REPORT ON CLAIRE ROBERTS FOR THE INQUIRY INTO HYPONATRAEMIA RELATED DEATHS IN NORTHERN IRELAND

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[redacted]

Professional experience.

My experience has been as a consultant paediatrician (general paediatrics) in a medium-size district general hospital (Pinderfields Hospital Wakefield) for 28 years. For the first 10 years or so after appointment when neurosurgical services were on site in Pinderfields, I worked with my consultant neurosurgical colleagues in providing an acute encephalopathy service for children for a population of about ¾ m.

Over this time I had experience in medical management having been chairman of the hospital medical committee for four years in the 1980s, acting as deputy member of the district management team and serving on the management board of the local hospital for learning disability. This was followed by appointment in 1993 as divisional coordinator of all non-surgical clinical specialties in Pinderfields Hospital and later by appointment as clinical director for women and children services and then, following the doubling in size of the children's unit after a merger with Pontefract Gen Hospital, becoming clinical director of children's services for what became a fairly large paediatric Department remaining so until just before I retired in 2006.

Over the same period I was Honorary Secretary of the British Paediatric Association and Vice President of its successor body the Royal College of Paediatrics and Child Health. I served on the Council of the Royal College of Physicians of London and was the paediatrician on the RCP working parties on medical audit around 1990. I refer to the reports from this committee. From 1996 I was seconded part-time to the Department of Health London as their paediatric adviser for seven years until the appointment of the National Clinical Director for Child Health after which I continued to assist the Department in the national service framework.

As the DH Paediatric Adviser I selected and commissioned the first NICE guidelines on children‘s problems and arranged for the extension of the Confidential Inquiry Into Stillbirths And Death In Infancy to cover all ages for deaths of children (now CEMACH). I also set up and chaired the national quality management board for newborn blood spot testing, and commissioned and set up the national audits for paediatric intensive care and neonatal intensive care. I have become familiar with the varying processes of hospital paediatric management and case records (and audit on which I have published) in visits to hospitals in the course of the Regional Inquiry into the deaths in Grantham Hospital (Allitt) , in research on presenting problems and investigations in around 20 paediatric departments, in attempts to develop a paediatric appropriateness of admission audit tool funded by DH, in visits acting on behalf the General Medical Council in development of performance assessment tools for consultant paediatricians and, when examining for membership of the Royal College of Paediatrics and Child Health. I have conducted external reviews of children’s services in London, the South East and W Midlands. Together with colleagues in Nottingham we have developed a number of evidence based presenting problem-based guidelines and jointly published a book on how to develop guidelines. Over the past 15 years I have also provided many medico-legal expert opinions in negligence claims.

INTRODUCTION

MY REPORT

The conclusions I draw are based upon my clinical experience, reference to relevant publications and also on my experience in clinical management.

THE REPORT IS STRUCTURED INTO CHAPTERS AND SET OF ANNEXES AS FOLLOWS

CHAPTER [1]

- **Summary of illness and subsequent events**
- **Headline comments on clinical care and clinical governance issues**
- [redacted]

CHAPTER [2]

- **Part [1] Claire's illness – Acute Encephalopathy**
- **Part [2] Detailed Commentary on The Clinical Care given to Claire when she was admitted with an acute encephalopathy at the age of nine years in October 1996**
- [redacted]

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- [redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]

ANNEX A :

GUIDANCE ON ACUTE ENCEPHALOPATHY AVAILABLE IN 1996

INTRODUCTION

ANNEX B :

MIDAZOLAM PRESCRIPTION POTENTIAL DOSE ERROR

ANNEX C

CLAIRE ROBERTS –DETAILED CLINICAL CHRONOLOGY AND COPIES OF SELECTED CLINICAL RECORDS

[redacted]

[redacted]

CHAPTER [1]

- **Summary of illness and subsequent events**
- **Headline comments on clinical care and clinical governance issues**
- [redacted]

SUMMARY OF ILLNESS AND SUBSEQUENT EVENTS

1. Claire was admitted aged 9y 9m to RBHSC with an acute encephalopathy under the care of the consultant general paediatrician. (admitted 21st of October 1996, died 23rd of October 1996). She had a past history of learning disability of uncertain origin (without cerebral palsy or dysmorphic features) and had been treated for tonic/clonic epilepsy from the age of 8 months until the age of 8 years but had no seizures from the age of 4 years some 5 years before this admission. Her antiepileptic therapy was stopped 18 months before the admission. She was judged to have a post epileptic encephalopathy followed by persistent non-convulsive epileptic status to account for the acute encephalopathy. Claire was treated by the general paediatric registrar and consultant paediatric neurologist on the basis of that diagnosis. She was treated with IV fluids (0.18% saline) and IV antiepileptic drugs. She later developed brain oedema which in turn led to her death. In her management consideration was given to viral or other infection in terms of preventive therapy. On admission on 21 October Claire was found to have a slight reduction in the blood sodium but at 9:30 PM the following day (26 hours after admission) a second blood test showed that the blood sodium was significantly lower at 121 mmol per litre. She had a respiratory arrest at 0300 on 23 October 1996 32 hours following admission with evidence of brain stem death and ventilatory support was withdrawn at 1845 hours on 23 October and she was pronounced dead. The immediate post death clinical diagnosis made was cerebral oedema; status epilepticus; inappropriate ADH secretion; ? Viral encephalitis. The clinicians considered that her death was from brain oedema complicating status epilepticus with a contribution from hyponatraemia and possible infection. The cause of death was revised after autopsy reporting in February 1997 to viral encephalomyelitis (and following an inquest held in 2006 to cerebral oedema due to meningoencephalitis, hyponatraemia due to excessive ADH production and status epilepticus).

2. Six years later following an Insight TV programme shown on 21 October 2004 Claire's parents contacted Royal Group of Hospitals. The Medical Director of the Royal Hospitals Trust, Dr McBride, reviewed the notes of Claire in late 2004 and asked Prof Young Consultant Clinical Biochemist and Professor of Medicine to review the records and provide a verbal report after which Dr McBride held a meeting on 6/12/2004 together with Prof Young and Dr Steen the consultant in general paediatrics under whom Claire had been admitted. From this meeting Dr McBride decided to refer Claire to the Coroner and a meeting was held next day with Claire's parents when it was reported to parents that hyponatraemia had been present in

Claire but that the treatment given to her was appropriate for the time in 1996 although that it had changed in 2004. An Inquest was held in 2006 and gave a verdict on the cause of death as cerebral oedema due to meningoencephalitis, hyponatraemia due to excess ADH production and status epilepticus.

HEADLINE COMMENTS ON CLINICAL CARE OF CLAIRE'S ILLNESS AND CLINICAL GOVERNANCE ISSUES

3. **Claire had an acute encephalopathy.** In summary acute encephalopathy is a disorder in which there is reduction of level of consciousness with or without associated focal neurological signs/paresis and with or without seizures. There is a risk of raised intracranial pressure which can be exacerbated by increased secretion of antidiuretic hormone (SIADH) leading to water retention and hyponatraemia and these both contribute to brain swelling. With advancing coma the brain stem control of respiration is impaired with carbon dioxide retention which in turn adds to brain swelling and threat to life. There is a wide range of causes.

4. Hyponatraemia is a common association with acute encephalopathy of any cause. Standard management for the time included prevention of hyponatraemia and/or therapy for it using intravenous normal saline or no less than 0.45% saline with careful blood test monitoring of the blood sodium and reduction of IV fluid volume. Claire was treated with 1/5 normal saline -a solution by the guidance of the time regarded as " contraindicated " in a child with acute encephalopathy. No reduction in volume below maintenance was made.

5. Claire was treated with antimicrobial therapy for viral and bacterial infection and this was appropriate.

6. No diagnostic investigations were done other than the blood electrolyte and full blood count and viral blood tests.

7. Standard guidance for the time was to carry out a range of blood and urine investigations for metabolic disease, toxins or organ failure such as liver failure. Brain imaging with CT scan was indicated. Strikingly, no EEG was done to confirm or refute the proposed diagnosis. The diagnosis of non-convulsive status epilepsy was not a high likelihood in Claire. She had experienced epilepsy from eight months of age to 4 years of age but this had settled and when present it had been tonic/clonic in nature and not myoclonic. On admission she had been off treatment for 18 months and had had no seizures for five years. No convincing history of an acute seizure prior to admission on 21 October was obtained. During her illness on 22 October she had a few episodes which could have been seizures although very short lasting. However the main problem was persistent reduction in conscious level with some neurological signs. Non-convulsive status epilepticus usually occurs in children with poorly controlled myoclonic or mixed epilepsy and (when present usually is manifest by frequent multisite jerking). Claire did not have this problem as the seizures had been well controlled and indeed she had been off therapy for 18 months.

8. Despite this history Claire was treated with a combination of antiepileptic therapy in the form of intravenous phenytoin and valproate following rectal diazepam. She was also given a drug used in refractory status epilepticus- Midazolam (when used this is usually as an infusion). Midazolam was advised for Claire by the paediatric neurologist both as a bolus IV dose and as a continuous infusion. This drug carries a significant risk of respiratory depression which itself can make brain swelling worse. It is not licensed for use in children for status epilepticus. In practice it has been advised as bolus in some children– e.g. *Medicines for Children 2003.* Mostly when used it has been as a continuous infusion with bolus usage being reserved in formularies for use for inducing anaesthesia or heavy sedation in intensive care. In Claire the *intended* IV bolus dosage calculated by the junior doctor based on Claire's body weight was 2 ½ times the advised bolus for sedation or induction of anaesthesia and for status epilepticus in UK and the written *prescribed* dose was 25 times those doses. (See Table below). It is not evident from the records whether any bolus dose was given although the paediatric neurologist and the nursing records made at the time stated that a bolus had been given. The relevant portion of the prescription sheet which should have been signed to indicate the bolus was given was not completed. The bolus would have been given by a junior doctor. It is not evident what source was used for the calculated dose.

TABLE : Midazolam IV bolus therapy

Indication	***Bolus Dose (microG) per Kg body weight***	***Source***
Sedation for procedure	<100	Medicines for Children 2001
Sedation in Intensive care	<200	Medicines for Children 2001 BNF for Children 2005
Induction for anaesthesia	<150	Medicines for Children 2001 BNF for Children 2005
Sedation for ventilated child	100	Alder Hey Book Childrens Doses 1994
Status epilepticus	Bolus not recommended or mentioned	Medicines for Children 2001 BNF for Children 2005 Alder Hey Book Childrens Doses 1994 Textbook Paediatrics Forfar & Arneil 1984 & 6th Edition 2003 Paediatric Vade Mecum Insley 1992 Advanced Paediatric Life Support Manuals BMJ 1st Ed 1993, 2nd 1997,3rd 2001.
Status epilepticus	<200	Medicines for Children 2003
Status epilepticus	< 300	Nelson T Book Pediatrics (US) 1999
Claire calculated dose	*500*	*Notes*
Claire prescribed dose	*5000*	*Prescription sheet*

9. **Clinical Governance issues**.

10. The clinical management of Claire Roberts was thus wanting in a number of respects. I am highlighting these to illustrate wider shortcomings in clinical governance.

11. The diagnosis and treatment were not consistent with widely available guidance on management of acute encephalopathy in 1996 in the form of advice provided in the major UK Textbook of Paediatrics by Forfar and Arneil. (See Annex A). This advises that 0.18% (1/5th normal) saline is contraindicated in management of this disorder. In Claire this fluid was used and the volume not reduced-a further recommendation.

There is a significant risk of brain oedema in the use of this fluid in acute encephalopathy which was discussed in this and other publications at the time.

12. A diagnosis of status epilepticus of non-convulsive nature was used in the management of Claire's illness and considered to be the cause of her death. There were not strong clinical indications that Claire had this condition and investigations were not carried out to confirm or refute it. Claire was treated with a range of antiepileptic therapy intravenously which included the use of Midazolam. It appears from the records that a potential or actual very significant overdose of this was used in bolus injection followed by an infusion. Midazolam can deepen coma. This dosage error does not appear to have received attention in the Trust reviews of Claire's death in 1996, 2004 or subsequently.

13. Although Claire was seen by a consultant paediatric neurologist 19 hours after admission, she was not seen by the consultant paediatrician responsible for her care until she collapsed some 33 hours after admission. Although advice was sought from the senior resident paediatrician (the registrar) in the evening just prior to her collapse, it is not evident that she was assessed clinically and inappropriate response was made to the low blood sodium which was found at this point. Tests should have been carried out earlier in the course of her illness and her therapy changed in response to findings of hyponatraemia which are likely to have been present.

14. Following Claire 's death an autopsy limited to the brain only was requested. This is problematic because it reduces the amount of diagnostic information available to explain the acute encephalopathy. The cause of Claire's acute encephalopathy remains uncertain, partly because of limited clinical and pathological investigation at the time.

[redacted]

16. Claire's parents were not fully informed by the clinicians about their perception of the severity of her illness. After her death and following the interview discussing the result of the autopsy findings held four months later, the hyponatraemia which had been a feature of her illness and thought by the clinicians to have contributed to Claire's illness and her death was not mentioned to them. The autopsy findings suggested that Claire had died from meningoencephalitis a finding which subsequently has been challenged.

[redacted]

[redacted]

67. CHAPTER [2]

68. Part [1] Claire's illness – Acute Encephalopathy

69. Part [2] Detailed Commentary on The Clinical Care given to Claire when she was admitted with an acute encephalopathy at the age of nine years in October 1996

[redacted]

71. PART [1] CLAIRE'S ILLNESS – ACUTE ENCEPHALOPATHY

72. **Acute Encephalopathy** is a condition which occurs acutely (suddenly) .

73. It is a condition associated with a reduction in conscious level with or without seizures, focal neurological signs or signs of raised intracranial pressure. It can be caused by a variety of conditions. These include bacterial or viral infection of the meninges or brain, vascular disorders such as stroke or vasculitis (the latter occurring in a range of immune diseases), demyelinating conditions including those associated with immune reaction to infection, brain swelling locally or generally associated with head injury, bleeding/ haematoma, brain tumour or abscess, raised intracranial pressure from hydrocephalus; or, impairment of brain function with or without swelling associated with metabolic disorders such as amino acid or organic acids inborn errors of metabolism, acquired mitochondrial disease such as Reyes syndrome, liver failure, renal failure, disturbed electrolytes especially low-sodium, episode of hypoxaemia, sickle cell disease, following severe seizure or associated with non-convulsive status epilepticus or tonic/clonic status epilepticus.. A similar presentation may occur with a range of poisons or toxins which may be medicinal drugs and others taken by accident or intention or household or environmental poisons including lead.

74. In acute encephalopathy, there is an increased incidence of hyponatraemia. Hyponatraemia may be associated with raised intracranial pressure from whatever cause and by causing neuronal swelling makes the pressure rise worse. There is an extensive literature on this which I will not rehearse. Hyponatraemia can be caused by water overload using low solute fluid and/or production of excess antidiuretic hormone. Thus an evolving brain swelling may complicate any of the disorders which cause acute encephalopathy. The use of low sodium intravenous fluid exacerbates this process.

75. The management of acute encephalopathy includes diagnosis and the consideration of differential diagnosis. It requires treatment of specific cause and consideration of prevention and treatment of complicating factors such as hyponatraemia. It also involves treatment of the associated problems of an acute encephalopathy of any cause such as seizures as well as treatment of seizures in epilepsy which may have caused the encephalopathy. New CNS signs may emerge when the brainstem is under pressure from the raised intracranial pressure and in such circumstances odd

movements may occur and the pupils may vary in responsiveness and / or eye movement disorders emerge during the illness.

76. Raised intracranial pressure may arise from brain swelling in any of the listed conditions and require treatment but it is also important to identify any causative conditions which themselves lead to an increase in intracranial pressure such as brain tumour, abscess or haematoma.

77. To identify such conditions imaging by CT is needed. This may indicate a need for neurosurgery. Raised pressure itself may be treated by fluid restriction to an extent although excessive fluid restriction used in the past may not have been helpful. If the condition progresses then elective intubation and ventilation may be used to maintain the blood carbon dioxide at a normal level. In the past and briefly for acute conditions, hyperventilation may be used to reduce blood carbon dioxide levels and thus reduce brain swelling but this is not used as much now as it was 1990s and 1980s.

78. Elective ventilation is used in severe progressive coma in order to prevent carbon dioxide retention which leads to worsening of brain swelling from arising from CO_2 retention from impaired ventilatory effort which can result from raised intracranial pressure imposing pressure upon the brainstem respiratory control centre or from sedation drugs.

79. In acute encephalopathy it is conventional to restrict fluid to the minimum necessary for example to produce a urine output of between 1-2ml per kilogram body weight per hour, carefully monitored and to ensure that low-sodium intravenous fluid is not used and the intravenous fluid of choice is either preferably normal or no less than half normal saline.

80. The role of specialist care in acute encephalopathy in summary is to identify the cause by investigation, treat the treatable (such as infection and/or complicating seizures or intracranial space occupying lesions),to take steps to prevent, identify and treat emerging signs of raised intracranial pressure by clinical monitoring, and if necessary to monitor intracranial pressure (which usually requires assistance of the neurosurgeon); treatment includes careful intravenous fluid prescription in volume and type avoiding low sodium fluids such as 0.18 % / 1/5th normal saline and resort when necessary to elective ventilation. In the presence of advancing and clear raised intracranial pressure, mannitol or steroids may be used and it is essential to ensure adequate perfusing pressure of the brain in the face of the raised pressure by circulatory support.

81. **PART [2] DETAILED COMMENTARY ON THE <u>CLINICAL CARE</u> GIVEN TO CLAIRE WHEN SHE WAS ADMITTED WITH AN ACUTE ENCEPHALOPATHY AT THE AGE OF NINE YEARS IN OCTOBER 1996 .**

Note: a full tabulated chronology of the clinical course is shown in Annex C with selected copy records

I consider the clinical care in the following way:

- **Care provided to Claire in accident and emergency and ward admission on evening of 21st October**
- **Care in the morning of 22 October and later by the general paediatric team**
- **Care in the evening of 22 October and issues relating to hand over at 5 PM on that day from the day registrar to the on-call registrar**
- **Care provided by the paediatric neurologist at 2 PM, 4 PM and 5 PM assessments on 22 October and the prescriptions of antiepileptic drugs**
- **The Collapse 23 October 1996 03:00 Hours and Care In Intensive Care**
- **Communication with Parents**

Care provided to Claire in accident and emergency and ward admission on evening of 21st October;

82. Claire (born 10/1/1987) was admitted aged 9y 9m on 21 October 1996 to RBHSC with an acute encephalopathy manifest as an onset over some hours of alteration in level of consciousness in the form of slurred speech, reduced social responsiveness and ataxia. This had started at school and been accompanied by some vomiting. She had a past history of epilepsy from age 8 months, had severe learning disability and had been treated for an attention deficit disorder. She had been seizure free for five years and had been weaned off antiepileptic medication 18 months before.

83. She was referred for admission by her general practitioner . She was seen in accident and emergency at 7:15 PM, was found to be drowsy and had asymmetry in her neurological signs. She had no fever. A diagnosis of encephalitis was queried and she was admitted after being assessed by the paediatric registrar at around 20:00 hours to the Ward. She was treated with intravenous fluids, blood tests were sent by 10 PM for full blood count, blood culture, urea and electrolytes and viral titres. The first blood test result noted at midnight showed a low sodium at 132 mmol/l and a slightly increased total white blood count at 16.5 (thou/ul) but no other abnormalities. She was observed overnight. She vomited on two occasions while on intravenous fluids.

84. **Comment on care in accident and emergency and ward admission on evening of 21st October;**

85. Management on the evening of admission in A&E and the in-patient ward (Allen ward) was acceptable in the differential diagnosis considered and initial treatment. Although use of 1/5th Normal Saline for IV maintenance fluid was within the range of current practice for the time for management of ill children, at this time also ideal/high-quality practice for acute encephalopathy any causation should have led to choice of IV fluid with higher sodium concentration. However before a significant

acute encephalopathy can be confirmed a period of observation was necessary to determine the duration of reduction in conscious level.

