Too rapid correction of hypernatraemia may lead to cerebral oedema and injury. Similarly,

rapid correction of hyponatraemia may also be associated with brain damage. Thus sodium levels must be brought back to normal, but at a rate that does not exceed 0.5–1 meq/l/h.

The electrolyte losses during dehydration depend on the reason for dehydration. In gastroenteritis, sodium losses in diarrhoea range from approximately 50 meq/l (rotavirus) to approximately 80 meq/l (cholera and enteropathogenic *Escherichia coli*). In renal dysfunction sodium losses may be minimal (diabetes insipidus) or significant (renal tubular dysfunction).

Hypernatraemia

Hypernatraemia in the dehydrated patient may be the end result of excessive loss of water (e.g. diabetes insipidus, diarrhoea), excessive intake of sodium (e.g. iatrogenic poisoning, or non-accidental injury) or a combination of both (children with gastroenteritis given excessive sodium in rehydration fluid).

The electrolyte content of the replacement solutions depends on the cause of the dehydration. In general 0.45% NaCl is a safe starting solution for rehydration. This is based largely on the electrolyte content of stool in diarrhoea. If a patient is dehydrated from diabetes insipidus then virtually no sodium losses have occurred and fluid replacement could be done with fluid containing 0–0.18% NaCl. By contrast patients with renal tubular dysfunction and natriuresis may require 0.9% saline to replace the renal losses of sodium. Measurement of Na content of urine and stool may facilitate replacement therapy considerably.

As part of the monitoring of therapy electrolyte specimens should be collected. Frequent reassessment of fluid and electrolyte needs by repeated weighing and biochemical measurement of serum electrolytes is the key to safe rehydration under all circumstances.

Ongoing therapy for severe hypernatraemic dehydration

Start with (calculated) maintenance fluid volume + (estimated) rehydration volume given as constant infusion over 24 hours using 0.45% saline with 5% dextrose. Weigh and check serum sodium levels every 4 hours. IF:	
Sodium levels are correcting at a rate of 0.5–1 meq/l/h, and the weight is increasing at the estimated rate for rehydration over 24–48 hours.	Therapy is appropriate.
Sodium levels are coming down at a rate of <0.5 meq/l/h, and the weight is correcting appropriately.	Decrease sodium content of IV fluid (e.g. change to 0.18% saline with dextrose). Could also consider careful administration of diuretic in the context of sodium overload.
Sodium levels are dropping >1–1.5 meq/l/h, and the weight is increasing too rapidly.	Decrease rate of fluid administration.
Sodium levels are dropping >1–1.5 meq/l/h and the weight is not increasing too rapidly.	Increase sodium content of replacement solution.

Hyponatraemia

Hyponatraemia may be due to excessive water intake or retention, excessive sodium losses or a combination of both.

If hyponatraemia is due to excessive water intake or retention, and the patient is not symptomatic, the restriction of fluid intake to 50% of normal estimated requirements may be adequate therapy. If however the patient is fitting from hyponatraemia, it may be appropriate to use hypertonic saline administration carefully to bring the sodium levels up towards normal at a rate not exceeding 1 meq/L/h.

In hyponatraemia in the context of excessive losses sodium intake will have to exceed the normal daily requirements. A reasonable starting fluid is 0.9% NaCl, with appropriate adjustment of fluid and electrolyte therapy on the basis of ongoing tests.

Potassium

Unlike sodium, potassium is mainly an intracellular ion and the small quantities measurable in the serum and extracellular fluid represent only a fraction of the total body potassium. However, the exact value of the serum potassium is important as cardiac arrhythmias can occur at values outside of the normal range. The intracellular potassium acts as a large buffer to maintain the serum value within its normal narrow range. Thus hypokalaemia is usually only manifest after significant total body depletion has occurred. Similarly, hyperkalaemia represents significant total body overload, beyond the ability of the kidney to compensate. The exception to both these statements is the situation in which the cell wall pumping mechanism is breached. A breakdown of the causes of hyper- and hypokalaemia is given in Table B.4.

Table B.4. Causes of hypo- and hyperkalaemia

Hypokalaemia	Hyperkalaemia
Diarrhoea	Renal failure
Alkalosis	Acidosis
Volume depletion	Adrenal insufficiency
Primary hyperaldosteronism	Cell lysis
Diuretic abuse	Excessive potassium intake
	In the critically ill neonate, inadequate cardiac output must always be excluded as a cause

Hypokalaemia

Hypokalaemia is rarely a great emergency. It is usually the result of excessive potassium losses from acute diarrhoeal illnesses. As total body depletion will have occurred, large amounts are required to return the serum potassium to normal. The fastest way of giving this is with oral supplementation. In cases where this is unlikely to be tolerated, IV supplements are required. However, strong potassium solutions are highly irritant and can precipitate arrhythmias, thus the concentration of potassium in IV solutions ought not to exceed 80 mmol/l when given centrally, except on intensive care units. Fortunately this is not usually a problem as renal conservation of potassium aids restoration of normal serum levels.

Patients who are alkalotic, hyperglycaemic (but not diabetic) or are receiving insulin from exogenous sources will have high intracellular potassium stores. Thus hypokalaemia in these cases is the result of a redistribution of potassium rather than potassium deficiency, and treatment of the underlying causes is indicated.

Hyperaldosteronism is a cause of hypokalaemic alkalosis. Patients with this condition will have salt and water retention and will be hypertensive on presentation. Secondary hyperaldosteronism is the body's natural response to hypovolaemia and salt deficiency and is thus a common cause of hypokalaemic alkalosis. As there is primary salt and water deficiency the patient is not usually hypertensive. The most common causes are diarrhoeal illness and salt-losing conditions such as cystic fibrosis. Other causes include external loss of fluid from intestinal stomas or drains. Although potassium replacement is required in this condition the main thrust of therapy has to be with salt and water replacement to re-expand the circulation and cut down on aldosterone production.

Hyperkalaemia

Hyperkalaemia is a dangerous condition. Although the normal range extends up to 5·5 mmol/l it is rare to get arrhythmias below 7·5 mmol/l. The most common cause of hyperkalaemia is renal failure – either acute or chronic. Hyperkalaemia can also result from potassium overload, loss of potassium from cells due to acidosis or cell lysis, hypoaldosteronism and hypoadrenalism.

The immediate treatment of hyperkalaemia is shown schematically in Figure B.1. If there is no immediate threat to the patient's life because of an arrhythmia then a logical sequence of investigation and treatment can be followed. Beta-2 stimulants, such as salbutamol, are the immediate treatment of choice. They act by stimulating the cell wall pumping mechanism and promoting cellular potassium uptake. They are best administered by a nebuliser. The dose to be given is shown in Table B.5. The serum potassium will fall by about 1 mmol/l with these dosages.