86. **Care in the morning of 22 October and later by the general paediatric team:**

87. The following morning she was seen by the daytime paediatric registrar Dr Sands responsible for the Ward who noted the changes in the blood tests, and considered that she might have "non-fitting status". Rectal diazepam was given around midday and Dr Sands made a referral to the consultant paediatric neurologist Dr Webb. Dr Webb saw her at 14:00 hours, 19 hours after admission. Claire's conscious level had been reduced throughout since admission and the GCS was 6 when she was seen by Dr Webb. After a clinical assessment, Dr Webb concluded that she had an acute encephalopathy most probably post ictal in nature. He made a note of a "normal" biochemical profile. He advised anti convulsant medication: intravenous phenytoin loading dose and maintenance, advised a blood test to be done at six hours to check the phenytoin level and proposed a CT scan the following day if she did not "wake-up". Claire had one seizure lasting about 5 min at 15:10 hours. Dr Webb then saw Claire again at 4 PM although there is no record made of this attendance (other than the insertion of 4 PM at the two o'clock consultation) and he recalls from his witness statement that he advised a bolus and infusion of Midazolam and this was prescribed at 15.25pm. Claire had an observed tightening of her teeth 16:30 hours lasting a few seconds. Dr Webb then reviewed Claire at 1700h. Intravenous infusion of Midazolam had been started in the interim and Dr Webb recorded that the bolus of Midazolam had been given.. Dr Webb also advised intravenous antibiotic and acyclovir (an anti-viral agent) although he noted that he did not think meningoencephalitis likely. He also advised adding intravenous sodium valproate bolus followed by an infusion every 12 hours.

88. Comment on care in the morning of 22 October and later by the general paediatric team;

89. Claire was admitted under the clinical care of the on-call acute general paediatric consultant Dr Steen. In my view she was the responsible consultant throughout Claire's stay. Referral was made for paediatric neurology advice and opinion by the general paediatric team (the registrar Dr Sands who was working under the supervision of Dr Steen). The paediatric neurology advice was provided by Dr Webb on the day following admission. There is no indication that consultant responsibility for Claire's care was transferred to Dr Webb either in documentation or from his own statement; for example, in his view about responsibility for fluid prescription and management upon which I comment later.(see para 222)

90. The role of Dr Steen Consultant in General Paediatrics

91. Claire had a persistent reduction in level of consciousness and by the morning following her admission at latest Claire should have been seen by Dr Steen. Claire was significantly unwell and a diagnosis of causation had not been made. It was correct for the paediatric team to refer for paediatric neurology advice but Dr Steen

should have been involved in the decision-making. Dr Steen did not see Claire until after the final and irreversible collapse some 33 hours following admission. There is no documented evidence that Dr Steen was aware of Claire's presence or of her illness. Neither is there documented evidence that the absence of consultant general paediatric input was perceived at the time nor after the review in 2004 as a major significant event. This should have been reported on the clinical significant event database. I review arrangements respecting consultant responsibility here and in Chapter 4 respecting delegation of care, particularly in absence.

92. I have noted the following **: document WS-143-1.** On page 7 there is an important statement which Dr Steen made to the Coroner *"I recalled that I had been aware that Claire was in the Ward at 9 AM on 22 October 1996 and that I had been contacted by the Ward to inform me that Dr Webb had taken over her management".* But there is no record of this discussion.

93. **Dr Sands Paediatric Registrar**. The paediatric registrar Dr Sands reviewed Claire on the Ward round in the morning but did not repeat the blood electrolytes which the previous evening had shown a slightly low sodium. Although there is little agreed guidance on the frequency with which children on intravenous fluid should have repeat sampling, a further sample was indicated specifically because Claire was significantly ill with, by then, persistent reduced level of consciousness and thus had a clear acute encephalopathy and had vomited even while on intravenous fluid. (This is unusual and suggests either gut obstruction or raised intracranial pressure or intracranial pathology). It was necessary to monitor the low sodium particularly in the context of an acute encephalopathy where the syndrome of inappropriate ADH is a well-recognised complication and can be manifest by a low sodium or a level which is falling.

94. The proposed diagnosis of non-convulsive epileptic status, whilst at possibility amongst other causes of acute encephalopathy, was not of high, or even moderate likelihood.

95. In the afternoon and evening of the 22 October 1996 Claire was managed jointly by the paediatric neurologist Dr Webb and by the general paediatric team of SHO and registrar. The general paediatric doctors prescribed the IV fluids used and calculated and prescribed and administered the IV anti epileptic drugs . The anti epileptic drugs were advised by Dr Webb (paediatric neurologist). The IV fluid used was chosen by the general paediatric team – without consultant involvement. I comment separately on the paediatric neurology management below.

96. Comment

97. The medical entries made by the junior staff on Allen Ward in the afternoon and later in the early evening were insufficient particularly in view of her deterioration in level of consciousness.

98. **Midazolam dose:** Antiepileptic drugs advised by the paediatric neurologist were prescribed and administered and this was appropriate in the overall management of

acute encephalopathy of any cause. However one, a bolus of Midazolam advised, was prescribed incorrectly. It is not evident from the contemporary records who advised the dose to be used and when and how. From his later statements (and the report made to parents in December 2004) Dr Webb had advised its use following his assessment of Claire at 2 PM but he did not record that in the notes nor at what time he advised that addition to the drugs he had already suggested. It is not evident whether he advised the dose to be used. If he did not advise the dose it is not evident what source was used by the SHO who carried out and recorded his calculation in the notes, calculating a dose which was a significant overdose for prescription (this was 2.5x the maximum advised for status epilepsy and 1 ½ x the dose for use in an intensive care unit – mostly for children on ventilator support). In writing the prescription the SHO multiplied his calculated dose by 10x. These errors were not noted by Dr Webb when he reviewed Claire at 5 PM when he made a record that the bolus had been given. It is not clear on what basis he made this judgement but if this was by reviewing the prescription, he should have noted the dose errors. Nor is it clear from the records what dose of Midazolam was given as bolus. It does seem that a bolus was given according to the nursing record at 3.25 pm 22 October (090-040-141). If the dose intended or prescribed had been given then the dose was such that it could lead to a significant reduction in conscious level, to potential depression of respiration with associated rising carbon dioxide level in the blood and the latter itself leading to brain swelling or aggravating it on top of the hyponatraemia. This was a major significant dose error in the circumstances. Had it been noticed, Claire should have been intubated and ventilated from around 5 PM. Furthermore this dose error was not noted at any medical audit review of Claire's death in 1996 nor by the pathologist who carried out the post-mortem. In respect of the latter point however, it would have been necessary for the pathologist to have reviewed the records because Dr Steen when completing her autopsy request form, did not mention the use of Midazolam (although she did record the use of rectal diazepam, intravenous phenytoin, intravenous valproate, acyclovir and cefotaxime). This dosage error was not identified in the 2004 case note review. (Nor in the medical reports provided for the Coroner and police service.). The regular drug prescription forms in photocopy notes do not seem to have a section to indicate that the dose has been given – if this is so then that is a deficiency. The once only section has a column for signature as given. This was not signed for the Midazolam bolus. (See Annex B)

99. **Care in the evening of 22 October and issues relating to hand over at 5 PM on that day from the day registrar to the on-call registrar**

100. Over the evening of 22 October the conscious level in Claire as measured by the Glasgow coma Scale, rose from 6 to 7 & 8 but fell again to 6 at 22:00 hr. At 19:15 hours and at 21:00 hours respectively, Claire had an episode of teeth clenching lasting a minute and an episode of screaming and drawing up of arms lasting 30 seconds. A blood test was sent at 21:30 hours to establish the blood phenytoin level and urea and electrolytes were requested. The blood result was available at 23:30 hours showing that the blood sodium had fallen to 121mmol/l. The senior house officer (Dr Stewart) considered the possibility of syndrome of

inappropriate ADH complicating the encephalopathy and consulted with the paediatric registrar (Dr Bartholome), the middle grade resident more senior paediatrician who advised reduction in the intravenous fluid rate from the existing maintenance requirement to 2/3 of maintenance requirement. Throughout Claire was treated with 0.18% saline in 4.3% dextrose. It was planned to send urine for osmolality. The reduction in volume did not take place. Between 2200 h 22 Oct and 0200 23 October Claire received a total of 247.6 ml (127 ml of 0.18% plus 10.6ml as Midazolam infusion plus 110 ml for Phenytoin /Acyclovir) that is 62 ml per hour. Thus the intended reduction of IV fluid volume advised at 23:30 to 2/3 requirement intended to be 41 ml/ hour did not happen. And there will have been additional IV fluid – probably 62ml/hour but not recorded- over 02:00 to 02:30 when the arrest occurred. (See Para 170)

101. The conscious level in Claire remained low with a Glasgow coma scale of 6. Her pupils remained responsive. Suddenly at 03:00 hours on 23 October, Claire had a respiratory arrest, was attended by the paediatric registrar who attempted unsuccessfully to intubate and resuscitated with mask and oxygen until the anaesthetic specialist attended. Claire was intubated and ventilated and transferred to the paediatric intensive care unit where she was found to have fixed dilated pupils. At 04:00 hours Claire was seen by Dr Steen, consultant paediatrician and by Dr Webb consultant paediatric neurologist. Claire was given mannitol, dopamine infusion and a CT scan was arranged which showed severe brain oedema. Further samples of blood were sent while Claire was on the intensive care unit one of which showed serum sodium of 152 and another 129 blood and osmolality was 274 with normal urea and glucose. At 08:00 hours, the intravenous infusion fluid was changed 0.9% saline. At 06:00 hours 23 October and again at 18:25 hours, brainstem death assessment was conducted. With parents agreement in the light of the results, ventilatory support was withdrawn at 18:45 hours. It was considered that on clinical grounds she had cerebral oedema secondary to status epilepticus. An autopsy limited to the brain was arranged with the consent of the parents.

102. **Comment on the care in the evening of 22 October and issues relating to hand over at 5 PM on that day from the day registrar to the on-call registrar.**

103. In the evening of the second admission day, when Claire was under the care of the general paediatric team, her blood sodium level was repeated and two hours later reported showing a significant reduction in blood sodium. By this time the level of consciousness had fallen. It is not evident whether the resident senior paediatrician-the registrar Dr Bartholome made a personal clinical assessment of her. The SHO on Allen ward recorded his concern about the possibility of syndrome of inappropriate ADH and proposed consideration of a change in the sodium content of the IV fluid . He referred the problem to Dr Bartholome who advised reduction in intravenous fluid volume rate but not any change in the intravenous fluid from 0.18%. This should have been done immediately. The intended reduction of infusion to 2/3 volume did not happen. It is not evident whether Dr Bartholome-the registrar on call in the hospital at night, was aware of Claire until this consultation. She should have

been. The daytime registrar (Dr Sands) should have handed over either personally or by telephone. Indeed given the severity of Claire's illness and the reduction in conscious level and the mixture of antiepileptic drugs including Midazolam that she was receiving, she should have been reviewed by the on-call registrar as a routine in the evening. Claire was receiving level I paediatric intensive care/high dependency care. By the standards of the day the handover should have taken place. A written recording of this handover however was not standard practice at the time although advised now. Handover has become a recognised risk area particularly in the 2000s especially as there is more frequent change of junior staff to meet junior staff hours. This was not the case in 1996.

104. The on-call registrar Dr Bartholome should have consulted the on-call paediatric consultant about the low sodium level associated with reduced conscious level. A consultation did not occur and it is not clear who the on-call consultant was. Elective intubation and ventilation should have been considered. A blood sample was sent for repeat sodium at 21:30h on 22 October but it was two hours before the result was seen by the doctors on the Ward. It is not clear why it took so long for this to happen. Nor how the result was transmitted to the Ward-was this by telephone (most likely) in which case why did it take two hours. It is not clear what the arrangements were for management of blood samples out of hours in RBHSC. There is a laboratory on site there but it not known to me if this is used out of hours or is the sample sent to the Royal Hospital main site. Was it necessary to call a technician in from home?

105. A consultant general paediatrician (or paediatric neurologist) should have been consulted by the junior doctors on 22 October at 23:30 when the blood sodium result was found to be low and Claire's conscious level had fallen. As Claire was on a Midazolam infusion (which can depress respiration) and was deteriorating, elective intubation and ventilation should have been considered at or before that time. Especially as the Midazolam dose was increased to 3ml/hour of infusion (160 microG/kg/hour) at 9.30pm (according to the nursing records- which generally are of good quality).

106. **Care provided by the paediatric neurologist at 2 PM, 4 PM and 5 PM assessments on 22 October and the prescriptions of antiepileptic drugs;**

107. After referral by Dr Sands , the general paediatric registrar, who spoke to Dr Webb around lunchtime, Claire was seen by Dr Webb consultant paediatric neurologist at 2 PM on 22 October, 19 hours after admission. By this time no attacks consistent with seizure had been recorded on the seizure chart although at 3 :25 PM she experienced a five-minute "strong seizure". This was followed at 4:30 pm by an episode of teeth tightening and groaning lasting a few seconds and again at 7:15pm lasting a minute and again at 9 PM lasting 30 seconds she had an episode consistent with seizure in the form of screaming and drawing up of arms. However, that was the sum total of her seizure activity.

108. At 2pm Dr Webb found her to have reduced conscious level, brisk reflexes and upgoing planters consistent with long tract signs. She had no papilloedema and he noted that her facial, palatal and laryngeal movements were normal (he was checking here to ensure that she had a gag reflex was able to protect her airway from secretion or vomit). Dr Webb concluded that she had an acute encephalopathy most probably post ictal. He made a note that biochemical profile was normal. He advised antiepileptic therapy

a. *starting IV phenytoin 18 mg/kilogram stat followed by 2.5 mg/kg 12 hourly. Will need blood levels 6 hours after loading dose. ii) hourly neuroobs iii) CT tomorrow if she doesn't wake up. Signed D Webb*

109. He reviewed her later at 4pm and 5pm. In the meantime a bolus IV dose followed by an continuing infusion of Midazolam were prescribed. The bolus was possibly omitted. If so it is not evident from the records by whom and by what means or why.

110. At 1700 :

a. *090-022-055*

b. *Dr Webb handwriting " Claire has had a loading dose of phenytoin + a bolus of Midazolam . She continues to be largely unresponsive. She responds by flexing her (L) arm to deep supra-orbital pain+ does have facial grimace-but no localisation. She has intermittent mouthing and chewing movements. Background from mum-contact with cousin on Saturday who had a gut upset. Claire had loose motions on Sunday+ vomiting Monday. She had some focal SZS on Monday with right side stiffening. Plan 1) cover with Cefotaxime and Acyclovir from 48 hours I don't think meningoencephalitis very likely.2) check viral cultures ? enterovirus -stool, urine, blood and T/S*

c. *3) add IV sodium valproate 20mg/kg IV bolus followed by infusion of 10 mg/kg IV over 12 hours." Signed D Webb*

111. **Comment on the Care provided by the paediatric neurologist at 2 PM, 4 PM and 5 PM assessments on 22 October and the prescriptions of antiepileptic drugs;**

112. The assessment of the paediatric neurologist on 22 October 1996 has a number of shortcomings. The investigation and management was not consistent with guidance at the time for investigation and management of acute encephalopathy including need for CT and EEG investigation and a range of blood tests (see below). And in particular the fluid management for acute encephalopathy of any cause required a reduction in infusion volume and increase in strength of sodium in the infusion fluid. Guidance available in 1996 even states "***In many cases treatment of cerebral oedema is required to be presumptive. Fluid should be restricted to 60% of estimated daily requirements; low sodium containing infusions like 5% dextrose or 0.18% saline in 5% dextrose are contraindicated….." (*** *Textbook of Paediatrics. Forfar & Arneil Third edition 1984 Page 791 et seq.)*

113. I refer to this later in and more detail is given in Annex A

114. RBHSC did not have guidelines in October 1996 but introduced "Paediatric Medical Guidelines " in May 1997. The second edition was later produced (a copy of which is no longer available) and a third edition in January 2003 which was renamed "Managing Medical Problems In Children. " The letter of 26/10/2011 from DLS encloses editions one and three. A fourth edition is in the process of being drafted but is not yet available.

115. 9/9/2011.Letter from DLS. " RBHSC did not in October 1996 and does not now have guidelines, procedures or protocols on the diagnosis and management of a child with reduced level of consciousness."

116. In a guideline on the child with reduced level of consciousness published in 2006, non traumatic coma (defined as GCS of <=12 for >=6hours) is reported as occurring as 30 per 100,000 children (N.I population = NNNN) *Bowker et at Arch Dis Child Edu&Prac Ed 2006;91:ep115-ep122*. The development of this guideline itself indicates concern that the condition needs to be managing in a more structured way and was produced following encouragement by a parental support group for Reye's syndrome who funded the its development to improve the management of acute encephalopathy in childhood. One of the country's leading experts in the management of Reyes syndrome-an acute encephalopathy mainly but not entirely affecting younger children, was Dr J Glasgow who was based at RBHSC. A more structured standard of management could thus be expected in RBHSC in the middle 1990s. Conventional management of Reye encephalopathy at that time included fluid restriction and monitoring serum osmolality.(e.g. *Recognition and early management of Reye's syndrome Dezateaux et al Arch Dis Child 1986;61:647-651)*.

117. The dose calculation of the bolus Midazolam and the prescribed dose were both well above advised doses (the infusion was within advised dose). Dr Webb did not notice this.

118. However by the time that Claire was seen by the paediatric neurologist she was known to have an established encephalopathy and the IV fluid should have been changed and this should have been part of the advice provided by the paediatric neurologist irrespective of any serum sodium results.

119. Claire had an acute encephalopathy of uncertain origin. The paediatric neurologist Dr Webb confirmed a diagnosis of non-convulsive epileptic status as his working diagnoses following his assessment at 14:00 hours, 16:00 hours and 17:00 hours and managed her specifically for that disorder. The clinical arguments however for this diagnosis were weak. Although Claire in infancy had at one time been considered to have infantile spasms which is a form of myoclonic seizure, the EEG was not consistent with that in 1987 at age 8 months nor was her later clinical course where she experienced episodes of tonic/clonic seizures which became reasonably well controlled. Non-convulsive status usually occurs in children with myoclonic or

mixed epilepsy particularly in children who have poorly controlled epilepsy. Claire had not had seizures since the age of four years and when admitted age 9 years had had no seizures for 5 years. She had been off antiepileptic drugs without seizure recurrence for 18 months. There is no clear record that she had a fit before admission. During the course of this acute illness Claire had a few short lasting events suggestive of seizure but these could have been explained as manifestations of altered pressure from the acute encephalopathy of any causation or a seizures generated by any underlying acute encephalopathy. It would be expected practice to confirm the diagnosis of non-convulsive status (or refute it) by arranging EEG. This investigation was available but not requested.

120. Advised practice at the time in 1996 (*Textbook of Paediatrics. Forfar & Arneil Third edition 1984 Page 791 et seq. and other publications see Annex A)* indicated a range of diagnostic tests including blood tests and CT scanning. These should have been carried out when Dr Webb assessed her-instead he planned to do a CT scan the following day if she did not improve. The CT scan was not on the same site as RBHSC and this investigation would have been cumbersome but was indicated. It is a deficiency of the hospital arrangements that in the mid-1990s a CT scan was not on site. It would help to know whether this deficiency had been documented by clinicians to management through the clinical directorate or medical advisory processes and there may be minutes which relate to this. I have noted that a CT scan is now on site but that it was only from 2002 that this became the case despite the fact that paediatric intensive care was provided in RBHSC and a regional paediatric neurology service which dealt with acute neurological problems. For a major regional children's centre this is a late addition to the range of supporting imaging facilities. An EEG was available within working hours.

121. Dr Webb should have been well aware of the significance of the slightly reduced blood sodium in a child with acute encephalopathy (in which there is a high risk of SIADH) which had been reported the previous night and he should have advised changes in the intravenous fluid regime both in terms of reducing infused volume and changing to a fluid with higher sodium content. He should have ordered further monitoring of the blood sodium but instead erroneously recorded that electrolyte results were normal. Although in his statements he ascribes this oversight to the fact that he thought the test had been done just before he saw Claire, this is difficult to understand because the entry of the result is in the notes in handwriting and timed The guidance available at the time on management of acute encephalopathy included taking steps to anticipate and attempt to prevent or manage the syndrome of inappropriate ADH which is well known to complicate and worsen acute encephalopathy/brain oedema. Instead of advising a fluid regime, as he should have done, he left the fluid management to the general paediatric team.