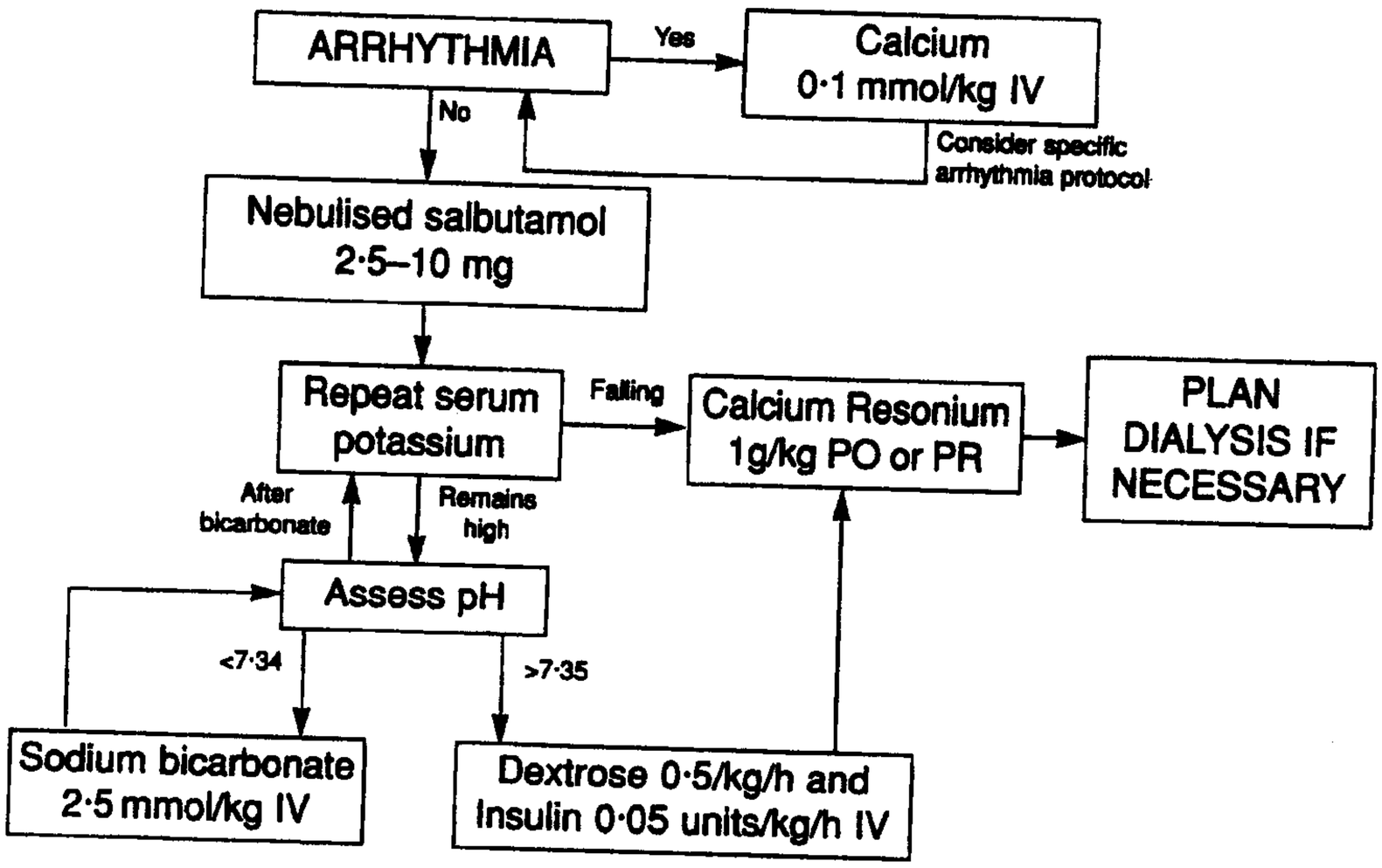


Figure B.1. Algorithm for the management of hyperkalaemia

Table B.5. Salbutamol dose by age

Age (years)	Salbutamol dose (mg)
<2·5	2·5
2·5–7·5	5
>7·5	10

Sodium bicarbonate is also effective at rapidly promoting intracellular potassium uptake. The effect is much greater in the acidotic patient (in whom the hyperkalaemia is likely to be secondary to movement of potassium out of the cells). The dosage is the same as that used for treating acidosis, and 1–2 ml/kg of 8.4% $NaHCO_3$ is usually effective. It is mandatory to also check the serum calcium, because hyperkalaemia can be accompanied by marked hypocalcaemia, particularly in patients with profound sepsis or renal failure. The use of bicarbonate in these situations can provoke a crisis by lowering the ionised calcium fraction, precipitating tetany, convulsions or hypotension and arrhythmias.

Insulin and dextrose are the classic treatment for hyperkalaemia. They are not, however, without risk, and the use of salbutamol has fortunately reduced the requirement for such therapy. It is very easy to precipitate hypoglycaemia if monitoring is not adequate. Large volumes of fluid are often used as a medium for the dextrose and, particularly in the patient with renal failure, hypervolaemia and dilutional hyponatraemia can then be a problem. Many patients are quite capable of significantly increasing endogenous insulin production in response to a glucose load, and this endogenous insulin is just as capable of promoting intracellular potassium uptake. It thus makes sense to start treatment with just an intravenous glucose load and then to add insulin as the blood sugar rises. The initial dosage of glucose ought to be 0·5 g/kg/h, i.e. 2·5 ml/kg/h of 20% dextrose. Once the blood sugar is above 10 mmol/l, insulin can be added if the potassium level is not falling. The dosage of insulin is initially half that used in diabetic ketoacidosis, i.e. 0·05 units/kg/h. This can then be titrated according to the blood sugar.

The above treatments are the fastest means of securing a fall in the serum potassium, but all work through a redistribution of the potassium into cells. Thus the problem is merely delayed rather than treated in the patient with potassium overload. The only ways of removing potassium from the body are with dialysis or ion-exchange resins such as calcium resonium. If it is anticipated that the problem of hyperkalaemia is going to persist then the use of these treatments ought not to be delayed. Dialysis can only be started when the patient is in an appropriate environment, but will be the most effective and rapid means of lowering the potassium. Ion-exchange resins can be used at the outset. The dosage of calcium resonium is 1 g/kg as an initial dose either orally or rectally, followed by 1 g/kg/day in divided doses.

In an emergency situation where there is an arrhythmia (heart block or ventricular arrhythmia) the treatment of choice is intravenous calcium. This will stabilise the myocardium but will have no effect on the serum potassium. Thus the treatments discussed above will still be necessary. The dosage is 0·5 ml/kg of 10% Ca gluconate (i.e. 0·1 mmol/kg Ca). This dose can be repeated twice. With a very high potassium, more than one treatment can be used simultaneously.

Calcium

Some mention of disorders of calcium metabolism is relevant because both hyper- and hypocalcaemia can produce profound clinical pictures.

Hypocalcaemia

Hypocalcaemia can be a part of any severe illness, particularly septicaemia. Other specific conditions that may give rise to hypocalcaemia are severe rickets, hypoparathyroidism, pancreatitis, or rhabdomyolysis, and citrate infusion (in massive blood transfusions). Acute and chronic renal failure can also present with severe hypocalcaemia. In all cases hypocalcaemia can produce weakness, tetany, convulsions, hypotension and arrhythmias. Treatment is that of the underlying condition. In the emergency situation, however, intravenous calcium can be administered. As most of the above conditions are

associated with a total body depletion of calcium and because the total body pool is so large, acute doses will often only have a transient effect on the serum calcium. Continuous infusions will also often be required, and must be given through a central venous line as calcium is so irritant to peripheral veins. In renal failure, high serum phosphate levels may prevent the serum calcium from rising. The use of oral phosphate binders or dialysis or haemofiltration may be necessary in these circumstances.

Hypercalcaemia

Hypercalcaemia usually presents as long-standing anorexia, malaise, weight loss, failure to thrive and vomiting. Causes include hyperparathyroidism, hypervitaminosis D or A, idiopathic hypercalcaemia of infancy, malignancy, thiazide diuretic abuse and skeletal disorders. Initial treatment is with volume expansion with normal saline. Following this, investigation and specific treatment are indicated.

B.3 DIABETIC KETOACIDOSIS (DKA)

DKA is a special case in which a relative or absolute lack of insulin leads to an inability to metabolise glucose. This leads to hyperglycaemia and an osmotic diuresis.

Once urine output exceeds the ability of the patient to drink, dehydration sets in. In addition, without insulin, fat is used as a source of energy, leading to the production of large quantities of ketones and metabolic acidosis. There is initial compensation for the acidosis by hyperventilation and a respiratory alkalosis but, as the condition progresses, the combination of acidosis, hyperosmolality and dehydration leads to coma. DKA is often the first presentation of diabetes; it can also be a problem in known diabetics who have decompensated through illness, infection or non-adherence to their treatment regimes.

History

The history is usually of weight loss, abdominal pain, vomiting, polyuria and polydipsia, though symptoms may be much less specific in under-5-year-olds who also have an increased tendency to ketoacidosis.

Examination

Children are usually severely dehydrated with deep and rapid (Kussmaul) respiration. They have the smell of ketones on their breath. Salicylate poisoning and uraemia are differential diagnoses that should be excluded. Infection often precipitates decompensation in both new and known diabetics, and must be sought.

Management

Assess

- **A**irway
- **B**reathing
- **C**irculation

Give 100% oxygen and place on a cardiac monitor.

Take blood for:

- Bicarbonate/blood gases
- Urea and electrolytes, creatinine, calcium, albumin
- Glucose
- Culture (if clinically indicated)
- Haemoglobin and differential white cell count

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Take urine for:

- Culture
- Sugar
- Ketones

The principles of management are to reverse shock, provide rehydration over 24–48 hours, avoid hypokalaemia, avoid rapid changes in serum osmolarity (focus especially on sodium and glucose levels), return glucose to normal levels and treat the underlying precipitating cause of the DKA.