122. The Collapse 23 October 1996 03:00 Hours And Care In Intensive Care

123. Claire deteriorated suddenly at 2:30 AM in the morning 23 October 1996 rapidly sustaining a respiratory arrest, was resuscitated intubated and ventilated. She was taken to the paediatric intensive care unit. Claire was resuscitated by the

registrar who required assistance from an anaesthetist in order to secure the airway with intubation and ventilation. It is not clear what the interval was between arrest and intubation during which Claire's respirations were managed with bag and mask. No notes were made by the resuscitating doctors-the anaesthetist or the registrar to document timings. This should have been done retrospectively as soon as Claire had been intubated and ventilated. This is a major shortcoming of record keeping.

124. At this point Dr Steen consultant paediatrician who had been on call when Claire was admitted on 21 October, was called to see her. It is not evident whether Dr Steen was on call for acute general paediatrics that night. In addition Dr Webb consultant paediatric neurologist attended at 4 AM 23 October together with Dr Steen. Before this arrest occurred, Claire had been given intravenous phenytoin, intravenous sodium valproate, acyclovir and cefotaxime as advised by Dr Webb at 17:00 hours on 22 October. She had also been given an infusion of Midazolam .

125. Although the admission nursing record to the intensive care unit indicates that the Midazolam infusion was still in place, Dr Steen notes at 04:00 hours that she had a blood phenytoin level at 20:30 hours the previous night of 23mg/l which is within the treatment range and also that the Midazolam was no longer running.

126. A blood sodium level was obtained in the paediatric intensive care unit but it is not evident from the laboratory forms at what time the samples were obtained. Copies are shown below and show one at a level of 152 and another at 139 mmol/l. Although both of these forms show their origin as the intensive care unit, with the name of Dr PM Crean on the top, there is no report of the time of the sample, its processing or reporting although the date is given.

127. This is not a good standard of quality in the laboratory reporting process and documentation. This should have been addressed through governance procedures.

128. Other comments upon the management in the intensive care unit are :

129. The IV fluid does not appear to have been changed from a 0.18% sodium until Dr Mc Kaigne records this at 08:00 hours.

130. Dr Robert Taylor took over in PICU at 0830 and at 10: 00h or thereabouts (7 hours post arrest) made a note.

131. The brainstem death procedures carried out by Dr Steen and by Dr Webb at 06:00 hours use a standard form which is of good quality but in response to the question about whether drugs are in use which might affect level of consciousness, the answer is given as no when in fact Claire had a blood level of phenytoin at or just below the treatment range (a drug which can affect level of consciousness) and also had in the previous hours had Midazolam although it is likely that this had cleared. She had also been given sodium valproate which may still have been present in the bloodstream. Consequently although this is not likely in any way to the affected the results of the assessment of brain death, it is a failure of adequate and proper documentation. There is a handwritten entry that that the blood sample at the time of brainstem death tests showed Na 129, K 3.6,Cl 94 urea 3.7, glucose 7.2 osmolality 274 but I am unable to find a laboratory report giving these findings nor was I able to find in the notes the printout of the results obtained at 21:30 hours on 22 October which showed significant deterioration in the form of a very low sodium Na (Na 121 K 3.3, Urea 2.9,Creatinine 33).

132. 090-050-154. **Witness statement dated 16/3/2005. Dr Steen.**

133. "Dr Webb and myself discussed Claire ‘s condition with her parents, emphasising that we felt she had cerebral oedema as confirmed by her CT scan which had resulted in coning of her brain and brainstem death. We also discussed the possibility of organ donation."

134. *"At 06:00 hours Dr Webb and myself completed brainstem death protocol and blood which was drawn for U&E at that time showed a sodium of 129 mmol/l ..”*

Comment It is difficult to establish the sequence of blood sampling during the period in intensive care. The laboratory printout reports do not contain information on timing of receipt of sample by the laboratory and this is a significant shortcoming and quality management issue. However it is possible to conclude from the laboratory number on the reports that the blood sodium estimation of 139 with an osmolality of 287 was obtained before the next one because the laboratory number is 20553 whereas the next one showing a serum sodium of 152 with osmolality 313 carries the number 20996.

Lab report number	***Na***	***K***	***Cl***	***Urea***	***Cr***	***Osm (285-290)***	***Ca***
20553	139	3	103	3.4	34	287	
20996	152	2.8		3.3		313	2.69

135. In the clinical note made by Dr McKaigne at 0710 on 23 October 1996 he refers to a serum sodium checked when the brainstem test was done from the blood gas analyser as 133 but then goes on to report a blood sodium from laboratory showing sodium 129, osmolality 274. But I was not able to find the lab report on this. He also reports that Dr Webb/Dr Steen discussed Claire's clinical condition with her parents "they initially appeared to be giving consent for organ donation “Dr Webb will speak again to both parents at 10 AM.

136. Communication with Parents

137. On Allen ward there is little contemporary documentation about communications with the parents. The impression that the parents gained was not of

a child who was very seriously ill and they have stated this in their reports when they decided to leave the Ward in the evening. Yet in retrospect in his witness statement Dr Sands indicates that both he and the nursing staff did feel that Claire was significantly unwell. In these circumstances this information should have been shared with parents. On the PICU at 18:25 hours on 23 October , Dr Steen entered a note "discussed with parents and agree that ventilation should be withdrawn. Consent limited PM given."

138. The nurse records note “explained to parents that Claire's brain had swollen and that CT scanning and brainstem tests showed Claire's brain had died only the ventilation was keeping her heart beating." Relative counselling record. This is a good record.

139. This appears to be the limit of the recording of discussions with parents about Claire's state. I believe that discussions by the doctors with the parents should have been recorded in more detail and why the autopsy was to be limited.

140. Father recalls that Dr Steen told him that there would be no need for an inquest.

141. There is little documentation following the collapse and admission to intensive care about what was said to the parents at that time and also the reason for selecting to choose a brain only autopsy which has limited some of the information which may shed light on the cause of the encephalopathy.

142. The issue of documentation of communication with parents was addressed in the 2010/2011 RCPCH multisite audit on the child with reduced level of consciousness and the results of that are shown in the extract below (full document is attached “ library of documents” accompanying my report) . Lack of recording of communications was frequently recorded

Care of Children and Young People Presenting to Hospital with a Decreased Conscious Level

6.8 Question 8: Documentation of Parental or Guardian involvement (Table 7)

Audit Question:
During the initial management and resuscitation of the child or young person presenting to hospital with a decreased conscious level, were their parents or guardians' involvement in their care documented in the clinical record?

- Parent or guardian allowed to stay with their child
- Parent or guardian informed regarding their child's possible underlying diagnosis or treatment
- Parent or guardian informed regarding their child's possible prognosis

Source of the standard:
The Management of a Child with a Decreased Conscious Level guideline and the Decreased Conscious Level Project Board Team

Table 7: Documentation of Parental or Guardian involvement during the initial management and resuscitation: Audit standards

Audit standards	Total audit sample	Cases meeting the standard	% Cases meeting the standard	Median percent (95% Confidence Interval)
parent or guardian allowed to stay with their child	1135	426	37.5%	33.3% (24.3%, 50.0%)
parent or guardian informed regarding their child's possible underlying diagnosis and treatment	1135	532	46.9%	50.0% (40.0%, 60.0%)
parent or guardian informed regarding their child's possible prognosis	1135	400	35.2%	35.1% (22.4%, 50.0%)

143.

264. **FLUID MANAGEMENT**

265. Volume. Calculation of maintenance total fluid needed for children is based on body weight in a well defined formula (see APLS handbook amongst other sources) as for each 24 h period:

First 10 kg body weight 100ml/kg

Next 10 Kg body weight 50ml/kg

Subsequent kg 20ml/kg

266. For 24 kg body weight as was the case in Claire, this adds up to 1580 ml per 24 hours total (oral and IV) that is 66ml/hour.

267. Over the 8 hours overnight 21-22 October 1996, Claire received 536 ml of 0.18% saline in 4 % dextrose that is 67ml/hour.

268. On the 22 October between 0800 and 2200h Claire received total of 960 ml (68ml/hour) made up as 943ml of maintenance 0.18% saline plus 10.9 ml fluid for the Midazolam infusion and 60 ml for the acyclovir. Phenytoin is also recorded on the fluid chart but it is not clear if this was in additional fluid. The fluid balance chart is not clear on this last point.

269. Between 2200 h 22 Oct and 0200 23 October Claire received a total of 247.6 ml (127 ml of 0.18% plus 10.6ml as Midazolam infusion plus 110 ml for Phenytoin /Acyclovir) that is 62 ml per hour. Thus the intended reduction of IV fluid volume advised at 23:30 to 2/3 requirement intended to be 41 ml/ hour did not happen. And there will have been additional IV fluid – probably 62ml/hour but not recorded- over 02:00 to 02:30 when the arrest occurred.

[redacted] [redacted]

[redacted] [redacted]

[redacted] [redacted]

Statement of Truth

I understand that my duty as an expert is to provide evidence for the benefit of the Inquiry and not for any individual party or parties, on the matters within my expertise. I believe that I have complied with that duty and confirm that I will continue to do so.

I confirm that I have made clear which facts and matters referred to in my report(s) are within my own knowledge and which are not. Those that are within my own knowledge I confirm to be true. The opinions I have expressed represent my true and complete professional opinions on the matters to which I refer, having studied all the relevant documents supplied to me.

I confirm that I have no conflict of interest of any kind, other than any disclosed in my report(s). I do not consider that any interest that I have disclosed affects my suitability as an expert witness on any issue on which I have given evidence. I undertake to advise the Inquiry if there is any change in circumstances that affects the above. I have no personal interest in supporting any particular point of view.

I understand that I may be called to give evidence.

Signed: Date: 5 Aug 2012

(RODERICK MAC FAUL)

Witness Statement Ref. No. 263/1

NAME OF CHILD: Claire Roberts

Name: Roderick MacFaul

Title: Consultant Paediatrician (Retired)

Present position and institution: Retired from Pinderfields Hospital Wakefield (2006)

Previous position and institution:

See attached cv

Membership of Advisory Panels and Committees:

See attached cv

Previous Statements, Depositions and Reports:

N/A

OFFICIAL USE:
List of reports attached:

Ref:	Date:	

Particular areas of interest:

General and Emergency Paediatrics with Special Interest in Paediatric Neurology

Development of Standards of Clinical Practice and Services including Clinical Governance and Audit (including National Audits)

See cv

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

Signed: | **Dated:** 5 Aug 2012

SUMMARY CV Dr Roderick MacFaul

Clinical practice.

From 1978 consultant paediatrician Pinderfields Hospital Wakefield and Hon Senior Lecturer University of Leeds (retired March 2006). Special interests in emergency paediatrics and care of childhood disability (having trained in paediatric neurology and general paediatrics). Research interests continue and are in use of acute paediatric services and acute illness management.

National professional contributions.

Former Honorary Secretary British Paediatric Association and first Vice President of its successor body the Royal College of Paediatrics and Child Health.

For 7 years up to summer 2003 Paediatric Adviser Department of Health England responsibilities included child health policy and service development inter alia set up and chaired national DH neonatal care review and DH paediatric high dependency working party, established the national paediatric intensive care and neonatal care audit programmes, facilitated the development of the British National Formulary for Children, provided supporting arguments for NHS plan targets, the set up of the National Service Framework and involvement in a number of its working groups and contributing to the NSF publications released in 2004 and 2005. Chaired the UK national newborn screening programme board until December 2005. Retired from Mid Yorks NHS Trust in March 2006 but part time national clinical lead for Connecting for Health child health programme set up in 2007 until June 2008.

CURRICULUM VITAE - RODERICK MACFAUL

Date of birth: [redacted]

Home Address:

[redacted]

Telephone: [redacted]

Present Position:

Consultant Paediatrician
Pinderfields General Hospital

Aberford Road
WAKEFIELD
WF1 4DG

Honorary Senior Clinical Lecturer
Department of Paediatrics & Child Health
University of Leeds

Tel: [redacted] Fax: [redacted]

Professional Interests:

Paediatric Neurology
Handicapped children and the care of physically disabled children
Member of British Paediatric Neurology Association
Member of North of England Neurological Association

Qualifications:

MB ChB	University of Leeds 1968
DCH	Royal College of Physicians and Surgeons, Glasgow 1970
MRCP (UK)	1973
FRCP	1986
FRCPCH	1997

Posts Held:

1968	House Surgeon, Otley General Hospital
1969	House Physician (Paediatrics), Seacroft Hospital, Leeds
1969 - 1971	General Practice in Army in Colchester
1971 - 1973	SHO and Registrar in Paediatrics, British Military Hospital, Singapore
1973 - 1975	Registrar in Paediatrics, British Military Hospitals, Germany
1975 - 1976	Registrar in Paediatric Neurology at Hospital for Sick Children, Great Ormond Street and in Developmental Medicine and Child Neurology at Newcomen Centre, Guy's Hospital, London Paediatric Registrar, Northwick Park Hospital
1976 - 1978	Senior Registrar in Paediatric Neurology, Hospital for Sick Children, Great Ormond Street Senior Specialist in Paediatrics, Cambridge Military Hospital, Aldershot

1978 -	Consultant Paediatrician, Pinderfields General Hospital, Wakefield

Prizes etc:

MB (Distinction in Medicine), University of Leeds (1968)

West Riding Practitioners Prize in Medicine, University of Leeds (1968)

Montefiore Prize in Military Surgery, Royal Army Medical College (1969)

Elected Honorary Fellowship Royal College of Paediatrics and Child Health (2000)

Elected Honorary Membership British Association Perinatal Medicine 2004

Administrative Activities:

Chairman	Wakefield Hospital Medical Committee (1982 - 85)
Chairman	District Research and Ethical Committee (1982 - 85)
Chairman	Medical and Surgical Equipment Sub-Committee (1982 - 85)
Chairman	Special Professional Committee (1982 - 85)
Consultant Member	General Unit Management Group (1984 - 86)
Deputy Consultant Member	District Management Team (1982 - 86)
Member	Yorkshire Regional Health Authority Neurological Services Working Group (1981 - 1991)
Divisional Co-ordinator	Medical Division. Pinderfields Hospital NHS Trust (1993 - 1996)
Clinical Director	Women & Children's Services, Pinderfields Hospital NHS Trust (1997 -98)
Clinical Director	Children's Services, Pinderfields & Pontefract NHS Trust(1998-2005)

Professional Activities:

Secretary	Yorkshire Regional Paediatric Society (1981 - 86)
Regional Representative	Council British Paediatric Association (1984 - 85)
Honorary Assistant Secretary	British Paediatric Association (1985 - 89)
Honorary Secretary	British Paediatric Association (1989 - 94)
Vice President	Royal College of Paediatrics and Child Health (1994 - 1997)
Medical Adviser Paediatrics & Child Health	Department of Health (1996 -2003) [part-time]

Committees & Working Parties:

Paediatric Committee Royal College of Physicians of Edinburgh (1987 - 1994)

Paediatric Committee Royal College of Physicians of London (1988 - 92)

Health Statistics Committee British Paediatric Association (1988 - 89)

Caring for Children in Health Services Committee (NAWCH, NAHA, RCN, BPA) (1986 - 89)

Medical Audit Working Party, Royal College of Physicians of London (1987 - 93)

Working Party Workload in Paediatric Units (BPA) (1986 - 87)

Central Manpower Committee (1989 - 95)

Standing Medical Advisory Committee (DoH) (1990 - 1996)

Working Party District Indicators of Quality of Care, Faculty of Public Health Medicine (1990 - 92)

Paediatric Board Royal College of Physicians of London (1992 - 1995)

Manpower Committee RCP London (1991 - 1994)

Audit Commission: Advisory Panel for Care of Sick Children in the NHS (1991 - 93)

Joint Working Party on Medical Services for Children BMA/Conference MRC + DoH (1992)

BPA Academic Board, Health Services Committee etc

London Implementation Group 1993 Children's Specialist Services

College Manpower Advisory Panel of CMC (Paediatric Rep) 1992 - 95

RCP Working Party on Staff Grade 1993

RCP Working Party on Alcohol and the Young 1993 - 94

Steering Committee BPA Appropriateness of Admission Audit (Chair)

Subgroup of Joint Working Party on Medical Services for Children on Training for CMO's and SCMO's (Chair)

Regional Advisers Committee BPA (Secretary) 1989 - 94

Executive Committee and Council BPA (Secretary) 1989 - 1994

BPA Research Unit Steering Committee 1994 - 1997

Council of National Association for Education of Sick Children 1994 - 1995

Medical Scientific Advisory Committee Children Nationwide (Chairman) 1994 -

SMAC Working Party on Sickle Cell and Haemoglobinopathy

SMAC Working Party on Community Care

Chairman Health Services Committee, British Paediatric Association/RCPCH 1994 - 1997

Member JCC Working Party on Paediatric Staffing

Chairman BPA/RCPCH Working Party on Future Configuration of Paediatric Units 1996

Chairman joint RCPsych/RCPCH Working Party on Dangerous and Disruptive Children 1996 -

Chairman RCPCH Working Party on Ambulatory Care 1996

Council member Royal College of Physicians 1994 - 1997

GMC Professional performance review development project for paediatrics 1996-1998

Medical Vice Chair Yorks and Humber Regional Clinical Excellence Awards Committee 2002-5

Examiner: Diploma in Child Health, RCP (1985 - 1991)
University of Sheffield - School of Medicine (Speech Therapy) 1985 - 1991
MRCP RCP London (1993 -)

Publications:

MacFaul R, Grant D B. Early detection of Congenital Hypothyroidism, Archives of Disease in Childhood 1977; 52: 87.

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Lead author of:

Paediatric Medical Staffing for the Nineties
British Paediatric Association 1991.

Towards a Combined Child Health Service
British Paediatric Association 1991.

Management Models for a Combined Child Health Service
British Paediatric Association 1992.

Hospital Paediatric Medical Staffing
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Purchasing Guide to Paediatrics and Child Health Services: 1994

Purchasing Health Services for Children and Young People. Vol I: Summary. British Paediatric Association 1994.

Future Configuration of Paediatric Units. 1996

Ambulatory Paediatrics. 1997

On Steering Committee of Caring for Children in the Health Services Consortium: RCN, NAWCH, BPA, NAHAT, producing following documents:

Where are the Children 1987.

Hidden Children 1988.

Parents Staying Overnight with their Children 1988.

DoH Advisory Groups:

Advisor to Nucleus Design 1992 and Health Building Note 1994 for Children's Departments (NHS Estates).

Advisor to National Casemix Office on Healthcare Resource Groups and Consultant Episodes.

Integrated Clinical Workstations Project Board and pilot project in England for Clinical Coding and Classification Centre (IMG).

OP HRGs for paediatrics NHSIA

Children's National Service Framework 2003/4 : (a) hospital services for children, (b) the ill child, (c) medicines for children

Paediatric Service and Standards Reviews 1992-2006

Paediatric Member of Regional Inquiry into Paediatric Services Grantham and Baby deaths (Allitt)

Review of Paediatric Services in London Region (& with Sir David Hull constructed the report and recommendations)

Review of Children's Services South Downs HA

Review of Children's Neurosurgical Services for South of Thames

Review of Paediatric Services (various dates) in : Northwick Park Hospital, Bradford, Heart of England – Birmingham, E London

Current Research Activities

Development of UK Appropriateness of Paediatric Admission Protocol (DOH/BPA Funding)

Paediatric Medical Episodes. National Casemix Office/BPA

Development of guidelines for paediatric admission. Queen's Medical Centre, Nottingham. Children Nationwide.

Development of acute illness severity scale for use in acute general paediatric practice. Research Unit RCPCH/ Well Child funding

Chair Scientific Medical Advisory committee Children Nationwide now WellChild

Referee Archives of Disease in Childhood

Evaluation of video telemedicine assessment of acutely ill children for Modernisation Agency

MEDICAL ADVISER IN PAEDIATRICS AND CHILD HEALTH- Department of Health England 1996 to 2003.

During the period of secondment the following have been undertaken

Screening

- Establishing the child health subgroup of the National Screening Committee and identifying a chairman and its terms of reference. Developing its interplay with child health surveillance and costing the child health services

- Specified and set up the national newborn bloodspot programme board and, for the health departments of England , Wales, Scotland and Northern Ireland, Chair UK Programme Board for blood spot screening 2003-2005.

Critical care for children

- Implementation of the Paediatric Intensive Care agenda.

- Specified and set up in 2001 a national PIC audit PICANet.

- Set up and chaired DH working party setting standards for high dependency care (level 1 intensive care) services in all hospitals where children are treated.

- Set up and chaired external reference group for national review of neonatal intensive care and produced its report in 2001 and the successful argument to ministers for £ 75m additional funding

- Specified, set up and agreed funding for national Neonatal Intensive care audit – chair DH steering group with Healthcare commission to commission it. Started January 2005.

Medicines for children

- Producing national guidance on the use of Vitamin K in new-born babies.

- Dealing with the issue of unlicensed medications for children. Involved in the establishment of the CSM paediatric strategy group jointly with the then MCA.

- With R&D division brokered drafted and agreed specification and funding for a national paediatric pharmacology research network

- Brokered the successful proposal to provide a BNF for children

Acute care for children

- Set up via RCPCH a profile of all paediatric units in E&W to enable service configuration reviews and assist in workforce planning

- Provided the workforce planning model used by DH and by RCPCH.

- Advised DH and NHS Estates in the requirement for the built environment for children's care in hospital

- Provided Emergency Care Clinical Director with report on the needs for emergency care in children highlighting the yet unresolved interplay in UK between primary accessed and hospital based specialist care..

- Carried out a study of out of hours needs of children for the Hospital at Night project showing that Paediatrics needed a different solution from adult services

- Specified and commissioned a study on impact of short stay paediatric units on hospital utilisation and costs (increases them)

- In 2000 originated the project and commissioned DH DVD training materials ' Spotting the Sick Child' for recognition of acutely ill children released with the NSF.

- Characterised the training and CPD needs for surgical and anaesthetic services for children for DH working with the RCs. Inter alia assisting with the identification of the range of speciality services for children and chairing a review on the retinoblastoma service.

- Identified the need and provided the argument in 2002 on the requirements for nurses with enhanced skills in general, neonatal and community paediatric practice

Child health

- Initiated work on the health needs of looked after children though later fully developed by Professor Margaret Lynch.

- Ensured that the health input to the millenium cohort study was strengthened

- Initiated work on children's well-being indicators for Social Care, commissioned report from NCHOD and with LRO arranged pilot in London.

- Commissioned a report on the health needs of school aged children.
- Commissioned ALSPAC to provide data on health demands in 7 year old children.

- Reviewed the school health services and provided a comprehensive document as foundation work for national service framework.

- Provided the advice and information to set the 'Quality Protects ' programme for the care of disabled children.

- Provided arguments for set up of NSF and the targets for child mortality and morbidity which are in the NHS plan Information strategy

- Arranged funding for scoping of child health information needs in 2001

- Worked with Healthcare commission to develop targets to be in place based on existing data collections

- Argued to get greater priority to the major information needs of children bridging the primary, community and hospital based service IT needs

- Initiated and steered together with Professor Paul Johnson and Dr Yvonne Arthurs the report on the Health of the Nations Children produced by NE PHO and published 2005.

Evidence based care

- Initiated the existing children's programme of topics for NICE : asthma inhalers, growth hormone, urinary tract infection, head injury and feverish illness in children.

- Set up and funded a pilot project for a structured enquiry into each in-hospital child death subsequently proposed to NICE and then to CEMACH now being adopted as a new confidential enquiry.

- Developing specification for an R&D programme for children's acute and chronic disorder health needs and care including what parents and cares expect from services. Liaised with NPSA.

- Provided a comprehensive horizon scanning overview of future paediatric demand and needs

DH continuing work 2004-7
Chair UK National Programme Board for newborn screening (retired June 2005)

Chair Programme Board for Healthcare commission National Neonatal Intensive Care Audit Programme

Steering group for report of the state of health of the nation's children for DH and DFES

Project lead for Connecting for Health on Children's Prescribing

Lead for CfH on digital development of the BNF for Children

2007-2008 National clinical lead child health programme NHS IT programme Connecting for Health
END

ANNEX A

GUIDANCE ON ACUTE ENCEPHALOPATHY AVAILABLE IN 1996

Textbook of paediatrics. Forfar & Arneil Third edition 1984 Page 791 et seq (similar in later editions)

.."the large number of possible causes of acute encephalopathy makes early specific diagnosis difficult or impossible; treatment may often need to be instituted urgently on empirical grounds (anticonvulsants, antimicrobial therapy, anti-brain oedema measures) while the results of investigations are awaited. A diagnosis of "viral encephalitis" should not be accepted until further investigation has excluded numerous other systemic or neurological disorders which may present with similar findings. Excluding accidental head injury, the most important causes of acute encephalopathy in infancy and childhood in temperate climates are infection (33%), asphyxia (20%) intracranial haemorrhage (16%), toxic/metabolic conditions (12%)….. In porphyria, a rare disorder, it is mentioned in this book on page 83 that inappropriate ADH secretion may occur).

"It should also be remembered that part of the spectrum of child abuse includes the intentional administration of drugs or other agents. These infants and children present difficult diagnostic problems if this possibility is not borne in mind."

"Continuing convulsions maybe subclinical (and detectable only with EEG monitoring) or easy to miss e.g. episodes of paroxysmal nystagmus or contribute deviation of the eyes: sucking chewing and swallowing movements frequently represent brainstem release phenomena secondary to swelling of the brain. Mid brain compression from cerebral shifts causes ophthalmoplegia. Further evidence of raised intracranial pressure and the celebration may be obtained by examining for evidence of the cerebral posturing and opisthotonus.."…

Decerebrate rigidities often accompanied by cycling movements of the lower limbs and doggy paddling movements of the upper limbs. It is important to note that papilloedema may be a late or absent sign even in the presence of significantly raised intracranial pressure.

The list of investigations advised similar to that in the later edition

In this text (Forfar and Arneil 1984) it is recommended on page 807 that children who have an acute encephalopathy with coma should have their urea, electrolytes, creatinine, calcium and osmolality done twice daily. The EEG should be carried out daily or continuously. Intracranial pressure monitoring in selected cases. Blood glucose four hourly. Treatment includes treatment of convulsions.

"The possible presence of raised intracranial pressure in acutely ill children is frequently overlooked and this is particularly the case if clinicians rely on the frequently absent 'classical signs ‘of raised intracranial pressure. The only reliable means of excluding raised intracranial pressure is to monitor it.

……………..

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

On page 809, the prognosis listed is that death occurs in 27% of coma, mild handicap and 13% and complete recovery 45%.

THE RELEVANT PAGES ARE SHOWN BELOW

Table 14:16

Suggested Investigations in Infants and Children Presenting with Undiagnosed Coma and Convulsions

Blood glucose (or Dextrostix)
Capillary or arterial gases
Haemoglobin; white cell count; differential with platelet count
ESR. Blood film
Coagulation screen
Blood culture; viral serology (paired sera)
Tuberculin testing
CSF examination (*see text)
Viral and bacterial cultures (nose; throat; urine; faeces)
Urea and electrolytes; creatinine; osmolality
Calcium, phosphate, alkaline phosphatase
Bilirubin; transaminases; ammonia (collect onto ice)
Chest X-ray; skull X-rays; skeletal survey
Urinalysis—Labstix; Phenistix; microscopy
Serum and urinary aminogram
Urinary porphyrins
Serum and urinary amino acids
Serum and urinary organic acids (if persistently ketotic or acidotic)
Serum and urinary toxicology (drugs; solvents; heavy metals)
Toxicology of gastric aspirate
Ultrasound (skull)
CT scan
EEG

fluid for diagnostic purposes if CSF pressure is not elevated above 15–20 mmHg. Once obtained, cerebrospinal fluid should be examined as soon as possible for cell count, glucose and protein levels, by Gram staining and in selected cases by Ziehl-Neelson staining. The more widespread application of microcentrifugation techniques (e.g. 'cytospin') has facilitated the early identification of unusual CSF constituents, e.g. tumour cells, macrophages, and the monitoring of treatment of meningitis and encephalitis. Modern immunological techniques (e.g. radioimmuno assay, countercurrent immunoelectrophoresis and enzyme linked immunadsorbent assay) are invaluable for the early detection of bacterial antigens e.g. pneumococcus and haemophilus. This allows the clinician to anticipate the natural history of a given meningitis and plan optimum antibiotic therapy. If blood-stained CSF is obtained and a traumatic tap is suspected this may be excluded by serial clearing of samples as CSF collection is undertaken; if clearing does not occur and intracerebral bleeding is suspected, CSF spectrophotometry may be undertaken. Fresh bleeding causes an oxyhaemoglobin peak whilst old blood from an established intracerebral bleed is associated with detectable bilirubin and methaemoglobin.

No potentially useful samples from patients suffering from encephalopathy should be discarded. *Gastric aspirate* may yield detectable drugs and toxins; analysis of *urine* may detect toxic metabolites and drugs undetected on assay of serum.

Ultrasound examination of the intracranial space is becoming increasingly accurate and may detect intracranial bleeding, significant brain shift, and ventricular dilatation. This is particularly applicable in infants where the patent anterior fontanelle provides a convenient ultrasonic window. As noted above the increasing availability of *CT scanning* has greatly facilitated the diagnosis of numerous brain lesions, e.g. cysts, tumour, abscess, necrotizing encephalitis (herpes simplex), tuberculoma, intracranial bleeding, cerebral oedema and hydrocephalus (see Fig. 14:63). Scanning should be carried out as early as possible to avoid inappropriate treatment or delay in specific measures, e.g. drainage of an abscess, antiviral chemotherapy, or clipping of a leaking aneurysm

Early *EEG examination* may reveal continuing unsuspected epilepsy indicating the need for more aggressive anticonvulsant therapy. Focal epileptic discharges or focal slow waves may indicate a local lesion such as focal necrotizing encephalitis due to herpes simplex or focal suppuration due to a pyogenic abscess. Most often the EEG in acute encephalopathy demonstrates diffuse slow wave activity compatible with recent convulsions, cerebral oedema, or diffuse viral or post-viral encephalitis.

MANAGEMENT OF INFANTS AND CHILDREN WITH ACUTE ENCEPHALOPATHY

The management of infants and children with acute disorders of the CNS depends on the nature and severity of the underlying condition and the results of preliminary investigations noted above. It is important to ensure that the patient's general condition is closely monitored and in selected cases admission to a medical intensive care area may be desirable. It is suggested that adequate monitoring should include measurement and close recording of the parameters listed in Table 14:17.

In addition, regular recordings should be made of pupillary reactions, response to stimuli, pulse, temperature, respiratory rate (with ventilator settings if applicable), fluid input and output, and daily weight. Care should be taken in ensuring regular changes of position to avoid pressure sores and positional deformity. Attention should be paid to oral hygiene, eye care, state of hydration and nutrition, and the presence of abdominal distension potentially due to bladder enlargement, ileus or severe constipation. Specific therapy is considered under the following headings.

1. Correction of ischaemia and hypoxia
2. Treatment of convulsions
3. Reduction of intracranial pressure
4. Treatment of infection
5. Correction of shock, homeostatic defects and intoxication.

Table 14:17

Intensive Care Monitoring in Patients with Encephalopathy and Coma

Blood gases	4 hourly
Dextrostix or blood glucose	4 hourly
Urea, electrolytes, creatinine, calcium, osmolality	Twice daily
Coagulation screen Liver function tests	Once daily (reducing after 48 hours)
ECG	Continuous
BP	Continuous
EEG	Daily or continuously
Intracranial pressure (see text)	Continuously (selected cases)

CORRECTION OF ISCHAEMIA AND HYPOXIA

An adequate airway must be ensured and in cyanosed patients oxygen administered empirically with early measurement of blood gas status. Carbon dioxide retention and hypoxaemia cause cerebral congestion and will exacerbate the cerebral oedema often seen in these patients. Mechanical ventilation may be required if there is evidence of respiratory failure or if apnoea occurs; hyperventilation is also an effective means of reducing cerebral blood flow and thus intracranial pressure. With these principles in mind many clinicians now choose to ventilate empirically where there is a history suggesting an ischaemic anoxic insult. For prolonged ventilation tracheostomy may be desirable. Care should be taken not to reduce the $P\text{CO}_2$ too quickly since this is associated with an early fall in CSF pH (in advance of serum) which may itself be responsible for an encephalopathy (Posner encephalopathy). Optimum reduction of intracranial pressure is obtained by reducing $P\text{aCO}_2$ so as to maintain it at 4–4.5 kPa (25 mmHg). Other measures to minimize and reduce cerebral oedema include fluid restriction, mannitol and dexamethasone (see Reduction of Intracranial Pressure). The use of high dose barbiturate therapy for the purpose of 'cerebral protection' remains controversial because of the dangers of hypotension and respiratory depression. The effectiveness of this group of drugs in ameliorating the effects of ischaemic anoxic cerebral injury in man has yet to be established. High dose barbiturate therapy should be restricted to centres where ventilation facilities exist and intensive monitoring is possible. Close supervision is necessary with regular measurements of serum barbiturate level, attention to problems of drug accumulation and maintenance of the EEG at a 'burst-suppression' level coinciding with maximal depression of cerebral metabolism.

TREATMENT OF CONVULSIONS

Convulsions must be terminated as soon as possible. Diazepam given by slow intravenous injection is the drug of first choice; a common error is to administer diazepam intramuscularly—it is ineffective in convulsing children given by this route. Paraldehyde by deep intramuscular injection into the lateral thigh is also highly effective, and may be preferred where veins are difficult to cannulate. As noted above fits may often occur in a partial form or be combined with chewing, lip smacking and swallowing movements with conjugate deviation of the eyes. A high index of clinical suspicion should therefore be maintained and in selected cases EEG monitoring arranged; this often reveals marked subclinical epilepsy responsible for an increase in metabolic demands of convulsing brain. Where continuing fits are a problem clinical action should be as outlined in the management of status epilepticus (see pp. 818–821). Drugs of choice include intravenous diazepam by continuous infusion, intermittent intravenous phenytoin, or in resistant cases thiopentone, chlormethiazole, or lignocaine by continuous infusion.

REDUCTION OF INTRACRANIAL PRESSURE

The possible presence of raised intracranial pressure in acutely ill children is frequently overlooked and this is particularly the case if clinicians rely on the frequently absent 'classical' signs of raised intracranial pressure (vide supra). As noted above the only reliable means of excluding raised intracranial pressure is to measure it. Continuous monitoring of intracranial pressure may be performed using a transducer measuring via a ventricular cannula or ventriculostomy reservoir. This renders CSF sampling easy and relief of pressure is possible by removal of cerebrospinal fluid or continuous drainage. In cerebral oedema where the ventricles are compressed a 'subarachnoid bolt' or subdural or epidural transducer may be used. The possibility of cerebral oedema should always be considered in states of disturbed consciousness or convulsions and is a particularly frequent component of cerebral asphyxia and trauma, status epilepticus, meningitis, encephalitis, Reye's syndrome, lead encephalopathy and cerebral abscess. Cerebral oedema or congestion is often exacerbated by injudicious administration of low-sodium-containing fluids. Intracranial pressure monitoring techniques have also demonstrated marked elevations in intracranial pressure during sleep, accompanying small upward fluctuations of $P\text{CO}_2$, with coughing, airways suction and intubation. Spontaneous plateau waves (Lundberg plateau waves) may also occur with high sustained levels of intracranial pressure with no clinical sign other than sudden death.

In many cases the treatment of cerebral oedema will require to be presumptive. Fluid should be restricted to 60 per cent of estimated daily requirements; low sodium-containing infusions like 5 per cent dextrose or 0.18 per cent saline in 5 per cent dextrose are contraindicated. The osmotic diuretic mannitol may be administered in a dose of 7 ml/kg of 20 per cent solution given over 20 min. This may be repeated if necessary and monitored by regular checks of osmolality which may be allowed to rise if indicated to 320 mosmol/kg. Other diuretics, e.g. frusemide may be required in the presence of pulmonary oedema. Dexamethasone 1–4 mg may be given early to stabilize cerebral capillaries and minimize endothelial leakage of albumin. Other measures to reduce intracranial pressure include hyperventilation (see above), and induced hypothermia using an autoregulated cooling blanket to maintain the body temperature at 31.5°C for 2–3 days. If shivering raises the core temperature chlorpromazine may be administered in a dose of 1 mg/kg. Reported experience with thiopentone and pentobarbitone in cerebral oedema and cerebral congestion related to Reye's syndrome and head injury suggests that an intravenous dose range of 1.5–5 mg/kg hourly may be effective in reducing raised intracranial pressure. Serum values are maintained between 25–40 mg/l (110–165 μmol/l). Again, intensive care monitoring with ventilation (p. 600) facilities and EEG monitoring (p. 683) are essential.

More widespread application of measures to control raised intracranial pressure is resulting in improved survival and reduced morbidity in conditions previously associated with high mortality, e.g. Reye's syndrome (see Shaywitz *et al.*, 1980).

INFECTION

When infection is suspected from preliminary history, physical examination or from examination of blood and CSF, specific therapy should be introduced early. Treatment may need to be presumptive pending full laboratory confirmation; a combination of penicillin and chloramphenicol will provide cover against commonly encountered bacterial pathogens. Some clinicians prefer high dose intravenous ampicillin (400 mg/kg per 24 hours), even though this drug provides inferior brain penetration to chloramphenicol, particularly in the absence of meningeal inflammation. Metronidazole may be added if the possibility of cerebral abscess arises and neuro-surgical advice should also be sought in case surgical drainage of an abscess becomes necessary. A diagnosis of tuberculosis may be difficult to confirm early and again specific therapy may be indicated if a low CSF glucose in association with lymphocytes in CSF is seen, even if preliminary Ziehl-Neelson staining proves negative.

Initiating therapy to combat infection may be only part of the treatment required and the possibility of other problems (e.g. hydrocephalus, cerebral oedema, inappropriate ADH secretion) complicating CNS infection must not be overlooked. Specific antiviral chemotherapy may be indicated when herpes simplex is confirmed by immunofluorescence of tissue obtained at brain biopsy. Although this technique allows a definitive diagnosis treatment with adenine arabinoside (Ara A; Vidarabine) may need to be commenced using clinical criteria only and the results of EEG and CT scanning (vide supra).

Specific chemotherapy for fungal, helminth and protozoal infection is discussed in Chapter 24.

CORRECTION OF SHOCK, HOMEOSTATIC DEFECTS AND INTOXICATION

General supportive measures including plasma expansion and pressor agents like dopamine or noradrenaline may be necessary to correct *shock* states. Severe *hypertension* (e.g. as in haemolytic uraemic syndrome or acute nephritis) should be corrected with diazoxide or hydralazine. *Bradycardia*, asystole, or ECG changes resembling myocardial infarction may be seen in association with cerebral lesions. If these are not abolished by reduction of intracranial pressure atropine should be given.

Coagulation disorders must be appropriately corrected; a coagulopathy which returns after correction carries a poor prognosis and usually implies multi-organ damage.

Hypoglycaemia should be corrected if necessary by 5 per cent intravenous glucose infusion with extra bolus doses of 20 per cent glucose as required. *Hyperglycaemia* is sometimes seen early with coma and fits and should be managed by appropriate manipulation of the infusion fluid. Insulin is rarely required. *Hypernatraemia* should be corrected *slowly* with fluids containing not less than 0.45 per cent saline because of the danger of precipitating cerebral oedema. *Hyponatraemia* due to water intoxication is a common finding: sodium levels less than 120 mmol/l may cause coma and fits. Hyponatraemia frequently results from over-administration of low sodium containing fluids combined with inappropriate ADH secretion. Management of hyponatraemia should include fluid restriction to at least 60 per cent of known daily requirements combined with diuretics e.g. 20 per cent mannitol 7 ml/kg or frusemide (4–40 mg depending on age). *Hypocalcaemia* should be corrected by continuous infusion of 10 per cent calcium gluconate as part of an intravenous electrolyte cocktail; bolus injections of calcium gluconate have a short-lived effect and may also impair cardiac function.

The management of *renal* (p. 1078) and *hepatic failure* (p. 491) may include consideration of dialysis and further modification of fluid balance and nutritional policy.

Nutrition should not be overlooked in patients with protracted coma. Parenteral nutrition carries a high risk of infection; amino acid mixtures may also exacerbate acidosis and hyperlipidaemic states produce spuriously low electrolyte values on assay. Continuous naso-gastric or naso-jejunal feeding with specially prepared mixtures (e.g. Clinifeed) are being increasingly employed. The dangers of aspiration should not be overlooked and infusion should be discontinued in the presence of abdominal distension or on obtaining excessive aspirate. *Acute gastric erosions* occur in comatose patients particularly when treated with dexamethasone and occasionally massive haematemesis may be seen. Alkali should be administered via the naso-gastric tube as a prophylactic measure; intravenous cimetidine (3 mg/kg 6 hourly) should be used with caution because of the risk of infection due to total loss of the gastric acid protective barrier.