In order to provide appropriate therapy and avoid complications, it is essential to monitor these patients meticulously. Hourly monitoring should include heart rate, respiratory rate and blood pressure (more frequently if these are unstable), oxygen saturation, neurological observations, urine output (if depressed level of consciousness or young child, insert urinary catheter) and fluid balance. Glucose must be monitored hourly (can use capillary specimens if reasonable perfusion, and where possible check with laboratory specimens). Serum electrolytes and acid–base must be monitored at least 2-hourly unless markedly abnormal, in which case hourly levels must be checked until more stable.

Shock is treated by the administration of oxygen and then 10–20 ml/kg of Ringer's lactate or 0.9% saline given over approximately 1 hour. Despite the fluid losses, shock is relatively uncommon in DKA.

Rehydration is administered by calculating the expected 24-hour maintenance requirement and the estimated fluid deficit. Administer maintenance fluids together with rehydration fluids, with rehydration calculated to happen over 24 hours. Initial rehydration can be given using normal saline, switching to 0·45% saline after the initial 1–2 hours. Once glucose levels fall below 14–17 mmol/l, 5% dextrose should be added to the fluid infusions. Actual fluid volumes given should rarely exceed 1.5–2 times the usual maintenance requirements. Fluid administration needs to be adjusted to the actual fluid balance on an hourly basis.

Insulin should be given by continuous infusion. The initial dose is 0·1 units/kg/h. Do not stop using insulin. This is the child's prime requirement. Administer the insulin by a separate line. Add 25 units of soluble insulin to 50 ml saline. This solution is 0·5 unit/ml:0·1 unit/kg/h is equal to 0·2 × weight in kg, as ml/h. Thus a 20-kg child would have 4 ml/hour, a 35-kg child 7 ml/hour. The insulin infusion should continue until the acidosis is cleared. If the blood sugar falls below 15 mmol/l, then additional dextrose must be added to the infusion, in order to maintain the glucose levels. The insulin dose can then be reduced to 0.05 units/kg/h but should not be reduced below this if acidosis remains.

Potassium supplementation should be started as soon as insulin therapy is initiated, unless the patient is (unusually) hyperkalaemic. Hypokalaemia is more of a risk than hyperkalaemia. Start with a concentration of 40 mmol/l of KCl in the infusion. While there is little evidence that phosphate supplementation is beneficial, severe hypophosphataemia should be treated. Potassium phosphate can be given instead of KCl in the presence of hypophosphataemia. If phosphate is given, then the serum calcium must be monitored closely as it may precipitate hypocalcaemia.

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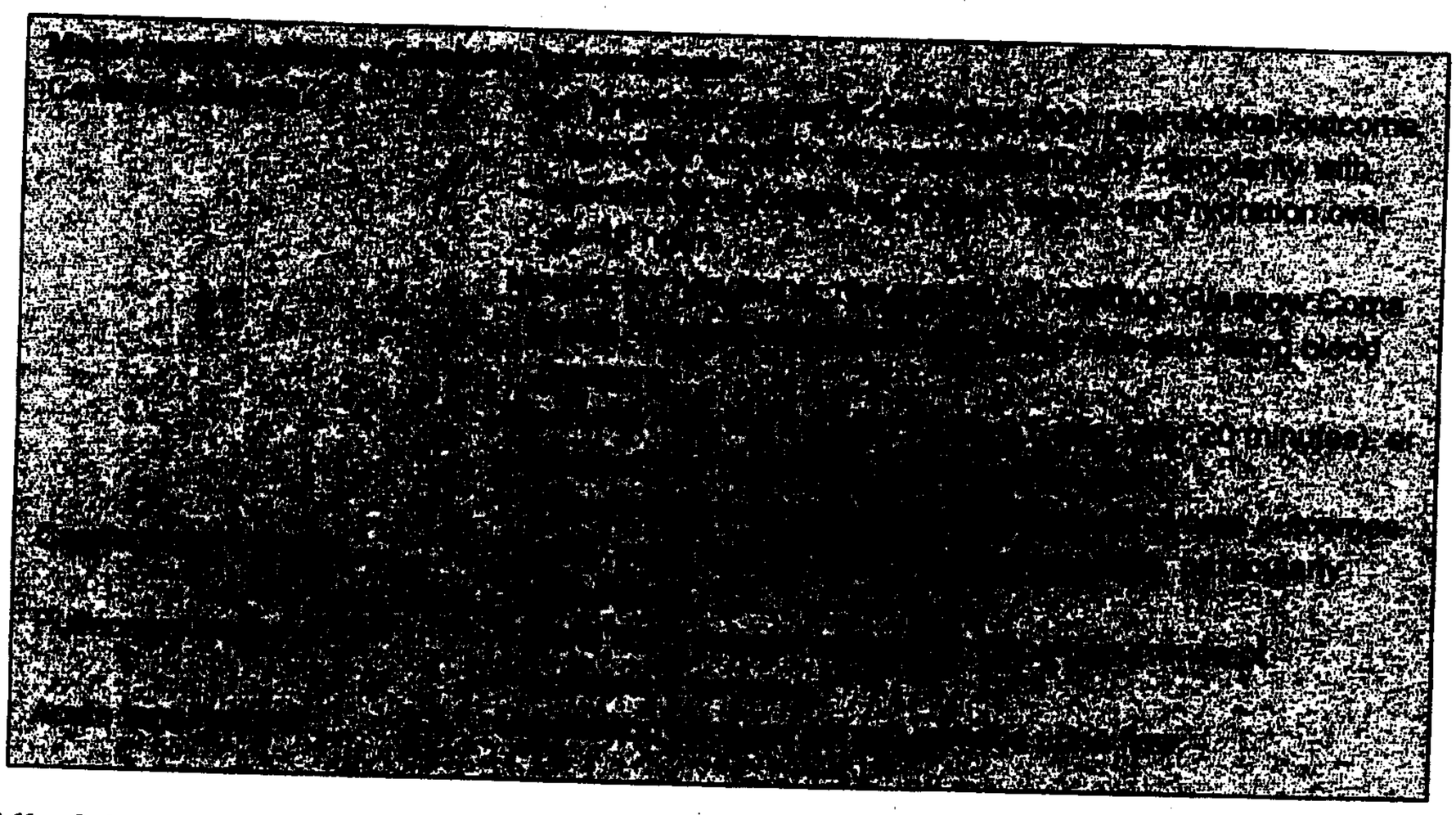
The acidosis of DKA is initially compensated for by hyperventilation. Acidosis will resolve with treatment of shock, insulin supplementation and rehydration. Treatment with

bicarbonate has been associated with the development of cerebral oedema and should therefore be avoided unless essential. If the pH remains less than 7.1 despite replacement of intravascular volume, and appropriate insulin and glucose therapy for several hours, it may be reasonable to give bicarbonate. This should be discussed with the endocrine team.

Regular, frequent (i.e. initially half-hourly) assessment of conscious level by the Glasgow Coma Score is required to recognise early cerebral oedema. This complication of diabetic ketoacidosis is uncommon but may be devastating. It usually occurs in the more severely ill, but not always. A headache may be the first indication of the condition and should be taken seriously. Early recognition of reduced conscious level should lead to measures for reducing raised intracranial pressure, and transfer to intensive care for intracranial pressure monitoring.

Complications



All of these complications require intensive monitoring on an intensive care unit.

[redacted]

TEXTBOOK OF
PEDIATRICS

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17th Edition

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CR - PSNI

096-022-167

quired nephrogenic DI may result from hypercalcemia or kalemia and is associated with the following drugs: lithium, docycline, foscarnet, clozapine, amphotericin, methicillin, ifampin. Impaired renal concentrating ability can also be seen ureteral obstruction, chronic renal failure, polycystic kidney e, medullary cystic disease, Sjögren syndrome, and sickle cell e. Decreased protein or sodium intake or excessive water e, as in primary polydipsia, can lead to diminished tonicity of nal medullary interstitium and nephrogenic DI.