The numerous examples of toxic encephalopathy may generally be managed by intensive supportive therapy (see the management of poisoning, Ch. 31). *Specific antivenins* may be appropriate for bites and stings which will generally be available in areas where these problems are endemic. *Chelating agents* may be employed in cases of heavy metal poisoning.

PROGNOSIS IN ENCEPHALOPATHY

The overall prognosis in infants and children presenting with acute encephalopathy is poor, particularly after ischaemic anoxic insults and in the presence of decerebration and coma (see Table 14:18). The prognosis is better following acute intoxication. Improvement in function may continue for several weeks after an acute illness. Vision may continue to improve up to 6 months after an episode of apparent total visual loss (cortical blindness). A 'locked in' state of akinetic mutism may persist for several months followed by complete recovery of speech. This may be potentially embarrassing for medical and nursing attendants who may have made inappropriate comments at an earlier stage in the illness assuming the patient to be comatose or in a vegetative state. As noted above intensive monitoring and early treatment of detected complications is at least as important as the underlying cause in many examples of encephalopathy. Prevention aside, attention to these aspects of management should help to reduce the mortality and morbidity in this group of conditions.

C.R. Steer

Table 14:18

Prognosis in Infants and Children Presenting with Acute Encephalopathy (Excluding Accidental Injury)

Outcome	Status Epilepticus	Decerebration	Coma
Death (%)	8	31	27
Significant Handicap (%)	19	20	15
Mild Handicap (%) or Complete Recovery (%)	73	11 / 38	13 / 45

FACIAL PALSIES

UPPER MOTOR NEURONE FACIAL PALSIES

The upper facial musculature has bilateral representation in the cerebral cortex. Thus a bilateral lesion is necessary to produce

PINDERFIELDS HOSPITAL PAEDIATRIC UNIT PROTOCOL (1999) FOR

12) COMA AND ACUTE ENCEPHALOPATHY

Acute coma and acute encephalopathy can be caused by a variety of disorders (see below)

It is :

- a reduced level of consciousness
- with or without fits
- with or without focal neurological signs

Beware brain swelling and raised intracranial pressure.

Inappropriate ADH secretion (low sodium in the blood).

Ensure blood pressure and perfusion is maintained.

Fluid balance should be two thirds of calculated requirement. Start with 0.45% saline in 5% or 10% Dextrose. Ensure that the urine output is 2 mls/kg of body weight/hour. If it drops below this consider winding fluid intake up.

Acute Encephalopathy

Airway, Breathing, Circulation [and record level of consciousness on AVPU or GCS]

Maintain airway, empty stomach with nasogastric tube

Full physical examination of the child noting particularly:

Signs of head trauma, blood pressure, papilloedema or bleeds in the retina.

Pulse rate and rhythm

Pupillary reactions

Record CNS signs and particularly focal signs

Is there a murmur

Has the child cyanotic congenital heart disease (brain abscess)

Do urgent capillary glucose and if hypoglycaemia give Dextrose intravenously in 10% solution intravenously in a dosage of 4 to 6 ml/kg of body weight.

Do full blood count and CRP, culture, PCV and do sickle test in a child with racial skin pigmentation.

Coagulation studies

Calcium, phosphate, alkaline phosphatase

Urea and electrolytes

Liver enzymes, ammonia and ALT; get results out of hours.

Blood gases

Blood glucose

Blood lead

Urine for metabolic and drug/ toxicology screen

Urine can be also analysed urgently as follows

Ketostix

Clinitest

Dinitrophenylhydrazine (these are particularly important in babies as they may provide an indication of a metabolic disorder

Skull x-ray

Chest x-ray

X-ray wrist for lead line or metabolic bone disease in renal failure

6) CT scan of brain

7) If pupils are sluggish or non responsive give Mannitol 20% solution intravenously in a dose of 1 g/kg of body weight over 10 minutes.

Consider ventilation and reducing PCO2 to 3.5 kpa.

Do not do a lumbar puncture

8) If Dexamethasone is given consider gastric protection with oral or IV Ranitidine or Cimetidine and also oral antacids.

Treat fits.

Consider cause.

9) Specific treatment. Cover with IV Ceftriaxone and also especially If fitting or focal signs use Acyclovir and consider urgent EEG. **If low sodium fluid restict and use normal or half normal saline**. Watch blood glucose and remember Addisons disease.

CAUSES

Head Injury (subdural and epidural haematomas), NAI.

Infections: Cerebral abscess, systemic infection, meningitis, encephalitis (eg herpes).

Cerebral anoxia/ischaemia:

Cardiorespiratory arrest and failure, airway obstruction

Shock, drowning, SIDS, suffocation.

Epilepsy: Post-ictal

Vascular: Intracranial bleeding

Hypertensive encephalopathy

Metabolic: Diabetes mellitus (hypoglycaemia, DKA) hepatic failure, Reye's Syndrome

Renal Failure

Hypo & hypernatraemia

Inborn error of metabolism

7) Poisoning/ingestion:

Alcohol, paracetamol, salicylates

Barbiturates, opiates, Iron, lead

Antidepressant, anticonvulsants

Glue Sniffing

8) Raised ICP:

Cerebral oedema

Hydrocephalus, tumour

NEXT PAGES EXTRACTS FROM TEXTBOOK OF PAEDIATRICS. FORFAR & ARNEIL 6TH EDITION

Table 20.53 Important causes of acute encephalopathy

Infectious and parainfectious encephalopathies
Meningitis (mainly bacterial, rarely fungal, protozoal and viral)
Cortical thrombophlebitis
Cerebral abscess and empyema
Primary viral encephalitis
Postinfectious encephalitis
Acute disseminated encephalomyelitis
Cerebral malaria
Severe systemic infections, including septicemia

Hypoxic ischemic encephalopathies
Perinatal asphyxia
Severe pulmonary disease
Carbon monoxide poisoning
Methemoglobinemia
Severe anemia
Status epilepticus
Near miss sudden infant death syndrome
Post cardiac arrest
Cardiac bypass surgery
Near drowning
Cardiac arrhythmias
Congestive cardiac failure
Hypotension
Disseminated intravascular coagulation
Hypoglycemia
Anesthetic accidents
Vitamin or cofactor deficiencies (B_{12}, B_6, folate, etc.)

Trauma
Accidental
Non-accidental

Exogenous toxins
Drugs:
  Antihistamines, anticholinergics, antidepressants, hypnotics & sedatives, analgesics, antiepileptics, anti-inflammatory, antimetabolites, antibiotics, etc.

Illicit substances:
  Alcohol, solvents, cannabis, cocaine, amfetamines, opiates

Environmental toxins:
  Carbon monoxide, phosphates, DDT, iron, lead, pesticides, heavy metals, insect & snake venoms, plants, etc.
Hypothermia
Heat stroke

Endogenous agents
Water intoxication
Electrolyte imbalances, esp. hypo & hypernatremia
Acidosis & alkalosis
Scalds

Endocrine disorders:
  Diabetes mellitus, hypoglycemia, hypo & hyperthyroidism, hypo & hyperparathyroidism, hypopituitarism, hypoadrenalism

Organ failure:
  Hepatic, renal, pancreas
Hypertension

Inborn errors of metabolism:
  Aminoacidopathies, organicacidurias, urea cycle defects, fatty acid oxidation defects, mitochondrial disorders, carnitine deficiency, porphyria

Cerebrovascular disease
Hemorrhagic stroke
Ischemic stroke
Epileptic seizure related
Postictal
Nonconvulsive status epilepticus
Postconvulsive status epilepticus

Anne

Table 20.55 Useful investigations in coma

Basic hematological & biochemical investigations, including glucose, Ca, Po_4, Alk P & LFTs
Markers of inflammation, including ESR & CRP
Blood & urine osmolality
Blood clotting studies
Bacteriological & virological studies including cultures, serology, PCRs, Mantoux, etc.
Neuroimaging:
Ultrasound, CT, MRI
Blood gases
Plasma ammonia
Plasma lactate
Urine toxicology
Blood toxicology – alcohol, lead & specific toxins where indicated
Blood anticonvulsant levels
Urine metabolic screen
Urine amino and organic acids
CSF examination including lactate and glycine if indicated
TFTs & other endocrine investigations if indicated
Blood & urinary porphyrins
Skeletal survey
EEG

AND FOLLOWING PAGES SHOW COPIES OF THE ADVANCED PAEDIATRIC LIFE SUPPORT COURSE MANUAL 1993

PATHOPHYSIOLOGY AND AETIOLOGY

Coma is a sign of significant "brain failure" and requires emergency treatment to prevent or minimise central nervous system damage.

In children, coma is caused by a diffuse metabolic insult (including cerebral hypoxia and ischaemia) in 95% of cases, and by structural lesions in the remaining 5%. Metabolic disturbances can produce diffuse, incomplete, and asymmetrical neurological signs. Early signs of metabolic encephalopathy may be subtle with reduced attention and blunted affect. The most common causes of coma are summarised in the box.

Disorders causing coma in children

Hypoxic – ischaemic brain injury
- Following respiratory or circulatory failure

Epileptic seizures

Trauma
- Intracranial haemorrhage, brain swelling

Infections
- Meningitis
- Encephalitis

Poisons

Metabolic
- Renal, hepatic failure, Reye's syndrome, hypoglycaemia, diabetes, hypothermia, hypercapnia

Vascular lesions
- Bleeding, arteriovenous malformations, arterial or venous thrombosis

Hypertension

Cerebral perfusion pressure

The initial priority in the management of the unconscious child is the maintenance of adequate airway breathing, circulation, and metabolic homoeostasis. Once this has been done, attention may then be given to the possibility of raised intracranial pressure and its effects.

In very young children, before the cranial sutures are closed, considerable expansion in the intracranial volume may occur if the process is slow. However, if the process is rapid and in children with a fixed-volume cranium, increase in volume due to brain swelling, haematoma, or cerebral spinal fluid (CSF) blockage will cause raised intracranial pressure (ICP). Initially cerebrospinal fluid and venous blood within the cranium decrease in volume. Soon, this compensating mechanism fails and as the intracranial pressure continues to rise the cerebral perfusion pressure (CPP) falls and arterial blood flow is reduced.

$$CPP = MAP - ICP$$

where MAP is mean arterial pressure. Reduced CPP reduces cerebral blood flow (CBF). Normal CBF is over 50 ml/100 g brain tissue/min. If the CBF falls below 20, the brain suffers ischaemia.

Increasing intracranial pressure will push brain tissue against more rigid intracranial structures. Two clinical syndromes are recognisable by the site of localised brain compression.

Central syndrome

The whole brain is pressed down towards the foramen magnum and the cerebellar tonsils herniate through it ("coning"). Neck stiffness may be noted. A slow pulse, raised blood pressure, and irregular respiration leading to apnoea are seen terminally.

Uncal syndrome

The intracranial volume increase is mainly in the supratentorial part of the intracranial space. The uncus, which is part of the hippocampal gyrus, is forced through the tentorial opening and compressed against the fixed free edge of the tentorium. If the pressure is unilateral (for example, from a subdural or extradural haematoma), this leads to third nerve compression and an ipsilateral dilated pupil. Next, an external oculomotor palsy appears, so the eye cannot move laterally. Hemiplegia may then develop on either or both sides of the body, depending on the progression of the herniation.

Further signs that may be indicative of raised intracranial pressure are discussed below under "Assessment and management".

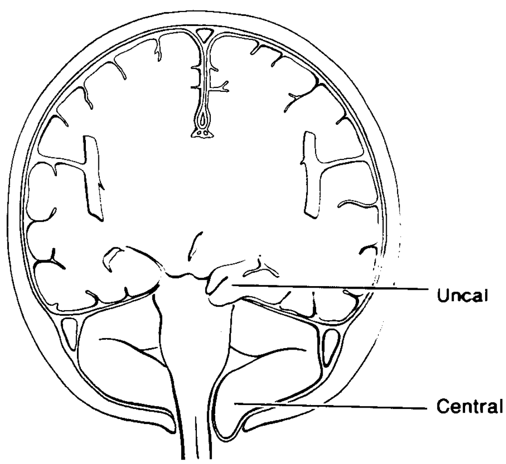

Figure 12.1. Herniations of the brain

ASSESSMENT AND MANAGEMENT

This must be sequential and methodical. Every effort should be made both to prevent secondary brain damage from hypoxia or ischaemia, from hypoglycaemia or from infection, and to minimise increased intracranial pressure.

Primary assessment and management

In the *primary* phase, airway, breathing, and circulation are assessed and stabilised. Urgent problems such as hypoglycaemia, sepsis, and raised intracranial pressure are addressed.

Airway

Establish and maintain an adequate airway.

Breathing

Give high-flow oxygen. Intubation and ventilatory support will be needed under the following conditions:

- Breathing is inadequate.
- There is no protective cough reflex or gag reflex.

Anr

A

1993	Recent advances in paediatrics. Author TJ David. Volume 11 in a series by Churchill Livingstone. Date 1993. If	In a chapter on management of acute encephalopathy is in infancy, the following statements were made in relation to management. "Maintenance of blood pressure and therefore vital organ perfusion is a priority. The quantity and type of fluids will be tailored to the circumstances. It is important to avoid large quantities of hypotonic solutions as they can promote cerebral oedema." Refers to methods of intracranial pressure monitoring and the use of mannitol and frusemide

1998	Hospital paediatrics. Third edition. Milner `and Hull. Churchill Livingstone	"If the Glasgow coma score is nine or less, where the airway is not secure or where there are bulbar signs the child should be sedated, intubated and ventilated." Treatment for raised intracranial pressure is suggested including sedation with Midazolam infusion in a dosage of 100 to 300 µg/kg/h In brainstem death assessment it is advised that it should be recorded if other drugs which affect consciousness had been given during the preceding 12 hours.

2003	Textbook of paediatrics. Forfar & Arneil 6th Edition Churchill Livingstone	Hyponatraemia: "there are some patients whose plasma sodium concentrations remain below the lower limit of the normal range (e.g. 132mmol/l) without symptoms and to excrete supplemental sodium to maintain this new steady-state. Hyponatraemia occurs as a result of water intoxication, prescription of hypotonic IV fluids, syndrome of inappropriate ADH, missed cases of acute renal failure.

		"Syndrome of inappropriate ADH is well recognised but it is frequently a misnomer. ADH secretion can be considered an appropriate evolutionary physiological response to illnesses or injuries which are sufficient severity to preclude drinking for several days. The most common causes are CNS injury and bacterial pneumonia. The retained water however often does not come from a physiological source but from a prescription to administer fluid in quantities that did not anticipate the ADH secretion. In any case the clinical picture water intoxication (hyponatraemia) develops. The diagnosis is made by proving that urine osmolality exceeds that of a hyperosmolar plasma and the treatment is usually fluid restriction." ….. "Rapid correction of hyponatraemia is justified in circumstances where severe symptoms have resulted from a rapid fall in serum sodium. If a good history is not available, symptoms are severe and serum Na is <120mmol/l a rapid initial correction is justified to values of 125mmol/l.. Further increase in serum sodium is best achieved more gradually was fluid restriction. In all other circumstances slow correction is advised by fluid restriction alone and the provision of normal rather than increased sodium supplements. The neurological symptoms associated with acute hyponatraemia are in part due to cerebral oedema and may improve with a hypertonic saline as the brain shrinks."…

ANNEX B

MIDAZOLAM PRESCRIPTION POTENTIAL DOSE ERROR

After Dr Webb had seen Claire at 2pm, the SHO made an entry in the notes (page 55) as follows

:

CH 328770

DATE	CLINICAL HISTORY, EXAMINATION AND PROGRESS
22/10/96	S/B. Dr Webb
	Still in status
	1. MIDAZOLAM 0.5 mg/kg STAT DOSE = 0.5 x 24
	= 12 mg IV Stat
	2. MIDAZOLAM 2mcg/kg/min = 2 x 24 mcg/min
	= 48 mcg/min
	= 48 x 60 mcg/Hr
	= 2880 mcg/Hr
	= 2.88 mg/HR. INFUSION
	= 69 mg/24 HRS.

At the same time a prescription was written by the SHO :

up:

EASTERN HEALTH & SOCIAL SERVICES BOARD
ROYAL BELFAST HOSPITAL FOR SICK CHILDREN
PRESCRIPTION SHEET

PARENTERAL DRUGS

REGULAR PRESCRIPTIONS

DRUG SENSITIVITY

Date Comm.	DRUG (Block letters please)	DOSE	Time of Administration AM 6	AM 8.30	MD 12	PM 12.30	PM 5.30	PM 6	PM 9.30	MN 12	Other Times	Method and other Instructions	SIGNATURE	Discontinued Date	Initials
[illegible]/96	PHENYTOIN	60mg		✓					✓			IV	[illegible]		
[illegible]/96	MIDAZOLAM	2mcg/kg/minute (=[illegible])										IVI infusion	[illegible]		
[illegible]/96	CEFOTAXIME	600mg		✓		✓	✓		✓			IV	[illegible]		
22/10/96	ACYCLOVIR	240mg		✓		✓			✓			IV	[illegible]		
22/10/96	HEPSAL	5mg		✓		✓	✓		✓			IV	[illegible]		
~~22/10/96~~	~~Sodium Valproate~~	~~[illegible]mg/[illegible]~~										IVI	[illegible]	22/10	[illegible]

DRUGS-ONCE ONLY PRESCRIPTIONS

Date Given	DRUG (Block letters please)	DOSE	Time of Admin.	Method of Admin.	SIGNATURE	Given by Initials
21/10/96	DIAZEPAM 5	5mg	12.15	PR	[illegible]	[illegible]
22/10/96	PHENYTOIN	638 mg	2.45pm	IV	[illegible]	[illegible]
22/10/96	MIDAZOLAM	120 mg	3.25pm	IV	[illegible]	
22/10/96	SODIUM VALPROATE	400mg	5.15pm	IV	[illegible]	[illegible]

CR – RVH

090-026-075

The *regular* prescription was written up as an infusion 2 mcg/kg/minute.

The *Drugs once only prescriptions* section shows a bolus dose written up of 120 mg (whereas the intended bolus was to be – from the history sheet note – 12mg). The column of the sheet recording as given is not completed by a signature. Was this given ? If so this was an overdose by x10 on intended and 25x the advised dose for status epilepticus.

The doses of Midazolam advised by the RCPCH *Medicines for Children* 2001 differ according to intended use.

184 **Midazolam** continued

DOSAGE continued

Child

Indication	Route	Age: 1 month–2 years	Age: 2–12 years	Age: 12–18 years	Frequency	Notes
Premedication	IM	← 70–100 microgram/kg →			single dose	Administer 30–60 minutes prior to surgery.
	Oral	← 500 microgram/kg (maximum dose 15mg) →			single dose	
Sedation for procedures	IV bolus	-		2mg	single dose	If after 2 minutes sedation is not adequate, incremental doses of 500 microgram – 1mg can be given. Doses >5mg are rarely needed.
	IV bolus or IM	← 50–100 microgram/kg →		-	single dose	Doses up to 300 microgram/kg may sometimes be needed.
	Oral	← 500 microgram/kg (maximum dose 15mg) →			single dose	
	Rectal	← 500–750 microgram/kg →			single dose	
	Intranasal	← 200–300 microgram/kg →			single dose	Half the dose can be given into each nostril.

185 **Midazolam** continued

Child continued

Indication	Route	Age: 1 month–2 years	Age: 2–12 years	Age: 12–18 years	Frequency	Notes
Sedation in intensive care	IV bolus (over 3–5 minutes)	← 100–200 microgram/kg →			single dose	This may not be needed if the patient is already receiving morphine. Reduce the dose in hypovolaemia, vaso-constriction and hypothermia. Low doses may also be adequate if the patient is also receiving an opiate. Adjust according to response.
		then				
	IV infusion	← 30–200 microgram/kg/hour →			continuous	
Induction of anaesthesia	Slow IV bolus	-	>7 years 150 microgram/kg	200–300 microgram/kg	single dose	In adults the dose should be titrated against individual response. Young fit unpremed-icated patients may require at least 300 microgram/kg. Those premedicated with an opiate usually only require a dose of 200 microgram/kg.