ENT OF CENTRAL DIABETES INSIPIDUS

l Therapy

an intact thirst mechanism and free access to oral fluids, on with complete DI can maintain plasma osmolality and in the high normal range, although at great inconven-. Neonates and young infants are often best treated solely fluid therapy, given their requirement for large volumes $/m^2$/24 hr) of nutritive fluid. The use of vasopressin analogs tients with obligate high fluid intake is contraindicated the risk of life-threatening hyponatremia.

pressin Analogs

ment of central DI in older children is best accomplished the use of the long-acting vasopressin analog dDAVP opressin). dDAVP is available in an intranasal preparation t 5–10 min) and as tablets (onset 15–30 min). The asal preparation of dDAVP (10 μg/0.1 mL) can be adminis- by rhinal tube (allowing dose titration) or by nasal spray. appropriate dose is determined empirically based on the l length of antidiuresis. The nasal spray delivers 10 μg (0.1 per spray and is the standard preparation used for treat- of primary enuresis in older children. Use of dDAVP in the ment of enuresis is a temporizing measure, because it does fect the underlying condition and should be used with n. To prevent water intoxication, patients should have t 1 hr of urinary breakthrough between doses each day. P tablets are available, but require at least a 10-fold se in the dose compared with the intranasal preparation. loses of 25–300 μg every 8–12 hr are safe and effective in ren.

s Vasopressin

l DI of acute onset following neurosurgery is best managed continuous administration of synthetic aqueous vaso- n (pitressin). Under most circumstances, total fluid intake be limited to 1 L/m^2/24 hr during antidiuresis. A typical r intravenous vasopressin therapy is 1.5 mU/kg/h, which s in a blood vasopressin concentration of approximately /mL. On occasion, following hypothalamic (but not transsphe- l surgery, higher initial concentrations of vasopressin may uired to treat acute DI, which has been attributed to the e of a vasopressin inhibitory substance. Vasopressin con- ions greater than 1,000 pg/mL should be avoided because ay cause cutaneous necrosis, rhabdomyolysis, and cardiac disturbances. Postneurosurgical patients treated with ssin infusion should be switched from intravenous to oral s soon as possible to allow thirst sensation, if intact, to help e osmolality.

MENT OF NEPHROGENIC DIABETES INSIPIDUS

tment of acquired NDI focuses on elimination, if possi- he underlying disorder, such as offending drugs, hyper- , hypokalemia, or ureteral obstruction. Congenital genic diabetes insipidus is often difficult to treat. The als are to ensure the intake of adequate calories for nd to avoid severe dehydration. Foods with the highest ratio of caloric content to osmotic load (Na < 1 mmol/kg/24 hr) should be ingested to maximize growth and to minimize the urine volume required to excrete the solute load. Even with the early institution of therapy, however, growth failure and mental retardation are common.

Pharmacologic approaches to the treatment of NDI include the use of thiazide diuretics and are intended to decrease the overall urine output. Thiazides appear to induce a state of mild volume depletion by enhancing sodium excretion at the expense of water and by causing a decrease in the glomerular filtration rate, which results in proximal tubular sodium and water reabsorption. Indomethacin and amiloride may be used in combination with thiazides to further reduce polyuria. High-dose dDAVP therapy, in combination with indomethacin, has been used in some subjects with NDI. This treatment may prove useful in patients with genetic defects in the V2 receptor associated with a reduced binding affinity for vasopressin.

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Chapter 553
Other Abnormalities of Arginine Vasopressin Metabolism and Action

David T. Breault and Joseph A. Majzoub

Hyponatremia (serum sodium < 130 mEq/L) in children is usually associated with severe systemic disorders and is most often due to (1) intravascular volume depletion, (2) excessive salt loss, or (3) hypotonic fluid overload, especially in infants. The syndrome of inappropriate antidiuretic hormone (SIADH) is an uncommon cause of hyponatremia in children, except following vasopressin administration.

The initial approach to the patient with hyponatremia begins with the determination of the volume status. A careful review of the patient's history, physical examination, including changes in weight, and vital signs helps determine whether the patient is hypovolemic or hypervolemic. Supportive evidence includes laboratory data such as serum electrolytes, blood urea nitrogen, creatinine, uric acid, urine sodium, specific gravity, and osmolality (Chapter 45.2) (Tables 553–1 and 553–2).

CAUSES OF HYPONATREMIA

Syndrome of Inappropriate Antidiuretic Hormone Secretion

SIADH is characterized by hyponatremia, an inappropriately concentrated urine (>100 mOsm/kg), normal or slightly elevated plasma volume, a normal-to-high urine sodium, and low serum uric acid. SIADH is uncommon in children, with most cases resulting from excessive administration of vasopressin in the treatment of central diabetes insipidus. It can also occur with encephalitis, brain tumors, head trauma, psychiatric disease, in the postictal period after generalized seizures, after prolonged nausea, pneumonia, tuberculous meningitis, or AIDS. SIADH is the cause of the hyponatremic second phase of the triphasic response seen after hypothalamic-pituitary surgery

TABLE 552-1 Differential Diagnosis of Hyponatremia

Disorder	Intravascular Volume Status	Urine Sodium
Systemic dehydration	Low	Low
Decreased effective plasma volume	Low	Low
Primary salt loss	Low	Low
Cerebral salt wasting	Low	Very high
SIADH	High	High
Decreased free water clearance	Normal or high	Normal or high
Primary polydipsia	Normal or high	Normal
Pseudohyponatremia	Normal	Normal
Factitious hyponatremia	Normal	Normal

SIADH = syndrome of inappropriate antidiuretic hormone secretion.

(Chapter 552). It is found in up to 35% of patients 1 wk after surgery and may result from retrograde neuronal degeneration with cell death and vasopressin release. Common drugs that have been shown to increase vasopressin secretion or mimic vasopressin action, resulting in hyponatremia, include carbamazepine, chlorpropamide, vinblastine, vincristine, and tricyclic antidepressants.

Systemic Dehydration

The initial manifestation of systemic dehydration is often hypernatremia and hyperosmolality, which subsequently lead to the activation of vasopressin secretion and a decrease in water excretion. As dehydration progresses, hypovolemia and/or hypotension become major stimuli for vasopressin release, further decreasing free water clearance. Urinary sodium excretion is low (usually <10 mEq/L) due to a low glomerular filtration rate and concomitant activation of the renin-angiotensin-aldosterone system. unless primary renal disease or diuretic therapy is present.

Primary Salt Loss

Hyponatremia can result from the primary loss of sodium chloride as seen in specific disorders of the kidney (congenital polycystic kidney disease acute interstitial nephritis, chronic renal failure), gastrointestinal tract, (gastroenteritis), or sweat glands (cystic fibrosis). The hyponatremia is not solely due to the salt loss, because the latter also causes hypovolemia, leading to an increase in vasopressin. Mineralocorticoid deficiency, pseudohypoaldosteronism (sometimes seen in children with urinary tract obstruction or infection), and diuretics can also result in loss of sodium chloride.

Decreased Effective Plasma Volume

Hyponatremia can result from decreased effective plasma volume, as found in congestive heart failure, cirrhosis, nephrotic syndrome, positive pressure mechanical ventilation, severe burns, bronchopulmonary dysplasia in neonates, cystic fibrosis with obstruction, and severe asthma. The resulting decrease in cardiac output leads to reduced water and salt excretion, as with systemic dehydration, and an increase in vasopressin secretion. In patients with impaired cardiac output and elevated atrial volume (e.g., congestive heart failure or lung disease), atrial natriuretic peptide concentrations are elevated further, leading to hyponatremia by promoting natriuresis. These patients usually have a very low urinary excretion of sodium. Unlike dehydrated patients, these patients may have excess total body sodium from activation of the renin-angiotensin-aldosterone system and demonstrate peripheral edema as well.

Primary Polydipsia (Increased Water Ingestion)

In patients with normal renal function, the kidney can excrete a dilute urine with an osmolality as low as 50 mOsm/kg. To excrete a daily solute load of 500 mOsm/m^2, the kidney must produce 10 L/m^2 of urine per day. Therefore, to avoid hyponatremia, the maximum amount of water an individual with normal renal function can consume is 10 L/m^2. Neonates, however, cannot dilute their urine to this degree, putting them at risk for water intoxication if water intake exceeds 4 L/m^2/day (approximately 60 mL/h in a newborn). Many infants develop hyponatremic seizures after being fed pure water without electrolytes rather than breast milk or formula.

Decreased Free Water Clearance

Hyponatremia due to decreased renal free water clearance, even in the absence of an increase in vasopressin secretion, can result from adrenal insufficiency or thyroid deficiency, or be related to a direct effect of drugs on the kidney. Both mineralocorticoids and glucocorticoids are required for normal free water clearance in a vasopressin-independent manner. In patients with unexplained hyponatremia, adrenal and thyroid insufficiency should be considered. Also, patients with coexisting adrenal failure and diabetes insipidus may have no symptoms of the latter until glucocorticoid therapy unmasks the need for vasopressin replacement. Certain drugs may inhibit renal water excretion through direct effects on the nephron, thus causing hyponatremia; these drugs include high-dose cyclophosphamide, vinblastine, cisplatinum, and carbamazepine.

Cerebral Salt Wasting

Cerebral salt wasting appears to be the result of hypersecretion of atrial natriuretic peptide and is seen primarily with central nervous system disorders including brain tumors, head trauma, hydrocephalus, neurosurgery, cerebral vascular accidents, and brain death. Hyponatremia is accompanied by elevated urinary sodium excretion (often more than 150 mEq/L), excessive urine output, hypovolemia, normal or high uric acid, suppressed vasopressin, and elevated atrial natriuretic peptide concentrations (>20 pmol/L). Thus, it is distinguished from SIADH, in which normal or decreased urine output, euvolemia, low uric acid, only modestly elevated urine sodium concentration, and an elevated vasopressin level occur. The distinction between cerebral salt wasting and SIADH is important because the treatment of the two disorders differs markedly.

Clinical Parameters to Distinguish Between SIADH, Cerebral Salt Wasting and Central Diabetes Insipidus

Clinical Parameter	SIADH	Cerebral Salt Wasting	Central DI
Serum sodium	Low	Low	High
Urine output	Normal or low	High	High
Urine sodium	High	Very high	Low
Intravascular volume status	Normal or high	Low	Low
Serum Uric acid	Low	Normal or high	High
Vasopressin level	High	Low	Low

Pseudohyponatremia and Other Causes of Hyponatremia

Pseudohyponatremia may result from hypertriglyceridemia. In this condition, elevated lipid levels result in a relative decrease in serum water content. As electrolytes are dissolved in the aqueous phase of the serum, they appear low when expressed as a fraction of the total serum volume. As a fraction of serum water, how-

ever, electrolyte content is normal. Factitious hyponatremia can result from obtaining a blood sample proximal to the site of intravenous hypotonic fluid infusion.

Hyponatremia is also associated with hyperglycemia, which causes the influx of water into the intravascular space. Serum sodium decreases by 1.6 mEq/L for every 100 mg/dL increment in blood glucose greater than 100 mg/dL. Glucose is not ordinarily an osmotically active agent and does not stimulate vasopressin release, probably because it is able to equilibrate freely across plasma membranes. In the presence of insulin deficiency and hyperglycemia, however, glucose acts as an osmotic agent, presumably because its normal intracellular access to osmosensitive sites is prevented. Under these circumstances, an osmotic gradient exists, stimulating vasopressin release.

TREATMENT OF HYPONATREMIA

Patients with systemic dehydration and hypovolemia should be rehydrated with salt-containing fluids such as normal saline or lactated Ringer solution. Because of activation of the renin-angiotensin-aldosterone system, the administered sodium is avidly conserved and a water diuresis quickly ensues as volume is restored and vasopressin concentrations decrease. Under these conditions, caution must be taken to prevent too rapid a correction of hyponatremia, which may result in central pontine myelinolysis characterized by discrete regions of axonal demyelination and the potential for irreversible brain damage.

Hyponatremia due to a decrease in effective plasma volume caused by cardiac, hepatic, renal, or pulmonary dysfunction is more difficult to reverse. The most effective therapy is the least frequently achieved: treatment of the underlying systemic disorder. For example, patients weaned from positive pressure ventilation undergo a prompt water diuresis and resolution of hyponatremia as cardiac output is restored and vasopressin concentrations decrease.

Patients with hyponatremia due to primary salt loss require supplementation with sodium chloride and fluids. Initially, intravenous replacement of urine volume with fluid containing sodium chloride, 150 to 450 mEq/L depending on the degree of salt loss, may be necessary; oral salt supplementation may be required subsequently. This treatment contrasts with that of SIADH, in which water restriction without sodium supplementation is the mainstay.

Emergency Treatment of Hyponatremia

The development of acute hyponatremia (onset < 12 hr) or serum sodium concentration less than 120 mEq/L may be associated with lethargy, psychosis, coma, or generalized seizures, especially in younger children. Acute hyponatremia may cause cell swelling and lead to neuronal dysfunction or to cerebral herniation. The emergency treatment of cerebral dysfunction resulting from acute hyponatremia includes water restriction and may require rapid correction with hypertonic sodium chloride. If hypertonic saline treatment is undertaken, the serum sodium should be raised only high enough to produce an improvement in mental status, and in no case faster than 1.5 mEq/L/hr or 12 mEq/L/24 hr.

Treatment of SIADH

Chronic SIADH is best treated by oral fluid restriction. With full antidiuresis (urine osmolality of 1,000 mOsm/kg), a normal obligate renal solute load of 500 mOsmoles/m^2 would be excreted in 500 mL/m^2 water. This, plus a daily nonrenal water loss of 500 mL/m^2, would require that oral fluid intake be limited to 1,000 mL/m^2/24 hr to avoid hyponatremia. In young children, this degree of fluid restriction may not provide adequate calories for growth (as discussed). In this situation, the creation of nephrogenic diabetes insipidus using demeclocycline therapy may be indicated to allow sufficient fluid intake for normal growth.

Treatment of Cerebral Salt Wasting

Treatment of patients with cerebral salt wasting consists of restoring intravascular volume with sodium chloride and water, as with the treatment of other causes of systemic dehydration. The underlying cause of the disorder, which is usually due to acute brain injury, should also be treated if possible. Treatment involves the ongoing replacement of urine sodium losses (volume for volume).

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Chapter 554 Hyperpituitarism, Tall Stature, and Overgrowth Syndromes

Pinchas Cohen

HYPERPITUITARISM

Primary hyperpituitarism is a rare event in children, but secondary hypersecretion of pituitary hormones is an expected finding in conditions in which deficiency of a target organ gives decreased hormonal feedback, as in primary hypogonadism or hypoadrenalism. In primary hypothyroidism, pituitary hyperfunction and hyperplasia can enlarge and erode the sella and, on rare occasions, increase intracranial pressure. Such changes should not be confused with primary pituitary tumors; they disappear when the underlying thyroid condition is treated. Pituitary hyperplasia also occurs in response to stimulation by ectopic production of releasing hormones such as that seen occasionally in patients with Cushing syndrome, secondary to corticotropin-releasing hormone excess, or in children with acromegaly secondary to growth hormone-releasing hormone (GHRH) produced by a variety of systemic tumors.

Primary hypersecretion of pituitary hormones by a suspected or proven adenoma is uncommon in childhood. The most commonly encountered pituitary tumors are those that secrete corticotropin, prolactin, or growth hormone (GH). With rare exceptions, pituitary adenomas that secrete gonadotropins or thyrotropin occur in adults. Hypothalamic hamartomas that secrete gonadotropin-releasing hormone are known to cause precocious puberty. It is suspected that some pituitary tumors may result from stimulation with hypothalamic-releasing hormones and in other instances, as in McCune-Albright syndrome (MAS), the tumor is caused by constitutive activating mutation of the G-protein Gs_α gene.

TALL STATURE

The normal distribution of height predicts that 2.5% of the population will be taller than 2 SD (97.5%) above the mean. However, the social acceptability and even desirability of tallness (heightism) make tall stature an uncommon complaint. Nevertheless, it is critical to be able to identify situations in which tall stature or an accelerated growth rate provides a clue to an underlying disorder. In North America, it is extremely unusual for male patients to seek help regarding excessive

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CHAPTER 458

Syndrome of Inappropriate Secretion of Antidiuretic Hormone

Penelope Terhune Louis and
James D. Fortenberry

P[illegible]HOPHYSIOLOGY AND DIAGNOSIS

[illegible]nagement in acutely ill children may be complicated [illegible].tions in the regulatory mechanisms of sodium and [illegible]er homeostasis. Antidiuretic hormone (ADH) plays an important role in responding to changes in extracellular volume by altering the renal clearance of free water to maintain appropriate serum tonicity. ADH release from the posterior pituitary and is influenced primarily by changes in plasma osmolality and effective circulating blood volume. Hypothalamic osmoceptors maintain osmolality over a narrow range, with 1% to 2% changes altering ADH secretion. The response to volume changes by the carotid body and left atrial stretch receptors is less sensitive, requiring 10% difference to stimulate or suppress ADH release.

Many disease states, medications, and pathophysiologic processes can alter ADH excretion and secretion (Table 458-1). In some of these entities, ADH release may be an appropriate response to the alterations sensed by body receptors, as in the decreased venous return produced by positive pressure ventilation. However, if ADH release is excessive or inappropriate in relation to either normal osmolality or volume status, the typical findings of the syndrome of inappropriate ADH secretion (SIADH) ensue. Often, SIADH is recognized in children and is established by five classic clinical criteria: hyponatremia with corresponding serum hypoosmolality; urine osmolality greater than appropriate for concomitant serum osmolality (i.e., less than maximally dilute); continued urine sodium excretion that is excessive for the degree of hyponatremia, with elevated urine sodium concentrations; normal renal, adrenal, and thyroid function; and absence of volume depletion.