NOTES

- **Administration: rectal, intranasal:** the injection may be given intranasally and rectally. **Oral:** if the injection is used orally the bitter taste may be disguised by apple or blackcurrent juice or chocolate sauce, however, oral liquids are available.
- Caution in patients with respiratory failure.
- Drug interactions: erythromycin and other macrolide antibiotics, cimetidine,

(i) DOSE CALCULATION

(ii) Claire was aged 9 years and weighed 24 kg – according to the history sheet calculation. Thus the maximum **bolus** dose for IV used should be 100 microG per Kg body weight. (2400 microG= 2.4 mg) when used for sedation for procedures or up to 300 microG/kg body weight when used for sedation in intensive care (7.2 mg) . But for status epilepticus (from Medicines for Children 2003) up to 200 microG/kg is advised. Thus the *intended* bolus dose of 12 mg was 5 x advised dose for procedure dose and 1.6x advised dose for intensive care and 2.5x the advised dose for status epilepticus . The *prescribed* bolus dose was 120 mg to be given at 3.25 pm is thus 25x the advised dose for status epilepticus.

(iii) If that ***bolus dose*** was given then it would have been a large overdose with excessive (potentially dangerous) sedation and potential respiratory depression with CO2 retention worsening brain swelling. A particular vulnerability however relates to when medication is being given by a doctor rather than a nurse. Intravenous medication is usually given by the doctor and is then made up by him/her. Current practice which was often not recorded in protocols in 1996 and subsequently is that this drawing up of dosage as well as the calculation of dosage according to body weight would be cross checked with the nurse. This offers the opportunity for a nurse to challenge if the dosage appears excessive. In respect of the Midazolam bolus dose, it is not evident whether this was given (but equally not evident that it was not given). If it was not given was this because a nurse challenged the dosage? If so that should have been recorded both in the medical and nursing records and raised as a serious potential clinical adverse event. Dr Webb records that the bolus had been given and presumably came to this conclusion from review of the prescription. The dose written up on prescription was a significant overdose with significant risk of respiratory depression. The failure to note this and the failure to identify this later in the clinical audit death review and later in 2004 is striking. Furthermore the consultants who were asked to review the case of Clare by the coroner did not notice this or comment on it.

(iv) If the ***bolus dose*** was omitted then this should have been written in the notes as “bolus not given” <u>and</u> the prescription entry scored through. In order to draw up a bolus dose for administration, the doctor would have had to use a number of ampoules/vials to do so.

a. The nurse records refer to “Hypnovel” a trade name. And this formulation may have been the one in use on the ward. The BNF 2005 gives non proprietary formulations as well. A number of ampoules may well have been used to assemble to 69mg dose added to the IV fluid for infusion. It would be helpful to know what formulation(s) were available in 1996 on Allen ward.

Source	***Concentration***	***Ampoule/vial volume -ml***	***Contains***
Proprietary	1mg/ml	50	50mg
Proprietary	5mg/ml	2	10mg
Proprietary	5mg/ml	5	25mg
Proprietary	5mg/ml	10	50mg
Proprietary	5mg/ml	18	90mg

Source	***Concentration***	***Ampoule/vial volume -ml***	***Contains***
Hypnovel	2mg/ml	5	10mg
	5mg/ml	2ml	10mg

b. However the following nurse record suggests a bolus dose was given .

i. 090-040-141. Nursing Kardex. Refers to period 2 PM-8 PM.

ii. "Continues on hourly CNS observation GCS 6-7. Stat dose IV phenytoin at 2:45 PM to have BD. S/B Dr Webb still status epilepticus given stat IV hypnoval at 3:25 PM. Continuous infusion running at 2mls/hr of hypnoval to be increased by 0.1 ml /5min until up to 3 mls per hour. Dr to write up. Given stat dose Epilim at 5:15 PM. Very unresponsive. Only to pain. Remains pale. Occasional episodes of tooth clinching. Commenced on IV [probably Cefotaxime] and IV acyclovir. First dose Cefotaxime due 9:30 PM some parents in attendance"

iii. additional note due phenytoin levels at 9 PM and then followed by tick and a entry of 23.4

(v) The intended ***infusion*** dosage from the history sheet calculation and prescription was 2 microG per kg body weight per minute. The IV prescription chart shown below indicates this was 64mg in 50 ml to be given at 2ml per hour. This would give 2560 microG per hour = 106 microG per kg body weight per hour.

(vi) This infusion dose is within the infusion rate advised in *Medicines for Children (2001)* of 30-200 microG per kg body weight per hour.(And up to 300 microG/kg/hour in an intensive care unit)

(vii) It appears this infusion dose was given. It is not clear when Dr Webb advised this dose or why he added Midazolam to the regime he had already advised at the 2pm visit.

(viii) ***Comment***: It is not certain that ***the bolus dose*** was given at all. But the error with the dosage intended and dosage written up should have been picked up by Dr Webb at his review of Claire at 17:00 h on the 22 October and also it could have been noted at the review of deaths in the audit meeting and reported as a major medicines error. There is no indication that it was. A ward pharmacist should review all prescriptions daily both as a safety and educational process. The signature space on the prescription chart to indicate as given is not ticked and this bolus dose probably was not given even though Dr Webb noted it as having been given.

(ix) Was a process of ward pharmacist review in place in 1996? It was in in place in many hospitals and a major teaching Children's hospital should have been particularly alert to drug errors. It is not clear what source of advice was used for the Midazolam dose used. Midazolam is not listed in the Paediatric Vade Mecum 1990 edition (Birmingham Children's Hospital reference). It is listed as 100 microG per kg body weight as bolus in intensive care for ventilated patients in the Alder Hey Hospital Book of Children's Doses 6th Edition 1994 and as 50-300 microG/kg/hour as infusion. (see scan of the page below) . Although not available at the time I give the relevant page from the BNF for Children from 2005. It may be possible to obtain a copy of the BNF for 1996 to check if ampoule sizes have changed.

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

CH 328770 **Page:** 136.

INTRAVENOUS FLUID PRESCRIPTION CHART

	AMOUNT (mls)	TYPE OF FLUID	NAME and AMOUNT of ADDITIVES	RATE mls/hr	TIME Start Finish	Prescribed by	ERECTED BY
1	500 mls	No 18 Soln		64 mls/HR		[illegible]	
2	50 mls.	N. SALINE	+ 6 mg MIDAZALAM. ~~[illegible]~~	2 mls/HR	OVER 24 HRS	[illegible]	[illegible]
3	500 mls	No 18. ~~[illegible]~~	20 mmol Kcl.	64 mls. ~~[illegible]~~		[illegible]	[illegible]
4							
5							
6							

PARENTERAL NUTRITION PRESCRIPTION CHART

TOTAL VOL.	TOTAL ENERGY
Per..........................Hrs. ....mls. ....mls/kg	................................kcals ....kcals/kg

PROTEIN	DEXTROSE Conc.	FAT Conc.
Vol. Cals.	Vol. Cals.	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.	

CR - RVH

090-038-136

FURTHER ADVICE SOURCES ON DOSAGE OF MIDAZOLAM IN CHILDREN

The following are relevant pages from British National Formulary for Children 2005 and from *Medicines for Children* 2003 (RCPCH and NPPA) and the last from Alder Hey Book of Children's Dosages 1994

FROM BNF CHILDREN 2005

Induction of anaesthesia
- By slow intravenous injection
  Child 7–12 years 150 micrograms/kg increased if necessary
  Child 12–18 years with premedication, initially 150–200 micrograms/kg; without premedication, initially 300–350 micrograms/kg; increase dose in steps of not greater than 5 mg every 2 minutes (max. 600 micrograms/kg)

Sedation in intensive care
- By intravenous injection and continuous intravenous infusion
  Child 1–6 months 60 micrograms/kg/hour *by continuous intravenous infusion* adjusted according to response
  Child 6 months–12 years initially 50–200 micrograms/kg *by slow intravenous injection* over at least 3 minutes followed by 30–120 micrograms/kg/hour *by continuous intravenous infusion* adjusted according to response
  Child 12–18 years initially 30–300 micrograms/kg *by slow intravenous injection* in steps of 1–2.5 mg every 2 minutes followed by 30–200 micrograms/kg/hour *by continuous intravenous infusion* adjusted according to response
  Note Initial dose may not be required and lower maintenance doses needed if opioid analgesics also used; reduce dose (or omit initial dose) in hypovolaemia, vasoconstriction, or hypothermia

Status epilepticus section 4.8.2

Administration For *intravenous infusion* dilute with glucose 5% or sodium chloride 0.9% or sodium chloride and glucose intravenous infusion; for neonates and children under 15 kg dilute to a concentration of 1 mg/mL.
For rectal administration of the injection solution, attach a plastic applicator onto the end of a syringe; if the volume to be given rectally is too small, water for injection may be added.
Injection solution may be given intranasally (unpleasant and may cause severe irritation of nasal mucosa)

Midazolam (Non-proprietary) PoM
Injection, midazolam (as hydrochloride) 1 mg/mL, net price 50-mL vial = £6.00; 5 mg/mL, 2-mL amp = 79p, 5-mL amp = 91p, 10-mL amp = £4.70, 18-mL amp = £6.80
Oral liquid, midazolam (as maleate), 2.5 mg/mL, 100 mL
Available as a manufactured special from Special Products Ltd.

Hypnovel® (Roche) PoM
Injection, midazolam (as hydrochloride) 2 mg/mL, net price 5-mL amp = 75p; 5 mg/mL, 2-mL amp = 90p

TEMAZEPAM

Cautions see notes above and under Diazepam (section 4.1.2 and section 4.8.2); **interactions:** Appendix 1 (anxiolytics and hypnotics)

Contra-indications see notes above and under Diazepam (section 4.1.2)

Side-effects see notes above and under Diazepam (section 4.1.2)

Licensed use tablets not licensed for use in children

Indication and dose
Premedication
- By mouth
  Child 1–12 years 1 mg/kg (max. 30 mg) 1 hour before surgery
  Child 12–18 years 20–30 mg 1 hour before surgery

[1]**Temazepam** (Non-proprietary) CD
Tablets, temazepam 10 mg, net price 28-tab pack = 95p; 20 mg, 28-tab pack = £1.65. Label: 19
Oral solution, temazepam 10 mg/5 mL, net price 300 mL = £9.95. Label: 19
Note Sugar-free versions are available and can be ordered by specifying 'sugar-free' on the prescription

Dental prescribing on NHS Temazepam Tablets or Oral Solution may be prescribed

1. See p. 16 for prescribing requirements for temazepam

15 **Anaesthesia**

Phenytoin (Non-proprietary) PoM
Injection, phenytoin sodium 50 mg/mL with propylene glycol 40% and alcohol 10% in water for injections, net price 5-mL amp = £3.40

Epanutin® Ready-Mixed Parenteral (Pfizer) PoM
Injection, phenytoin sodium 50 mg/mL with propylene glycol 40% and alcohol 10% in water for injections. Net price 5-mL amp = £4.88

Oral preparations
Section 4.8.1

MIDAZOLAM

Cautions section 15.1.4

Contra-indications section 15.1.4

Side-effects section 15.1.4

Licensed use *injection* not licensed for use in status epilepticus

Indication and dose

Status epilepticus

- By intravenous administration

Neonate initially 150–200 micrograms/kg as a single dose followed *by a continuous infusion* of 1 microgram/kg/minute (increased by 1 microgram/kg/minute every 15 minutes until seizure controlled; max. 5 micrograms/kg/minute)

Child 1 month–18 years *by continuous infusion* of 1 microgram/kg/minute (increased by 1 microgram/kg/minute every 15 minutes) until seizure controlled; max. 5 micrograms/kg/minute

- By buccal administration (preferred) or by intranasal administration

Neonate 300 micrograms/kg as a single dose

Child 1–6 months 300 micrograms/kg as a single dose

Child 6 months–1 year 2.5 mg as a single dose

Child 1–5 years 5 mg as a single dose

Child 5–10 years 7.5 mg as a single dose

Child 10–18 years 10 mg as a single dose

Administration injection may be diluted in glucose 5% or sodium chloride 0.9%; rapid intravenous injection (less than 2 minutes) may cause seizure-like myoclonus in preterm neonate. Buccal liquid may be given intranasally. Injection may be given bucally, intranasally or by mouth

Preparations
Section 15.1.4

Epistatus® (midazolam buccal liquid 10 mg/mL) is available from specialist manufacturers

Amsed® (midazolam oral liquid, sugar-free, 2.5 mg/mL) is available from specialist manufacturers

4 Central nervous system

FROM MEDICINES FOR CHILDREN 2003 (BELOW)

EXCIPIENTS
See manufacturers SPC for further details.

LICENSED STATUS
Licensed for use in all age groups.

Midazolam

Short-acting benzodiazepine with hypnotic, anxiolytic, amnesic, muscle relaxant and anticonvulsant activity.

USES
Premedication, sedation prior to short procedures and in intensive care situations, anticonvulsant, induction of general anaesthesia. In palliative care, for relief of anxiety (including for sedation during acute terminal haemorrhage), dyspnoea, intractable seizures and terminal agitation.

PRESENTATION
Injection: (as hydrochloride) 10mg in 2mL and 10mg in 5mL – Hypnovel®; 1mg in 1mL, 50mL – non-proprietary; 5mg in 1mL, 2mL, 5mL, 10mL and 18mL – non-proprietary.
Syrup (buccal liquid): 10mg in 1mL – Epistat (manufactured 'special').
Syrup: 2.5mg in 1mL – Amsed (manufactured 'special').

DOSAGE
Newborn infant (birth to 1 month)

Indication	Route	Age	Frequency	Notes
		birth–1 month		
Sedation	IV infusion	1 microgram/kg/minute for the first 24 hours then decrease to 500 nanograms/kg/minute in babies <33 weeks post-conceptional age to avoid accumulation.	continuous	Can be used for up to 4 days with apparent safety in the ventilated newborn baby.

Child

Indication	Route	Age			Frequency	Notes
		1 month–2 years	2–12 years	12–18 years		
Premedication	IM	← 70–100 microgram/kg →			single dose	Administer 30–60 minutes prior to surgery. Monitor from time of administration.
	Oral	← 500 microgram/kg → (maximum dose 15mg)			single dose	
Sedation for procedures	IV bolus	–		2mg	single dose	If after 2 minutes sedation is not adequate, incremental doses of 500 microgram – 1mg can be given. Doses >5mg are rarely needed.
	IV bolus or IM	50–100 microgram/kg		–	single dose	Doses up to 300 microgram/kg may be needed.
	Oral	← 500 microgram/kg → (maximum dose 15mg)			single dose	
	Rectal	← 500–750 microgram/kg →			single dose	
	Intranasal	← 200–300 microgram/kg →			single dose	Half the dose should be given into each nostril.

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Child continued

Indication	Route	Age 1 month–2 years	Age 2–12 years	Age 12–18 years	Frequency	Notes
Sedation in intensive care	IV bolus (over 3-5 minutes)	← 30-300 microgram/kg →			single dose	This may not be needed if the patient is already receiving morphine, or is sedated post-op. Reduce the dose in hypovolaemia, vasoconstriction and hypothermia. Low doses may be adequate if the patient is also receiving an opiate. Adjust according to response.
	IV infusion	then 500 nanogram - 3.3 microgram/kg/minute			continuous	
Induction of anaesthesia	Slow IV bolus	-	>7 years 150 microgram/kg	200–300 microgram/kg	single dose	In adults the dose should be titrated against individual response. Young fit unpremedicated patients may require at least 300 microgram/kg. Those pre-medicated with an opiate usually only require a dose of 200 microgram/kg.
Status epilepticus	IV bolus	← 150-200 micrograms/kg →			single dose	Initial bolus. Follow with infusion as below.
	IV infusion	1 microgram/kg/minute increasing by 1 microgram/kg/minute every 15 minutes until the seizure stops Maximum of 5 microgram/kg/minute			continuous	Start with the initial bolus above before commencing the infusion. Not yet an established drug in this area. Most experience in PICUs.
	Buccal/ intranasal	DOSE BY WEIGHT <6 months 300 microgram/kg	1-4 years 5mg	10mg	single dose	Buccal administration is the preferred route over intranasal administration.
			5-9 years 7.5mg		single dose	
		DOSE BY AGE ≥6 months 2.5mg	>10 years 10mg		single dose	
Intractable seizures in palliative care	IV infusion/ SC infusion	← 5mg/24 hours →			continuous	Initial dose can be titrated up to 40mg/24 hours.
Anxiety in palliative care	IV infusion/ SC infusion	← 2.5mg/24 hours →			continuous	

Dose adjustment in renal and liver disease: dose should be reduced in severe renal impairment and liver failure.

ADMINISTRATION

Buccal/intranasal/oral: syrup (buccal liquid) may be given intranasally. Injection can be given bucally, intranasally or orally. Nasal route of administration is unpleasant, but has a rapid onset of action (5–15 minutes). Bitter taste when injection given orally may be disguised by administration in e.g. apple or blackcurrant juice, or chocolate sauce.
IV/IM: injection may be diluted in NaCl 0.9% or glucose 5%.
Rectal: injection can be given rectally.

Patient should be supine and remain so throughout any procedures. It is recommended that patients should remain under medical supervision for at least an hour after receiving midazolam.

CONTRA-INDICATIONS & WARNINGS
Caution: following IV bolus, profound hypotension and apnoea have been seen in neonates and children already receiving opiates. Paediatric patients with chronic respiratory insufficiency, hepatic or renal dysfunction, severe fluid/electrolyte imbalance, congestive heart failure or cardiovascular instability require special caution when receiving parenteral midazolam – lower doses and continuous monitoring are recommended. *Warnings:* Administration by IV bolus is not recommended in neonates. Avoid intra-arterial injection and extravasation. Loss of efficacy has been reported in some patients receiving long-term sedation in ICU, physical dependence may develop resulting in withdrawal symptoms if treatment is abruptly terminated. Safety after 14 days of use is not established.

INTERACTIONS
Erythromycin and other *macrolide antibiotics, quinupristin/dalfopristin* and *cimetidine* inhibit the metabolism of midazolam resulting in reduced clearance, prolonged half-life, and increased volume of distribution producing raised and prolonged plasma midazolam concentrations resulting in profound sedation. *Itraconazole, ketoconazole* and possibly *fluconazole* markedly raise the plasma concentration of midazolam thereby increasing the sedative and amnesic effects, as do antivirals including *efavirenz, nelfinavir, saquinavir, indinavir,* and *ritonavir*.
Diltiazem and *verapamil* markedly increase the plasma levels and the effects of midazolam. *Grapefruit juice* can increase the bioavailability of oral midazolam by as much as 50%. *Theophylline, carbamazepine* and *phenytoin* may antagonise the sedative effects of benzodiazepines. Larger doses of midazolam are likely to be needed to produce sedation in *theophylline* treated patients. Respiratory depression may occur if *theophylline* is discontinued without reducing the midazolam dose. Enhancement of central depressive effect may occur when midazolam is used concomitantly with *opiates, anticonvulsants, sedative antihistamines, antipsychotics, antidepressants* and other *anxiolytic/sedative agents*.

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PREGNANCY
Midazolam crosses the placenta. Small risk cannot be excluded but there is no indication that the risk of congenital anomalies in the children of women treated with midazolam during pregnancy is likely to be great. Use during labour has been reported to cause irregularities in fetal heart rate, hypotonia, hypothermia, poor sucking and respiratory depression and use immediately prior to caesarian section has caused severe respiratory depression in the neonate requiring active resuscitation. Not recommended by manufacturer unless considered essential and not recommended at all in the last trimester.

BREAST-FEEDING
Midazolam should be used with caution in lactating mothers, as the drug is known to be excreted in breast milk. A WHO working group on Drugs and Human Lactation concluded that the use of this drug for a short period while breast-feeding is probably safe. It does seem to be controversial, however, the American Academy of Pediatrics state that the effects of midazolam on the nursing infant are unknown but may be of concern. The manufacturers do not recommend the use of midazolam in breast-feeding mothers.

SIDE-EFFECTS
CNS: drowsiness, prolonged sedation and ataxia are the most frequent adverse effects. Paradoxical reactions such as agitation, involuntary movements, hyperactivity, hostility, aggressiveness and excitement have been seen in children. Convulsions or abnormal movements have been seen in neonates and encephalopathic withdrawal symptoms have been encountered after 1-2 days use in neonates. There have been reports of life-threatening and fatal adverse respiratory and cardiovascular events occurring after IV administration. Facilities for resuscitation should always be available and respiratory and cardiac function continuously monitored. Treatment beyond 1-2 weeks, especially at large doses has been associated with an acute benzodiazepine withdrawal syndrome. Infusions should be gradually reduced over several days. When treatment has been given for several days and gradually withdrawn, patients may be awake but sedated for a further 12-24 hours reducing their ability to cough and expectorate. Diazepam is the treatment of choice for withdrawal symptoms. Dependence may develop after regular use even in therapeutic doses for short periods.
GI: nausea, vomiting, constipation, dry mouth and hiccup.
Local: intranasal use can cause irritation of the mucous membranes, which may be severe in some patients. Pain, tenderness and thrombophlebitis have occurred following IV administration.

POISONING/TOXICITY
Symptoms: overdosage can cause CNS depression and coma or paradoxical excitation. Long-term use such as in the intensive care situation has been suggested to be associated with drug accumulation and development of a severe encephalopathic illness in infants, with drowsiness, dystonic posturing, and choreoathetosis developing 1-2 days after treatment is stopped and persisting for a week or more.
Treatment: the effects of midazolam can be reversed by flumazenil. This may precipitate convulsions in patients with epilepsy.

PHARMACOKINETIC PROPERTIES
Absorption of midazolam from oral, buccal, intranasal and IM sites is rapid.
Approximate time to onset of effect:

	Time to onset	Duration of effect
Buccal	5 minutes	
IM	5-15 minutes	1-6 hours
Intranasally	5-10 minutes	45-60 minutes
Oral/rectal	10-30 minutes	20-90 minutes
IV	2-3 minutes	30-60 minutes

Extensive first pass metabolism results in a low systemic bioavailability (<50%) after oral administration. Midazolam is extensively bound to plasma proteins, about 96%. Bioavailability is higher but variable after IM injection. Although supplied as the water-soluble acid salt, at physiological pH midazolam becomes highly lipophilic and rapidly crosses the blood brain barrier. It has a large volume of distribution and an elimination half-life of 2-5 hours. Elimination is prolonged in neonates (3-12 hours - mean 6 hours) and in patients with liver disorders. Elimination half-life is shorter in children 3-10 years of age (1-1.5 hours). Metabolism is in the liver, the major metabolite being less active than midazolam with a half-life of approximately 1 hour. Metabolites are excreted in the urine mainly as glucuronide conjugates. Metabolism also occurs in the intestinal mucosa to a significant extent following oral administration.

EXCIPIENTS
Contact manufacturers for further details.

LICENSED STATUS
Hypnovel® 10mg/2mL is licensed in children for sedation in intensive care units, for premedication before induction of anaesthesia in children and conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia. Amsed and Epistat are 'specials' and as such are unlicensed. Other routes and indications are not licensed.

FURTHER INFORMATION
Oral midazolam has been prepared by mixing injectable midazolam in apple juice, raspberry and cherry syrups and carbonated cola beverages though little stability data is available for these formulations. Amsed and Epistat syrups are available from Special Products Limited.

Milrinone lactate

A phosphodiesterase III inhibitor with positive inotropic and vasodilator properties. Administration of milrinone results in an increase in cardiac output, stroke volume, decreased intra-cardiac filling pressure, and decreased systemic resistance with no significant change in heart rate or myocardial oxygen consumption.

USES
Treatment of congestive heart failure. Treatment of low cardiac output states following cardiac surgery. Treatment of patients refractory to escalating doses of catecholamines. Prophylaxis in patients at high risk of developing low cardiac output syndrome following cardiac surgery.

PRESENTATION
Injection: 1mg in 1mL, 10mL ampoule – Primacor®.

DOSAGE

Route	Age				Frequency (times daily)	Notes
	birth-1 month	1 month-2 years	2-12 years	12-18 years		
IV injection	← 50-75 microgram/kg →			50 microgram/kg	1	Loading dose. Given over 60 minutes.
IV infusion	← 250-750 nanogram/kg/minute →				continuous	Maintenance infusion. Dose titrated according to haemodynamic and clinical response. Maximum dose 1 microgram/kg/minute.

FROM ALDER HEY BOOK OF CHILDREN'S DOSES 1994

Sulphoacetate 5 mg Sorbic Acid with glycerin, sorbitol and water.		use Relaxit®			Insert whole nozzle into rectum.
MIDAZOLAM injection 2 mg/ml, 5 mg/ml ampoules.	i.v. bolus over 3-5 minutes	100 mcg/kg		single dose	Benzodiazepine. Sedation for ventilated patients. **Loading dose.**
continued	**then** i.v. infusion	**then** 50-300 mcg/kg/hr		**then** continuous	**Maintenance dose.** Adjust according to response. Infuse in D5 or NaCl 0.9% at a concentration of 0.5 mg/ml (or see "Infusion" section).

NOTE:DOSE GIVEN IS TOTAL DAILY DOSE UNLESS STATED OTHERWISE 137

ANNEX C

CLAIRE ROBERTS –DETAILED CLINICAL CHRONOLOGY AND COPIES OF SELECTED CLINICAL RECORDS

Date	***Time***	***Hours post ad***	***Events(source) CH 328770 RH papers***
4/9/87			090-015-028. Discharge letter from paediatrics RBHSC diagnosis aged eight months was salaam attacks. Dr Hicks consultant paediatric neurologist. Generalised seizures lasting up to 3 min over three days some three seizures prior to admission and followed by two absence attacks and then six generalised convulsions within one day each of lasting and minute with cyanosis. Tonic/chronic. Treated with Tegretol, then phenytoin. Full investigations for the time but no sca13 n. Concern about development. Aged eight months. seizures following discharge continued at this time on Epilim and taken off Tegretol. EEG no hypsarhthymia.
30/5/1996			090-013-018. Letter from Dr Gaston to Dr McMillin. Clinic attendance. "Has moderate learning difficulties and history of seizures from six months to 4 years of age. She has been off Epilim for the past year and seizure free”
2/8/1996			090-013-016. A copy of a letter to Dr McMillin from Dr Gaston consultant community paediatrician. Summarising a recent assessment. Extracts-performance school not good easily distracted inattentive and active. Learning disabilities. Trial of Ritalin. 10 mg of breakfast. One week first as placebo. On the next page 7 handwritten updating phone call on 11/9/96. One week Ritalin 10 mg in the morning mother to phone. 20/9/1996, doing well staleness. 2/10/96 dry mouth, viscous, pacing, query

Date	*Time*	*Hours post ad*	*Events(source) CH 328770 RH papers*
			agitated/unsettled 30 min after Ritalin?? Social awareness. Therefore restart on weekend just 5 mg mother to call five days later.
21/10/96			Accident and emergency department record. 090-010-012. Triage 1857 complaint lethargy, vomiting and pale. Epileptic. Medication non-. H/o typewritten off form and lethargy. GP referral with H/O seizure. Apyrexial O/A pale and drowsy O/A H/O mental handicap. 1903 temperature 36.9, pulse rate 96, respiratory rate 24, PEARL bag urine >. Handwriting Emla 715 S/B medical registrar admit Allen Ward. Records signed Jackson 2045.
21/10/96			090-011-013. GP handwritten referral letter. "Nine-year-old girl with severe learning disabilities and past history of epilepsy. Fit free for three years-weaned off Epilim 18 months ago. No speech since coming home. Very lethargic at school today. Vomited x 3 speech slurred. Speech slurred earlier. O/E pale, pupils reacting-does not like light. No neck stiffness, temperature. Tone ↑↑ Right side planter↑↑ Left planter↓↓ ENT NAD. Chest clear. Query further fit query underlying infection
21/10/96			090-012-014. Medical note by Dr O'Hare. 7:15 PM. Nine-year-old girl. H/O learning difficulties, epilepsy-no fits for three years, off antiepileptic medication. Today vomiting (-

Date	*Time*	*Hours post ad*	*Events(source) CH 328770 RH papers*
			non-bilious) since this evening. ^{0} diarrhoea/cough/pyrexia speech very slurred, hardly speaking. O/E drowsy, tired. Apyrexial. ^{0} Lymphadenopathy.PERLA ^{0} neck stiffness. Ears NAD, Heart Sounds I + II + O. Pharynx-unable to examine. (Diagram abdomen) soft, non-tender, ^{0} mass, ^{0} KLS, BS √ (diagram chest) resonant, A/E good nil added. Planters↓↓ R+L (but see GP letter) no apparent weakness, tone ↑ R L B + ++ T + ++ S + ++ K + ++ A + ++ admit Encephalitis query. 2045
21/10/96	8pm	1	090-022-050. Admission notes written in same handwriting "nine-year-old admitted via A&E. PC vomited at 3 PM and every hour since. Slurred speech and drowsy. Off from yesterday. Loose motions three days ago. HPC severe learning difficulties, seizures six months-year. Controlled by Na valproate age 4 – X1 seizures. Anticonvulsant gradually weaned until Epilim stopped

Date	***Time***	***Hours post ad***	***Events(source) CH 328770 RH papers***
			H&S speech-speech in sentences, meaningful. Hearing N vision N scribbling, feed herself with supervision, cannot dress herself. Gross motor walking, running, up-and-down, stairs, favours left side of body, T??? Special school Dun xx rd road. Dr Gaston ??? Previously Dr???. Recently tried Ritalin.-Dry mouth then became agitated-dry mouth.DH nil ALL nil FH [scheme drawn] O/E 37 CVS I&II 80/minute. RS clear, abdomen soft not tender no masses, CNS fundi normal, discs not blurred, PERLA VII, √IX √,X √ LOS (?) Sit up and staring vacantly? Ataxic power not assessed. Tone upper limbs right cogwheel rigidity, left ↑tone lower limb ↑tone ↑tone (reflexes my summary 2 ++ right, + left apart from knee 2+ planters down going. Ankle clonus + +) SENS not responding to parents voice/intermittently responding, responding to deep pain. (DD symbol) 1. viral illness,2. Encephalitis (scratched out) Inv F BC,U&E,BCx viral titres +/- LP – afebrile Mx IV fluids, IV diazepam if? Seizure activity. Reassess after fluids Signed Dr O'Hare
21/10/1996	12mn	5	090-022-052 12 midnight. Slightly more responsive-no

Date	*Time*	*Hours post ad*	*Events(source) CH 328770 RH papers*
			meningism. Observe and reassess a.m. Signed same Dr [possible different writing below with results] Na 132 ↓ K 3.8,U 4.5,Gluc 6.6,Cr 36,Cl 96 Hb 10.4,PCV 31,WBC 16.5 ↑,Platelets 422,000 signed SHO xxxxxxxx??
21/10/1996			090-038-133. Intravenous fluid chart. By 23:00 hours had 24 mls given. Thereafter cumulative amounts aiming at 64 mls per hour. By 07:00 hours 22/10 had total 536 mls. Over this time had six small vomits and passed urine once
21/10/1996	10 PM	3h	090-040-140. Nursing Kardex. Extracts. Child pale and lethargic. Apyrexic observations within normal limits. Bloods taken. IV fluids 5/N saline commenced at 64 mls per hour. Two small bile stained vomits following admission to ward. S/B Dr and registrar-to be reviewed following blood results and direction of IV fluids. Blood investigations ticked.
22/10/1996	7 AM	12 hours	090-040-140. Nursing Kardex. Slept well. Much more alert and brighter this morning. One further bile stained vomit. IV fluids continued as listed. No oral fluids taken. Apyrexic , observation satisfactory
22/10/96	??		Ward round Dr Sands Admitted? Viral illness. Usually very

Date	***Time***	***Hours post ad***	***Events(source) CH 328770 RH papers***
			active, has not spoken to parents as per normal. Wretching, no vomiting. Vagueness/vacant (apparent to parents) no seizure activity observed. Attends Dr Gaston. Six month old seizures and Ix for this NAD. U&E Na 132 F BC-WCC ↑16.5 Gluc 6.6. O/E apyrexic pale colour. Little response compared to normal CNS pupils sluggish to light. Difficult to see fundi. Bilateral long tract signs. Ears-blank-throat difficult to full see. Impression non-fitting status [then in another handwriting is inserted at sometime/encephalitis/encephalopathy] page 090-022-053. Plan rectal diazepam. Dr Webb. D/W Dr Gaston re-PMHx.
22/10/1996	2 PM	19	090-040-140. Nursing Kardex. (This refers 8 AM-2 PM) Slept for periods during early morning. Bright when awake. No vocalisation but indecipherable active. Late morning Claire became lethargic and "vacant". Parents can sound as Claire is usually very active. Seen by Dr Sands. Status epilepticus-non-fitting-continues overleaf. 090-040-141. Nursing Kardex. Rectal diazepam 5 mg PR given and commenced on CNS observations hourly. To be seen by Dr Webb and query CT scan in a.m. Seen by Dr Webb-to have IV phenytoin. Parents not in attendance.

Date	***Time***	***Hours post ad***	***Events(source) CH 328770 RH papers***
22/10/1996	2pm	19	"Neurology thank you Nine-year-old girl was known learning difficulties-parents not available. Grandmother Hx vomiting+ listless yesterday p.m.-followed by prolonged period of poor responsiveness. On no AED . Note appeared to improve following rectal diazepam 5 mg at 12:30 PM O/E afebrile, no meningism, pale. Rousable. eye opening to voice, non-verbal, withdraws from painful stimulus. Reduced movements right side? Against gravity all 4 limbs. Mild increase tone both arms. Reflexes symmetrically brisk. Clonus -sustained both ankles.Toes ↑↑. Sits up, eyes open and looks vacantly. Not obeying commands.PEARL -5 mm. Optic discs pale. No papilloedema. Facial palatal and laryngeal movements appear (N) impression-I don't have a clear picture of prodrome+ yesterdays episodes. Her motor findings today are probably long standing but this needs to be checked with notes. The picture is of acute encephalopathy most probably post ictal in nature. I note (N) biochemical profile. Suggest i) starting IV phenytoin 18 mg/kilogram stat followed by 2.5 mg/kg 12 hourly. Will need blood levels 6 hours after loading dose. ii) hourly neuroobs iii) CT tomorrow if she doesn't wake up. Signed D Webb
22/10/96	Between the 2 documented Paed		In a different handwriting by TP Sxxx below the end of Dr Webb's entry on page

Date	***Time***	***Hours post ad***	***Events(source) CH 328770 RH papers***
	neurolo consults		090-022-054 24 kg. Phenytoin 18 mg/kg loading dose= 18x 24= 632 mg. 24 kg phenytoin 2.5mg kg xxx= 60 mg 12 hourly either IV or orally check levels at 9 PM
22/10/1996	1510	20	From the Record of attacks observed : " Lasted frequently strong seizure at 3.25pm " duration 5 min
22/10/1996	1600	21	090-053-165 from statement made by Dr Webb "It would appear from the notes that I reviewed Clare during the afternoon and because of concerns about on-going seizure activity recommended the use of Midazolam (anticonvulsant). The next note reads "seen by Dr Webb, still in status" and then goes on to document the calculations undertaken to prescribe Midazolam was a bolus and then as a low-dose infusion. Following the therapy I reviewed and examined Claire again and this contact is documented in the notes timed 5 PM" This visit is confirmed by Mr Roberts in his chronology.
22/10/1996	???		Handwritten entry by probably SHO on 090-022-055 S/B Dr Webb. Still in status. Midazolam 0.5MG/KG stat dose= 0.5X24=12mg IV STAT Midazolam 2 mcg/kg/min = 2x24mcg/min=48mcg/min =48x60 mcg/hr =

Date	***Time***	***Hours post ad***	***Events(source) CH 328770 RH papers***
			2880mcg/hr=2.88mg/hr infusion= 69mg/24 hrs
22/10/1996	1700	22	090-022-055 Dr Webb handwriting " Claire has had a loading dose of phenytoin + a bolus of Midazolam . She continues to be largely unresponsive. She responds by flexing head (L) arm to deep supra-orbital pain+ does have facial grimace-but no localisation. She has intermittent mouthing and chewing movements. Background from mum-contact with cousin on Saturday who had a gut upset. Claire had loose motions on Sunday+ vomiting Monday. She had some focal SZS on Monday with right side stiffening. Plan 1) cover with Cefotaxime and Acyclovir from 48 hours I don't think meningoencephalitis very likely.2) check viral cultures ? enterovirus -stool, urine, blood and T/S 3) add IV sodium valproate 20mg/kg IV bolus followed by infusion of 10 mg/kg IV over 12 hours." Signed D Webb
22/10/1996	8 PM		090-040-141. Nursing Kardex. Refers to period 2 PM-8 PM. "Continues on hourly CNS observation GCS 6-7. Stat dose IV phenytoin at 2:45 PM to have BD. S/B Dr Webb still status epilepticus given stat IV hypnoval at 3:25 PM. Continuous infusion running at 2mls/hr of hypnoval to be increased by 0.1 ml /5min until up to 3 mls per hour. Dr to write up. Given stat dose Epilim at 5:15 PM. Very unresponsive. Only to pain.

Date	***Time***	***Hours post ad***	***Events(source) CH 328770 RH papers***
			Remains pale. Occasional episodes of tooth clinching. Commenced on IV [probably Cefotaxime] and IV acyclovir. First dose Cefotaxime due 9:30 PM some parents in attendance" additional note due phenytoin levels at 9 PM and then followed by tick and an entry of 23.4
22/10/1996	9:30 PM	26 ½	090-040-138. Nursing Kardex. [undated on form] 1/5 N at 64 mls per hour. Cannula resited this afternoon. 9:30 PM First dose of IV acyclovir erected by Dr and run over one hour. Hypnoval infusion increased by 0.1 ml every 5 min until running at 3 ml/hr as prescribed by Dr- completed at 10:40 PM.
22/10/1996	11 PM	28	090-040-138. Nursing Kardex. [undated on form] IV phenytoin erected by Dr and run over one hour-cardiac monitor in situ throughout infusion. Due to U&E results No. 18 solution with 20 mmol KCL directed as ordered by registrar. To have fluid restriction at 41 mls/Hour. Hourly CNS observations recorded. Temperature elevated at 10 PM-paracetamol given by day staff. Other observations within normal limits In column to the right is Glasgow coma Scale 6.
22/10/1996	2330	28 ½	Handwritten entry into note. 090-022-056 Na 121 K 3.3, Urea 2.9,Creatinine 33 Phenytoin 23.4 m?/L (10-20) hyponatraemia-? Fluid overload with low sodium fluids? SIADH Imp ? Need for ↑ Na concentration in fluids. -D/W registrar-↓ Fluids to 2/3 of present

Date	***Time***	***Hours post ad***	***Events(source) CH 328770 RH papers***
			value-41 mls/hour send urine for osmolality. SHO[//name]
22/10/1996			090-038-135. Intravenous fluid chart from 08:00 hours until 02:00 hours (23/10). Total 1070. Important here is that Midazolam prescription appears from 16:30 hours. The cumulative volume of this being 21.5 mls. Phenytoin started IV at 23:00 hours and an amount of 60 mls and 110 mls with a total of 170 mls is included in the oral column but is probably the IV volume. Passed urine three times. Two small mouthfuls of vomit. Weight recorded 24.1 kg
22/10/1996			090-039-137 neuro observation chart. Includes TPR and BP. Stable. Indicates severe weakness of arms and legs.
22/10/1996			090-042-144. Record of attacks observed. 3:10 PM "lasted frequently strong seizure at 3.25" duration 5 min state afterwards sleepy. For 30 seconds teeth tightened slightly duration few seconds state afterwards asleep 7:15 PM teeth clenched and groaned. Duration 1 min state afterwards asleep 9 PM episode of screaming and drawing up of arms. Pulse rate ↑ 165 bpm pupils large but reacting to light. Dr informed. Duration 30 seconds state afterwards asleep.
23/10/1996	2:30 AM	31 ½	090-040-138.& -139 Nursing Kardex.