Urine has to be only submaximally dilute to establish a diagnosis of SIADH. Normally, the kidneys can dilute urine up to 50 to 150 mOsm/kg. With urine hypotonic to plasma, the tonicity of serum possibly can fall below normal and can be maintained at subnormal levels, producing hyponatremia. Hyponatremia may not be present early in the process and develops only when fluid retention occurs.

The associated increase in urinary sodium excretion is an interesting finding. Typically, aldosterone secretion is normal and the filtered sodium load does not increase; therefore, a third

TABLE 458-1. Disorders and agents associated with the syndrome of inappropriate antidiuretic hormone secretion

Central nervous system
Meningitis
Encephalitis
Head trauma
Tumor
Hypoxia-ischemia
Guillain-Barré syndrome
Subarachnoid hemorrhage
Acute intermittent porphyria
Cavernous sinus thrombosis
Anatomic abnormalities
Vasculitis
Brain abscess
Hydrocephalus
Acute psychosis
Rocky Mountain spotted fever
Spinal fusion
Craniopharyngioma (triphasic postoperative response)
Drugs
Enhancement of antidiuretic hormone release
Morphine
Vincristine
Beta-adrenergic agonists
Cyclophosphamide
Carbamazepine
Barbiturates
Halothane
Clofibrate
Nicotine
Phenothiazines
Adenine arabinoside
Potentiation of antidiuretic hormone action
Chlorpropamide
Indomethacin
Intrathoracic processes
Tuberculosis
Viral, bacterial, fungal pneumonia
Mycoplasmal pneumonia
Empyema
Asthma
Pneumothorax
Cystic fibrosis
Positive-pressure ventilation
Positive end-expiratory pressure
Tumor
Patent ductus arteriosus ligation
Miscellaneous
Pain
Stress (postoperative)
Nausea, vomiting
Bacterial endocarditis
Malignancy
Infant water intoxication (postulated)
Idiopathic

Adapted from Kaplan SL, Feigin RD. SIADH in children. Adv Pediatr *1980;27:247.*

factor—possibly atrial natriuretic peptide—that has been proposed may suppress proximal tubular reabsorption of sodium in response to expanded extracellular volume.

SIADH must be differentiated from the many clinical conditions that cause hyponatremia in children. Physical examination and evaluation of simultaneous urine and serum sodium concentrations and osmolalities, urine specific gravity, and serum electrolytes will help to exclude such disorders as hyponatremic dehydration, congestive heart failure, and renal insufficiency. Serum cortisol levels are recommended because patients with adrenal insufficiency may demonstrate a component of inappropriate ADH secretion and might present a similar picture if well compensated. Thyroid function tests also should be considered. Water-loading procedures are dangerous and unnecessary for diagnosis.

Physical findings in SIADH are related to the associated disease process. Despite mildly increased total body water, typically edema formation is not seen. Symptoms are related to the presence and duration of hyponatremia. Anorexia, nausea, mental status changes, and convulsions are more likely to occur with a serum osmolality of less than 240 mOsm/kg H_2O and a serum sodium concentration of less than 120 mEq/L of acute onset.

ASSOCIATED DISORDERS

In children, SIADH occurs most often in association with central nervous system (CNS) disorders. Laboratory evidence of SIADH was noted in almost 60% of children presenting with bacterial meningitis. ADH levels in patients with meningitis also were elevated significantly in comparison with normal and febrile controls. The duration and degree of hyponatremia were shown to correlate significantly with subsequent development of seizure and subdural effusions. A leak of endogenous ADH across inflamed meninges has been suggested to explain these findings, but laboratory markers of inflammation did not show a correlation with arginine vasopressin (AVP) levels. SIADH occurs with other CNS infections, including brain abscesses and encephalitis, and with Rocky Mountain spotted fever, most likely secondary to hypothalamic involvement from rickettsial vasculitis. Such CNS disturbances as head trauma, perinatal hypoxia, brain tumors, subarachnoid hemorrhage, anatomic defects, and Guillain-Barré syndrome may produce SIADH.

Intrathoracic disturbances are less common causes in children. Pulmonary tuberculosis is well recognized, but viral, fungal, bacterial, and mycoplasma pneumonias also have been cited. Disorders that lead to decreased left atrial pressure, such as positive-pressure ventilation or pneumothoraces, can induce excessive ADH release by diminishing venous return. This condition is perceived inappropriately by stretch receptors as evidence of decreased circulating blood volume. ADH levels probably are elevated by a similar mechanism in status asthmaticus, leading one to reconsider the vigorous use of intravenous fluids often recommended in initial management.

Many drugs have been implicated in the production of SIADH, acting either by increasing endogenous central ADH release or by enhancing its renal tubular effects (see Table 458-1). Frequently used agents include chemotherapeutic agents, morphine, beta-adrenergic agonists, and indomethacin. Reportedly, carbamazepine-induced SIADH was reversed by concomitant use of phenytoin, which inhibits ADH secretion. Phenytoin may minimize SIADH while treating seizures associated with CNS insult.

Many other disorders can induce SIADH. Ectopic production of ADH may occur in adults with bronchogenic carcinoma, leukemia, and thymoma. Transient increases in ADH secretion also occur as part of the triphasic ADH response after resection of craniopharyngiomas. ADH secretion caused by the effec increased epinephrine release from pain or stress, nausea vomiting, the use of morphine, or the surgical procedure i may be excessive in the general postoperative setting; poste spinal fusion for scoliosis is a common association. A syndr of hyponatremia with water intoxication has been describe otherwise normal infants receiving dilute formula at ho AVP levels that were increased inappropriately were found some of these infants.

MANAGEMENT

Appropriate treatment of the underlying disease process is esse tial to the resolution of SIADH. However, fluid restriction remai the cornerstone of acute therapy and prevention of symptoms patients at risk. Intake should be limited to insensible losses (8(to 1,000 mL/m²/day) with appropriate sodium content to allo the slow excretion of excess fluid, diminishing extracellular vc ume and thus decreasing urinary sodium excretion.

The fluid management of meningitis patients has undergor increasing scrutiny. Although SIADH may occur in this settin many affected patients may be volume-depleted and may hav associated hyponatremic dehydration. In a study by Powell al., children with meningitis were assigned randomly to receiv either fluid restriction (two-thirds maintenance) or maintenanc fluid therapy plus estimated deficit replacement during the in tial 24 hours of therapy. Initially, plasma AVP concentration were elevated in both groups but returned to normal after 2 hours of therapy in patients who received maintenance an deficit therapy; levels were unchanged in fluid-restricte patients. ADH reduction was presumed to be secondary to cor rection of hypovolemia and sodium deficits. Fluid restriction i an animal model of bacterial meningitis also produce decreased cerebral flow and increased cerebrospinal fluid lacti acidosis. Therefore, probably an appropriate approach is to giv maintenance plus replacement fluids to meningitis patient who initially do not demonstrate laboratory evidence o SIADH. Close monitoring of electrolytes should continue dur ing the first 24 to 48 hours of therapy, and the presence o hyponatremia should prompt the evaluation of urine osmolality and sodium concentration to rule out SIADH.

Hypertonic (3%) saline infusion should be used only in patients whose hyponatremia has induced seizures or coma. Concomitant use of furosemide can act to increase free water excretion relative to sodium excretion and can diminish the volume expansion induced by hypertonic saline. The use of furosemide alone, with replacement of measured urine electrolyte losses, also has been suggested. Corticosteroids have been used in combination to increase sodium retention, but their use remains controversial. Lithium carbonate and demeclocycline inhibit ADH effects on the renal tubule and can correct hyponatremia, but significant complications limit their use in children.

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Oski's Pediatrics

Principles and Practice

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096-022-173

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CHAPTER 406

Reye Syndrome

Penelope Terhune Louis

Reye syndrome, first described in 1963, is an acute, life-threatening, postinfectious, metabolic encephalopathy that affects predominantly school-aged children, occasionally infants, and rarely adults. Over the years, the disease and its clinical manifestations have received widespread recognition.