Date	***Time***	***Hours post ad***	***Events(source) CH 328770 RH papers***
			Slight tremor right hand noted lasting a few seconds. Breathing became laboured and grunting-respiratory rate 20 per minute.02 saturation is 97%. Claire stopped breathing. Dr contacted immediately. Oxygen and suction given. Registrar attempted to pass ET tube but unsuccessful-anaesthetist called and ET tube inserted. Transferred to intensive care unit at 3:25 AM. No medication/drugs given.
[Presumed 23/10/1996]	3 AM	32	Medical note Reg "Called to see. Had been stable when suddenly she had a respiratory arrest and developed fixed dilated pupils. When I saw her she was Cheyne Stoking and requiring oxygen via face and mask. Saturation with bagging in high 90s good volume pulse. I attempted to intubate-not successful. Anaesthetic colleague came and intubated her orally with 6.5 tube transferred to PICU
Presumed 23/10/1996]	4 AM	33	Handwritten entry on 090-022-057. Looks like Dr Steen. "9 ½ year girl with learning difficulties admitted 32 hours ago with ↓ Level of consciousness.SB Dr Webb with [SYMBOL diagnosis] acute encephalopathy? Aetiology. Covered with acyclovir and Cefotaxime. Loaded with phenytoin + valproate added at 17:00 hours. ??XX p.m. phenytoin level equals 23.4.Na 121 K 3.3 fluids restricted to 2/3 maintenance observations otherwise stable. 3 AM Registrar asked to see because of respiratory difficulties Cheyne Stoke breathing -intubated and transferred to ICU. At present intubated+ ventilated

Date	***Time***	***Hours post ad***	***Events(source) CH 328770 RH papers***
			has had some Midazolam but it is no longer running. Pupils fixed and dilated. Bilateral papilloedema L>R no response to painful stimuli BP 90/65 HR= 100 /minute plan mannitol stat, dopamine infusion, urgent CT scan. " In the margin are written the results of the blood tests.
23/10/1996	4:40 AM	33 ¾	Neurology Dr Webb. SIADH- hyponatraemia, hypo osmolality and cerebral oedema + coning following prolonged epileptic seizures pupils fixed and dilated following mannitol diuresis no eye movements for CT scan
23/10/1996	05:30 hours	34 ½	090-022-058 CT scan report that " there is severe diffuse hemispheric swelling, with complete effacement of the basal systems. No focal abnormality is identified. Dr Kennedy.
23/10/1996	6 AM	35	Dr Webb. Brain stem death evaluation pupils 8.9 mm unresponsive Dolls eye movements Corneals absent-no gag response Iced calorics 14 mls to both ears-no response. No response (motor or autonomic) to deep supra-orbital pain.

Date	***Time***	***Hours post ad***	***Events(source) CH 328770 RH papers***
			Apnoea test in progress. CT cerebral herniation. Under no sedating/paralysing medication Claire fulfils criteria for brainstem death. The evaluation should be repeated in 4-6 hours.
23/10/1996			090-031-102 U&E sample untimed from PICU Na 152 Serum osmolality 313
23/10/1996	0710	36	090-022-058 Dr McKaigne [Con Anaesthetist PICU] "nine year old girl admitted to PICU from Allen Ward. Suffered a respiratory arrest. Was initially bagged and intubation performed by ?? Clark(SpR) anaesthetics on the Ward. At the time of intubation vomitus was noted in Oro pharynx-liquid material. No solid material. Following intubation trachea was sucked out and a small amount of watery material was aspirated. Oral ET tube then changed to nasal tube in PICU. Initially admitted to hospital with decreased level of consciousness with the clinical picture of acute encephalopathy. Status epilepticus subsequently developed requiring phenytoin, valproate, and Midazolam . Serum Na also noted to be low ↓ 121 presumably on the basis of SIADH In PICU hyperventilated and given mannitol 0.5G/KG pupils fixed and dilated. BP ~95 systolic. Peripheral dopamine infusion commenced. Arterial line right dorsalis pedis and right ??? Triple 5/8. Then transferred to CT. Transfer uneventful. CT shows severe cerebral

Date	***Time***	***Hours post ad***	***Events(source) CH 328770 RH papers***
			oedema. One set of brainstem tests performed by Dr Webb/Dr Steen. Serum Na also checked at the same time (133 - blood analyser) PIC no respiratory effort with ABGs pH 7.13, pO2 124.5 pCO2 79.2 Plan maintain circulatory support Claire is a potential organ donor, dopamine infusion to maintain SBP ~100 mmHg close check on serum Na and osmolality and urine output if serum Na > 150 and osmolality > 300 then commence desmopressin. One need conc K infusion. Maintenance fluids with dextrose 4%/saline/18% ventilate to pCO2 35 Dr Webb/Dr Steen had discussed Claire's clinical condition with her parents. They initially appeared to be giving consent for organ donation but Dr Webb will speak again to both parents at ~ 10 AM. Chest x-ray shows central line and ET tube in good position. There is some mottling of both hilar regions more so on the right side. There has been a deterioration in ABGs pO2 76 on FI O2 0.6 I would be concerned that this picture could be explained by pulmonary aspiration or early neurogenic pulmonary oedema. Any potential transplant centre should be alerted to possibility of pulmonary aspiration. Lab sample at time of brainstem tests: Na 129, K 3.6,Cl 94 urea 3.7, glucose 7.2 osmolality 274
23/10/1996	0800	37	Check two hourly U&Es change maintenance fluids to 0.9% saline

Date	***Time***	***Hours post ad***	***Events(source) CH 328770 RH papers***
			Signed McKaigne 090-022-060
23/10/1996	??		090-022-061 hypotensive BP 70/? With D.I given HPPF 500 mls needs DDAVP to limit polyuria . Appears BS death informally but only seven hours post arrest. Na 129 (from 121). Plan maintain BP > 100 DDAVP
23/10/1996	1825	47 ½	090-022-061 " Diagnosis of brainstem death protocol completed. No spontaneous respirations– CO2 70mmHg. Discussed with parents and agree that ventilation should be withdrawn. Consent limited PM given." Dr Steen
23/10/1996	1845	47 ¾	Dr McKaigne ventilation discontinued at 1845. Dr Steen writing "Death certificate issued - cerebral oedema 2 ^{o} to status epilepticus
29/10/1996			Handwritten discharge letter "case note discharge summary" 090-009-011 reports cerebral oedema, status epilepticus, hyponatraemia, ventilated, central line, CT scan. Ventilation withdrawn after discussion with parents at 18:45 hours on 23/10/96.
1/11/1996			Letter from SHO on intensive care unit to GP. Discharge summary. 090-006-008
11/11/1996	3.35pm		New handwritten entry difficult to decipher not the same handwriting as before "spoke at length with Mr and Mrs Robert earlier today. They are naturally still trying to come to terms with what happened to

Date	*Time*	*Hours post ad*	*Events(source) CH 328770 RH papers*
			Claire . I talked through the events before her death and also talked generally with them. They are naturally anxious to discuss the PM results with someone. I will pass this on to Dr Steen ASAP" signature indecipherable
18/11/1996			090-004-006. Letter from Dr Steen to parents offering a meeting. Includes a leaflet from the meningitis research foundation on death "I know meningitis was not Claire's problem but when I read the leaflet I thought some of the comments in it were very real and perhaps would be of help to you."
11/2/97			090-003-003. Autopsy report Date of necropsy 24/10/96. This report dated 11/2/97. Pathologist Dr Herron. "In summary the features here are those of cerebral oedema with neuronal migration defect and a low-grade sub acute meningoencephalitis. No other discrete lesion has been identified to explain epileptic seizures………. A metabolic cause cannot be entirely excluded…………….. as this was a brain and the autopsy, it is not possible to comment on the other systemic pathology in the general organs……."
5/3/1997			Letter dictated by Dr Heather Steen to Dr McMillin, general practitioner. Reporting cervical tissue showing abnormal neuronal migration which would explain Claire's learning difficulties. States that Dr Webb and Dr Steen have seen Claire's parents and discussed the post-mortem findings with them. "Mr Roberts wanted a short summary of the post-mortem report which Dr Webb will

Date	***Time***	***Hours post ad***	***Events(source) CH 328770 RH papers***
			send to him shortly."
21/3/1997			Letter from Dr Webb dictated 28/to/1997. (090-001-001)To parents "in summary of the findings were of swelling of the brain with evidence of a developmental brain abnormality (neuronal migration defect) and a low-grade infection (meningoencephalitis). The reaction in the covering of the brain (meninges) and the brain itself (cortex) is suggestive of a viral cause. The clinical history of diarrhoea and vomiting would be in keeping with that. As this was a brain in the autopsy it is not possible to comment on other abnormalities in the general organs. No other structural abnormality in the brain has been identified."

ANNEX B CLINICAL CHRONOLOGY FROM RECORDS-CLAIRE ROBERTS (born 10/1/1987) for 21-23 October 1996

090-026-075. Prescription chart. The dates are obscured partly by the folder punch but the following points. Phenytoin 60 mg is prescribed IV for 8:30 AM and 9:30 PM. There does not appear to be any column to indicate whether it has been given. Diazepam was given rectally at 1215 on 22nd/10/1996. Phenytoin was given 2:45 PM IV 635 mg there is there a column for who has given it on the drugs once only section IV. Sodium valproate 400 mg IV 5:15 PM and that is indicated as given.
090-027-018 PICU admission section

NUTRITION/HYDRATION RECORD urinary catheter inserted 22/10/96 mentions Midazolam infusion in situ .
090-028-088 record of relative counselling which mentions respiratory arrest and ventilatory support. Dr Webb Dr Steen. The form is incorrectly dated 22/10/96.
090-038-136 IV fluid prescription chart. Indicates 50 mls normal saline used for the Midazolam at 2 mls an hour over 24 hours to include 60 mg of Midazolam or could be 64. Also number 18 solution with 20 mmol KCl at no time at 41 mls but then scratched out and unclear what this means.

LABORATORY RESULTS

Lab results. 090-030-096. Blood tests taken 21/10/96. IgM for mumps, measles, herpes simplex and zoster CMV or negative. No and no significant growth also adenovirus, Q fever, Mycoplasma, PLGV influenza a and B. Reported 31/10/1996.

On 090-031-099.

The result of the blood electrolytes on 21/10/1996. Date of report 22/10/96. There is no time given on this report. Time the sample/receipt by laboratory is usually kept and would have been expected.

The next sample is on 090-031-100. From intensive care. Data specimen 23/10/1996. Blood sodium 139. What was the time of the sample.

090-031-101. Not clear whether this was from PIC or from the ward. Blood phenytoin level report. Specimen received 23/10/1996 at 4:20. Why is a date of receipt on this report but not on others. No time was stated on the form. Phenytoin 19.2 mg/L (range 10 to 20)

090-031-102. Electrolyte results no time. Date of specimen 23/10/1996 and from intensive care unit.

090-031-105. Minor acid chromatography from the urine reported normal also mucopolysaccharides. Ketones. Date of the specimen is when she was admitted under Dr Hicks as an infant but not clear which date.[Important because makes metabolic encephalopathy is unlikely from inborn error]. Similarly blood derivate and lactate were done.

090-032-108. Haematology report. Leucocytes given 16.52. No differential white count. No time on specimen but was from Allen Ward on 21/10/1996.

ROYAL BELFAST HOSPITAL FOR SICK CHILDREN

Fluid Balance and I.V. Prescription Sheet

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Date 22/10/96

Weight 24.1 Kg

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

IVsite

TIME (hr)	INTAKE: INTRAVENOUS 1 Level	Amount	2 Level	Amount	ORAL Fluid	Amount	OUTPUT: Urine	Aspirate or Vomit	Stool	Comment
08.00	No 1	68								[illegible]
[illegible]00		110								[illegible]
[illegible]00		179			sips of water.					[illegible]
11.00		259					P.U large → Diao			✓ S. Sperce (Stc
12.00		308								✓ [illegible]
13.00		350								[illegible]
14.00										
15.30		527								✓ [illegible]
16.00		562	[illegible] Midazolam 2ml/hr.							✓ K Taylor
17.00		616		0.8						✓ [illegible]
18.00		677		2.7						✓ [illegible]
19.00		769		5.5			PU			✓ [illegible]
20.00		806		6.7						✓ [illegible]
21.00		868		8.7	I.V Acyclovir ↑ 60	—	P.U.			✓ [illegible]
2[illegible]		943		10.9		60				① ② ✓ [illegible] red
[illegible]		1014	@3mls	13.9	PHENYTOIN					① ② [illegible]
24.00		1037		16.8	110	—		small mouthfuls		① ② [illegible]
01.00		1037		19.3		170		small mouthfuls		① ② [illegible]
02 00		1070		21.5						① ② [illegible]
03.00										
04.00										
05.00										
06.00										
07.00										

Total Intake		Total Output		No. of Vomits	No. of Stools
Intravenous.........ml	Oral.........ml	Urine ....ml	Aspir^n ....ml	....	....

24 – Hour INTAKE	24 – Hour OUTPUT
.........ml	.........ml

090-038-135

CR - RVH

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EASTERN HEALTH & SOCIAL SERVICES BOARD
ROYAL BELFAST HOSPITAL FOR SICK CHILDREN
PRESCRIPTION SHEET

PARENTERAL DRUGS

REGULAR PRESCRIPTIONS

DRUG SENSITIVITY

Date Comm.	DRUG (Block letters please)	DOSE	AM 6	AM 8.30	MD 12	PM 12.30	PM 5.30	PM 6	PM 9.30	MN 12	Other Times	Method and other instructions	SIGNATURE	Discontinued Date	Discontinued Initials
[illegible]/96	PHENYTOIN	60mg		✓					✓			IV	[illegible]		
[illegible]/96	MIDAZOLAM	2mcg/kg/minute (= 64mcg/minute)										IV infusion	[illegible]		
[illegible]/96	CEFOTAXIME	600mg		✓		✓	✓		✓			IV	[illegible]		
22/10/96	ACYCLOVIR	240mg		✓		✓			✓			IV	[illegible]		
22/10/96	[illegible]	5mg		✓		✓	✓		✓			IV	[illegible]		
~~[illegible]~~	~~Sodium Valproate~~	~~[illegible]~~										~~IV~~	[illegible]	22/10	[illegible]

DRUGS-ONCE ONLY PRESCRIPTIONS

Date Given	DRUG (Block letters please)	DOSE	Time of Admin.	Method of Admin.	SIGNATURE	Given by Initials
22/10/96	DIAZEPAM	5mg	12.15	PR	[illegible]	[illegible]
22/10/96	PHENYTOIN	630mg	2.45pm	IV	[illegible]	[illegible]
22/10/96	MIDAZOLAM	120mg	3.25pm	IV	[illegible]	
22/10/96	SODIUM VALPROATE	400mg	5.15pm	IV	[illegible]	[illegible]

CR – RVH

090-026-075

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ROYAL BELFAST HOSPITAL FOR SICK CHILDREN

RECORD OF ATTACKS OBSERVED

NAME: claire Roberts U.N. .... AGE: .... WARD: Allen

DATE	TIME	EXACT DESCRIPTION OF ATTACK	DURATION	STATE AFTERWARDS	INITIAL
22/10	3.10 pm	Lasted frequently Strong Seizer at 3.25	5min	Sleepy	MUM
	4.30	teeth tightened slightly	few secs	asleep	
	7.15 pm	teeth clenched + groaned	1 min	asleep.	
	9pm	Episode of screaming and drawing up of arms. pulse rate ↑ 165 bpm. pupils large but reacting to light. Dr Informed.	30secs	asleep	McCann

CR – RVH 090-042-144

NEUROSURGICAL UNIT ROYAL VICTORIA HOSPITAL

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NAME: Claire Roberts

CENTRAL NERVOUS SYSTEM OBSERVATION CHART

Record Observations Hrly hours

DATE: 22/10/96

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

Eyes open	Spontaneously	4	
	To speech	3	
	To pain	2	
	None	1	
Best verbal response	Orientated	5	
	Confused	4	
	Inappropriate Words	3	
	Incomprehensible Sounds	2	
	None	1	
Best motor response	Obey commands	5	
	Localise pain	4	
	Flexion to pain	3	
	Extension to pain	2	
	None	1	
SCALE TOTAL 3–14			9 7 6 6 7 7 8 6 6 6 6

INTRACRANIAL PRESSURE

PUPILS			
RIGHT	REACTION		
	SIZE		M M S S M S S S L M M S M
EQUALITY			E E E E E E E E E E E E
LEFT	REACTION		
	SIZE		M M S S M S S S L M M S M

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

VITAL SIGNS

PULSE RATE (red)

RESPIRATORY RATE

LIMB MOVEMENTS		
ARMS	NORMAL POWER	
	MILD WEAKNESS	
	SEVERE WEAKNESS	
	NO MOVEMENT	
LEGS	NORMAL POWER	
	MILD WEAKNESS	
	SEVERE WEAKNESS	
	NO MOVEMENT	

O₂ SATS 99 98 99 98 99 98 97 96 96 97

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

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

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

IC 6319 OS1212

CR - RVH

090-039-137

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R.B.H.S.C.
INTENSIVE CARE UNIT

DR P.M.CREAN

Surname ROBERTS
Forename CLAIRE
Age/DOB 10\01\87 Sex F
Hosp.No. 328770

ML

SERUM		VALUE	ADULT RANGE
Sodium	=	152* mmol/l	(135 TO 145)
Potassium	=	2.8* mmol/l	(3.5 TO 5.0)
Urea	=	3.3 mmol/l	(3.3 TO 8.8)
Calcium	=	2.69* mmol/l	(2.10 TO 2.57)
Ser.Osmolality	=	313* mmol/kg	(285 TO 290)

Date of Specimen 23\10\96
Lab.No. 20996
Date of Report 24\10\96

G.S.Nesbitt
R.V.H. BIOCHEMISTRY

CR - RVH

090-031-102

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R.B.H.S.C.
INTENSIVE CARE UNIT

DR P.M.CREAN

Surname ROBERTS
Forename CLAIRE
Age/DOB 10\01\87 Sex F
Hosp.No. 328770

GSN

SERUM		VALUE	ADULT RANGE
Sodium	=	139 mmol/l	(135 TO 145)
Potassium	=	3.0* mmol/l	(3.5 TO 5.0)
Chloride	=	103 mmol/l	(98 TO 108)
Urea	=	3.4 mmol/l	(3.3 TO 8.8)
Creatinine	=	34* umol/l	(40 TO 110)
Ser.Osmolality	=	287 mmol/kg	(285 TO 290)

Date of Specimen 23\10\96
Lab.No. 20553
Date of Report 23\10\96

G.S.Nesbitt
R.V.H. BIOCHEMISTRY

CR – RVH 090-031-100

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Admission

R.B.H.S.C.
ALLEN WARD

Surname ROBERTS
Forename CLAIRE
Age/DOB 10\01\87 Sex F
Hosp.No. 328770

ML

SERUM		VALUE	ADULT RANGE
Sodium	=	132* mmol/l	(135 TO 145)
Potassium	=	3.8 mmol/l	(3.5 TO 5.0)
Chloride	=	96* mmol/l	(98 TO 108)
Urea	=	4.5 mmol/l	(3.3 TO 8.8)
Creatinine	=	36* umol/l	(40 TO 110)
Glucose	=	6.6 mmol/l	(4.0 TO 8.0)

M.

Date of Specimen 21\10\96
Lab.No. 19924
Date of Report 22\10\96

G.S.Nesbitt
R.V.H. BIOCHEMISTRY

CR – RVH 090-031-099

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Ward: alle

Name of Patient: Claire Roberts

Number: 328770

REGULAR PRESCRIPTIONS — DRUG RECORDING SHEET

Date	6 a.m.	8.30 a.m.	12 noon	12.30 p.m.	5.30 p.m.	6 p.m.	9.30 p.m.	12 mn.	Other Times
22/10/96					C	8.15pm	D		11.9[illegible]

CH 328770 Page: 52. Clare Roberts

CLINICAL HISTORY, EXAMINATION AND PROGRESS

DATE	
Δ.	1. Viral illness
	2. Encephalitis
Inv.	FBC –
	U+E –
	BCx –
	Viral titres ± LP – afebrile.
Mx.	IV fluids,
	IV diazepam if ? seizure activity.
	Re-assess after fluids. [signature]
12MN	Slightly more responsive – No meningism.
	Observe + reassess am. [signature]
	Na 132 ↓ Hb 10.4
	K⁺ 3.8. PCV .31
	U 4.5 WCC 16.5 ↑
	Gluc. 6.6. platel. 422.000
	Cr 36.
	Cl. 96.
	Nopeon CS(?)
22/10/96	W/R Dr Sands
	Admitted ? Viral illness.
	Usually very active, has not spoken to parents as per normal
	Wretching. No vomiting.
	Vagueness/Vacant (apparent to parents)

090-022-052

CR – RVH

(i)

(ii) **CLAIRE NEUROLOGICAL OBSERVATION CHART**

Time (22-23/10/96)	***GCS x/15***
1 pm	9
2 pm	Not done
3 pm	7
4 pm	6
5 pm	6
6 pm	7
7 pm	7
8 pm	8
9 pm	6
10 pm	6
11 pm	Blank [calc at <6 by me] entry omits pain response " sluggish"
12mn	Blank but [calc by me 6]
1am	6
2am	6