Characteristically, a prodromal illness, most often influenza or varicella infection, is followed in 3 to 5 days by the onset of persistent and intractable vomiting. Initially, patients are well oriented but irritable and lethargic. Some patients have no change in consciousness and remain only lethargic, with no progression to unconsciousness. The serum alanine aminotransferase and serum asparate aminotransferase levels are three to 30 times normal. The serum bilirubin level rarely exceeds 1 mg/dL. Serum ammonia concentrations are variable at presentation. As the encephalopathy worsens to a hyperexcitable state, the patient is intermittently out of contact with the environment. Further progression to a deeper comatose state is characterized by decerebrate and decorticate posturing, hyperventilation and, finally, flaccid paralysis with loss of involuntary ventilatory control. The comatose patient uniformly has an elevated ammonia concentration ranging from three to 20 times normal. The encephalopathy typically persists for 24 to 96 hours, with gradual improvement in survivors. Recovery of consciousness in patients with permanent neurologic impairment may require weeks.

Criteria for the case definition of Reye syndrome include the following: an acute, noninflammatory encephalopathy documented clinically by an alteration in consciousness and, if available, cerebrospinal fluid containing less than eight leukocytes per microliter; hepatopathy documented by liver biopsy on autopsy or a threefold or greater increase in the alanine aminotransferase, serum asparate aminotransferase, or serum ammonia level; and no more reasonable explanation for the cerebral or hepatic abnormalities.

Accurately assessing the severity of the illness is important because the therapies for severely affected children are aggressive, invasive, and dangerous. Several staging systems have been developed, culminating in the National Institutes of Health Staging System. The system used most extensively includes electroencephalographic information that previously was believed to have prognostic value. The electroencephalographic criteria have been replaced and the resulting National Institutes of Health Staging System consists of the following five stages:

- Stage I: Lethargy; follows verbal commands; normal posture; purposeful response to pain; brisk pupillary light reflex; and normal oculocephalic reflex
- Stage II: Combative or stuporous; inappropriate verbalizing; normal posture; purposeful or nonpurposeful response to pain; sluggish pupillary reflexes; and conjugate deviation on doll's eye maneuver
- Stage III: Comatose; decorticate posture; decorticate response to pain; sluggish pupillary reaction; and conjugate deviation on doll's eye maneuver
- Stage IV: Comatose; decerebrate posture and decerebrate response to pain; sluggish pupillary reflexes; and inconsistent or absent oculocephalic reflex
- Stage V: Comatose; flaccid; no response to pain; no pupillary response; no oculocephalic reflex

Since the 1960s, more than 3,000 cases of Reye syndrome have been reported to the Centers for Disease Control and Prevention, with a case fatality rate varying from 26% to 42%. From 1967 to 1973, between 11 and 83 cases were reported annually. Between 1974 and 1983, the reporting frequency increased to a peak of 555 cases between 1979 and 1980. Thereafter, a steady decline in cases has occurred such that Reye syndrome now is a rare disease.

PATHOGENESIS

Despite intensive study, the pathogenesis of Reye syndrome remains incompletely defined. Whether the pathogenesis can be explained by a primary injury to the mitochondria of multiple organs, including the brain, liver, and muscle, with its metabolic consequences, or by a primary hepatic injury that leads to metabolic consequences producing the biochemical abnormalities and encephalopathy remains unclear. Morphologic and biochemical studies have confirmed the presence of a characteristic injury. Pleomorphic, enlarged mitochondria with disrupted cristae, electron-lucent matrices, and reduced numbers of dense bodies are characteristic of the hepatic pathology of Reye syndrome. Associated reductions in mitochondrial enzymes involved in ureagenesis and gluconeogenesis and in enzymes associated with the citric acid cycle have been observed. Further evidence of mitochondrial injury is suggested by the finding of dicarboxylic acids in the urine and serum.

Morphologic and biochemical studies of the brain in patients with Reye syndrome have revealed swollen astrocytes and myelin blebs. Alterations in the morphology of the mitochondria have been identified only in neurons. Despite these morphologic changes, mitochondrial enzyme activities in the brain are not reduced as they are in the liver. This finding is somewhat surprising because it suggests that brain mitochondrial injury may play an unimportant role in the observed encephalopathy of Reye syndrome.

The role of salicylates in the pathogenesis of Reye syndrome remains unclear, although salicylate use commonly precedes

the onset of the syndrome. Serum salicylate concentrations are increased in patients with the disorder compared with those in control patients; however, no correlation has been found between coma grade and serum concentration. Salicylates are known to stimulate macrophages that are activated by a viral infection, endotoxin, and phagocytosis. The stimulation of macrophages results in the release of tumor necrosis factor and interleukin-1, which are mediators of the toxic and metabolic effects that are similar to those observed in Reye syndrome.

In 1982, the Committee on Infectious Disease of the American Academy of Pediatrics issued a statement warning against the use of salicylates in children with possible varicella or influenza infection, and a program of public education was initiated. Some authors have cited the reduction in aspirin use and the decrease in the occurrence of Reye syndrome as an argument to support the association between aspirin administration and this disorder. Other authors dispute these conclusions, stating that even the prospective, controlled, epidemiologic study performed by the U.S. Public Health Service showed histologic support for the diagnosis of Reye syndrome in only 27% of the patients, and no electron-microscopical evidence was presented. This decline in Reye syndrome was seen at the same time as knowledge of metabolic diseases was rapidly expanding, and an alternative explanation may be that fewer patients with an underlying genetic-metabolic disease were being incorrectly diagnosed as having Reye syndrome.

Based on available evidence, apparently a primary mitochondrial injury stimulates multiple metabolic disturbances, resulting in hyperammonemia, free fatty acidemia, lactic acidosis, and dicarboxylic acidemia. The metabolic abnormalities and the underlying mitochondrial injury synergistically lead to the observed pathophysiology through mechanisms that remain incompletely understood. Fatty acids, dicarboxylic acids, salicylates, and other factors may inhibit mitochondrial ureagenesis and potentiate their individual metabolic effects. Alternatively, they may inhibit adenosine triphosphate synthesis and lead to profound reductions in high-energy phosphate, which is required to catalyze an array of enzymatic reactions.

TREATMENT

The treatment of children with Reye syndrome ranges from relatively simple provision of glucose to children with stage I findings to extremely complex neurologic intensive care for children with more severe stages of the disease. Therapy is significantly dependent on the stage of the disease in patients with Reye syndrome.

Children who are in stage I require close neurologic evaluation, frequent glucose level determinations, and daily measurements of ammonia, liver enzymes, and electrolyte levels. Hypoglycemia is avoided by the provision of intravenous glucose, coupled with close monitoring of the glucose level. Children with stage I Reye syndrome have an excellent prognosis if they undergo observation in the hospital and receive glucose and electrolyte intravenous therapy.

Children who have disease of stage II or higher require significantly more care and must be treated in the hospital's intensive care facility.

In all patients with stage III disease or stage II disease progressing toward stage III, aggressive therapy should consist of intubation, hemodynamic monitoring, intracranial pressure monitoring and control, and ammonia reduction therapies.

Fluid and Electrolytes

Several types of electrolyte disturbances are seen in patients with Reye syndrome, the most well recognized of which is hypoglycemia. Abnormalities of potassium, calcium, and phosphorus also may be present. In the presence of inappropriate antidiuretic hormone secretion or diabetes insipidus, fluid balance is disordered.

Respiratory Support

Patients with stage I disease do not require respiratory support but adequate oxygenation must be ensured. Those with more severe stages of Reye syndrome need aggressive support to prevent hypoxia and hypercapnia. All children with stage III Reye syndrome should undergo intubation and hyperventilation electively.

Ammonia-Reducing Strategies

Aggressive attempts to reduce ammonia levels may include peritoneal dialysis, exchange transfusion, charcoal hemoperfusion, and total body washout with the use of cardiopulmonary bypass.

Hemodynamic Monitoring and Support

Arterial and central venous pressure lines are placed to monitor meticulously the fluid and cardiovascular status.

Coagulopathy

Most patients with Reye syndrome have a bleeding diathesis, which should be treated with the necessary blood products when clinical bleeding is noted.

Temperature Control

Controlling the temperature in children with Reye syndrome is important because decreases may contribute to hemodynamic instability and increases cause an increase in the cerebral metabolic rate.

Intracranial Pressure Management

The most significant advances in the care of children with this disease appear to be in the areas of supportive care and management of intracranial hypertension. Measures to decrease intracranial pressure include elevating the head of the bed, administering controlled mechanical hyperventilation, and using osmotic diuretics. The use of high doses of barbiturates in the treatment of elevated intracranial pressure in patients with Reye syndrome is controversial. Although this pharmacologic treatment seems to be effective in reducing intracranial pressure, it also is associated with significant complications.

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ROYAL BELFAST HOSPITAL FOR SICK CHILDREN

Fluid Balance and I.V. Prescription Sheet

Date 21/10/96

Weight 24.1 Kg

Name	D.O.B.	Hosp. No.
Claire Roberts	10/1/87	328770

TIME (hr)	INTAKE						OUTPUT			
	INTRAVENOUS				ORAL		Urine	Aspirate or Vomit	Stool	Comment
	1 Level	Amount	2 Level	Amount	Fluid	Amount				
09.00										
10.00										
11.00										
12.00										
13.00										
14.00										
15.00										
16.00										
17.00										
18.00										
19.00										
20.00										
21.00	S/N Saline @ 61 mls/hr.				P.T.A.					
22.00	—									
23.00		24					Heal Unit			V Gm Rendal
24.00		80								V Gm Rendal
01.00		146					Small Unit			V Gm Rendal
02.00		200								V Gm Rendal
03.00		286					Small			V Gm Rendal
04.00		333			PU.		Small Unit			V Gm Rendal
05.00		404					Small			V Gm Rendal
06.00		460								V Gm Rendal
07.00		536					Small Vomit			V Gm Rendal
										V Gm Rendal

Total Intake		Total Output			
Intravenous 536 ml	Oral — ml	Urine ml	Aspir^{n} ml	No. of Vomits	No. of Stools

24 – Hour INTAKE 536 ml

24 – Hour OUTPUT 74 ml

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Name..... Date...../...../..... Hosp. No..... Wt. 24 .....Kgs.

10 40
10 20
4 4

INTRAVENOUS FLUID PRESCRIPTION CHART

	AMOUNT (mls)	TYPE OF FLUID	NAME and AMOUNT of ADDITIVES	RATE mls/hr	TIME Start	TIME Finish	Prescribed by	ERECTED BY
1	500 ml	0.18% NaCl 4% Dextran	/	64 ml/hr				
2								
3								
5								
6								

PARENTERAL NUTRITION PRESCRIPTION CHART

TOTAL VOL.

Per.....Hrs. .....mls.

.....mls/kg

TOTAL ENERGY

.....kcals

..... kcals/kg

PROTEIN

Vol. Cals.

DEXTROSE Conc.

Vol. Cals.

FAT Conc.

Vol. Cals.

Amino Acids (grams)	Nitrogen (grams)	Nitrogen/Cal Ratio	CHO (grams)	Other Additives
Fat (grams)	NaCl mmols	Na Lactate mmols	K+ mmols	
Cl− mmols	Ca++ mmols	Mg++ mmols	$PO_4^{=}$ mmols	
Addamel (mls)	Solvito (mls)	Vitlipid (mls)	Critical Ag. Conc. 75	

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ROYAL BELFAST HOSPITAL FOR SICK CHILDREN

Fluid Balance and I.V. Prescription Sheet

Date 22/10/96

Weight 24.1 Kg

Name	D.O.B.	Hosp. No.
Claire Roberts	10/1/87	328770

IV site

TIME (hr)	INTAKE						OUTPUT			
	INTRAVENOUS				ORAL					
	1 Level	Amount	2 Level	Amount	Fluid	Amount	Urine	Aspirate or Vomit	Stool	Comment
10.00	No 1	68								
10.00		110								Bfast
10.00		179			cup of water.					Bfast
11.00		259								Bfast
12.00		308					P-U large - blue			S.specs (blue)
13.00		356								Bfast
14.00										Bfast
15.00		527								
16.00		562	4th Morphine 2ml/hr.							Pdl
17.00		616		0.8						V.Tests
18.00		677		2.7						V.P.dl
19.00		769		5.5						V.P.dl Bacon
20.00		806		6.7			PU			V.P.dl
21.00		868		8.7	I.V Acyclovir 60	—				V.P.dl
22.00		943		10.9		60	P.U.			V.P.dl
23.00		1014	3rd Bolus	13.9	PHENYTOIN					2 LNCCan red
24.00		1037	TH	16.8	110	—				1 LNCCan (2 Lucas)
01.00		1037		19.3			small mouth fuls			1 Empty. 2 Empty
02.00		1070		21.5		170	small mouth fuls			2 LNCCan 2 LNCCan
03.00										1 Empty 1 Empty
04.00										
05.00										
06.00										

Total Intake		Total Output			
Intravenous.....ml	Oral.....ml	Urine	Aspir^{n}	No. of Vomits	No. of Stools
		.....ml	.....ml	.....	.....
24 – Hour INTAKE 76		24 – Hour OUTPUT			
.....ml		.....ml			

Name..... Date...../...../..... Hosp. No..... Wt..... .....Kgs.

4

INTRAVENOUS FLUID PRESCRIPTION CHART

	AMOUNT (mls)	TYPE OF FLUID	NAME and AMOUNT of ADDITIVES	RATE mls/hr	TIME Start	TIME Finish	Prescribed by	ERECTED BY
1	500mls	No 8 Soln		64 mls/HR				
2	500mls.	N. Saline	+ 60mg MIDAZOLAM.	21mls/HR.	OVER 24 HRS			
3	See mfg	No 18.	20 mmol/kcl.	64 mls.				
5								
6								

PARENTERAL NUTRITION PRESCRIPTION CHART

TOTAL VOL.

Per.....Hrs. .....mls.

.....mls/kg

TOTAL ENERGY

.....kcals

..... kcals/kg

PROTEIN

Vol. Cals.

DEXTROSE Conc.

Vol. Cals.

FAT Conc.

Vol. Cals.

Amino Acids (grams)	Nitrogen (grams)	Nitrogen/Cal Ratio	CHO (grams)	Other Additives
Fat (grams)	NaCl mmols	Na Lactate mmols	K+ mmols	
Cl— mmols	Ca++ mmols	Mg++ mmols	PO_4= mmols	
Addamel (mls)	Solvito (mls)	Vitlipid (mls)	Critical Ag. Conc. 7%	

096-022-179

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NEUROSURGICAL UNIT ROYAL VICTORIA HOSPITAL

NAME: Clare Roberts

CENTRAL NERVOUS SYSTEM OBSERVATION CHART

Record Observations Hrly Hours

DATE: 22/10/96 — 23/10/96

TIME: 1pm, 3, 3, 4pm, 5, 6, 7, 8, 9pm, 10pm, 11pm, 12md, 1am, 2am

				Observations
COMA SCALE	Eyes open	Spontaneously	4	
		To speech	3	✓ (first entry)
		To pain	2	✓
		None	1	✓ (subsequent entries)
	Best verbal response	Orientated	5	
		Confused	4	
		Inappropriate Words	3	
		Incomprehensible Sounds	2	✓ (later entries)
		None	1	✓ (earlier entries)
	Best motor response	Obey commands	5	✓ (first entry)
		Localise pain	4	✓
		Flexion to pain	3	✓
		Extension to pain	2	
		None	1	
COMA SCALE TOTAL 3–14				9, 7, 6, 6, 7, 7, 8, 6, 6, 6, 6
INTRACRANIAL PRESSURE				
PUPILS	RIGHT	REACTION		✓ (all entries)
		SIZE		M, M, S, S, M, S, S, S, L, M, M, S, M
	EQUALITY			E (all entries)
	LEFT	REACTION		✓ (all entries)
		SIZE		M, M, S, S, M, S, S, S, L, M, M, S, M

Eyes closed by swelling = C

PUPILS RECORD:
1. REACTION — REACTS: ✓ NO REACTION: —
2. SIZE — SMALL: ● MEDIUM: ● LARGE: ●
3. EQUALITY — EQUAL: E UNEQUAL: L or R WHICHEVER LARGER

BLOOD PRESSURE: 240, 230, 220, 210, 200, 190, 180, 170, 160, 150, 140, 130, 120, 110, 100, 90, 80, 70, 60, 50, 40, 30, 20, 10

TEMPERATURE °C: 40.0, 39.5, 39.0, 38.5, 38.0, 37.5, 37.0, 36.5, 36.0, 35.5, 35.0

PULSE RATE (red)

RESPIRATORY RATE

LIMB MOVEMENT			
ARMS	NORMAL POWER		
	MILD WEAKNESS		
	SEVERE WEAKNESS		✓ (entries)
	NO MOVEMENT		
LEGS	NORMAL POWER		
	MILD WEAKNESS		
	SEVERE WEAKNESS		✓ (entries)
	NO MOVEMENT		

Record right (R) and left (L) separately if there is a difference between the two sides.

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096-022-180