This is a report by

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requested by the *Inquiry into Hyponatraemia-Related Deaths*

It is a final narrative which attempts to summarise the sequence of events though Adam Strain's life, from the perspective of a paediatric nephrologist, including those ones that led to his death.

17/03/2012

Purpose of this report

I have written 15 previous documents about Adam Strain's management, and taken part in a number of experts' meetings over a period of nearly 2 years. Some of these documents have taken overviews, but many are technical in nature and necessarily consider some small details at great length. In looking back over them, I feel that by reading them as they stand, there is a real danger of losing the wood for the trees.

I have therefore written this summary report to try to counter this difficulty. I aim to use it to sum up my final position on some of the issues which I feel are most important and which fall within my specialist expertise, but without repeating too many of the lengthy arguments.

To achieve this aim, I will reference previous explanations from my previous reports, which I have now relabelled as R1 to R15, as listed below:

R1	04/08/2010	First witness statement
R2	11/08/2010	Replies to Dr Booker following first witness report
R3	12/10/2010	Responses to Inquiry Team about first witness report
R4	04/12/2010	Second witness statement; further clarifications about previous reports
R5	15/03/2011	Third witness statement; response to Dr Taylor's police interviews
R6	07/11/2011	Report on conduct of paediatric nephrologists' management
R7	07/11/2011	Completed Inquiry fluid balance tables
R8	11/11/2011	Further responses to queries, including details of Adam's PD
R9	01/12/2011	Responses to queries raised about report R6
R10	10/02/2012	Replies to Dr Dyer's report on CVP measurements
R11	16/02/2012	Responses to (a) Dr Taylor's admission of errors, and revised fluid balance position, discussion about live-donation of kidneys, and comparison of experts' fluid balance figures
R12	20/02/2012	Response to Dr Kirkham's suggestions of PRES and intracerebral thrombosis diagnoses
R13	15/03/2012	Review of literature on child water intoxication
R14	15/03/2012	Update on CVP measurement issues, including zeroing
R15	16/03/2012	Update on water balance figures, oliguria during surgery, value of measuring pre-op urine sodium

Medical background and pre-transplant management

Adam was born with dilated (stretched-up) urinary tracts and poorly developed dysplastic kidneys which did not work normally. His kidney function was known to be poor from very early on. This particular combination of findings in the urinary tracts is most commonly seen in boys, and forms the single most common sub-group of children who develop kidney failure and require transplantation during childhood. For that reason, its features are familiar to all paediatric nephrology units within the UK and Ireland.

The current health-care arrangements for managing children with serious kidney diseases were in place before Adam's birth. In this system, children like him are all managed by a paediatric nephrologist working in a regional centre. Sometimes their care may be shared with paediatricians in other district hospitals as well as with their GPs, but the paediatric nephrologist will take all of the specialist medical decisions about them, and will advise closely on day-to-day ones as well, such as advising on immunisation programmes, etc. This is because ordinary care may have to be modified in some children with kidney impairment.

In Adam's case, Dr (later Professor) Savage took on the primary medical caring role for Adam. It is clear that he undertook this task with meticulous care, and made himself readily available to Adam's mother, Debra Slavin, to allow her to contact him easily. It is also clear that Dr Savage worked closely with his medical colleagues, sharing cover with Dr Mary O'Connell as necessary, and with non-medical colleagues including specialist nurses and dieticians. This is how the care of such children is ideally conducted.[R6 & 9]

The particular medical problems faced by children with dysplastic kidneys are well known to paediatric nephrologists, and Adam's case was in many ways absolutely typical of children with this condition. Usually, the tubules of the kidney are predominantly affected in dysplasia, rather than the glomeruli. This leads to these children being likely to maintain a urine output of poor quality urine, even well after their ability to clear impurities from the blood forces them to have artificial kidney replacement. Thus, he continued to pass urine whilst being peritoneally dialysed, and while waiting for a kidney transplant. This is relatively common in children with kidney failure, but seldom seen in adults, who typically do not pass any urine at that stage.[R1]

One of the consequences of passing moderately large amounts of urine, and being unable to regulate its concentration or its salt content very well, is that most of these children tend to waste water and salt in an uncontrolled manner into their urine. This leads to them being unusually thirsty, and requiring more than normal amounts of water. It also means that they usually need to have extra sodium added to their diet. Often, some of this has to be as sodium bicarbonate (an alkali) as well as sodium chloride (common table salt) to counteract the kidney's failure to excrete enough acid from the body.[R15] This is exactly what was seen in Adam.

Children with these difficulties are at risk of becoming hyponatraemic quite easily, for 2 main reasons. First, they may lose more sodium in their urine than they are being given regularly. This is seen as they grow and their salt losses gradually exceed their intakes, so the oral dose needs to be increased. It also follows other mild illnesses which prevent them from keeping feeds down to match their relentlessly ongoing salt losses. This salt-depletion type of hyponatraemia happened 10 times early on in Adam [R1], 9 times as a result of too little oral intake, and once when he received the correct volume of intravenous fluid during and after surgery, but with less than half as much sodium in it as he normally needed orally. The anaesthetist then was also Dr Taylor. In each case, the hyponatraemia took many hours to develop, and he did not have any specific symptoms related to it.

The second cause is dilutional hyponatraemia which is due to the child being given large amounts of water quicker than they are able to lose it from their kidneys.[R1&4] This causes an excess of water to be retained within the body, which then inevitably dilutes the concentration of the sodium in the body water. This happened once early on in Adam [R1], and I will explain below that I am sure that this was the cause of his death at the time of his transplant operation. On the first occasion, Adam had reasonably well maintained background kidney function, but developed acute reversible kidney failure during an operation on his ureters on 23/11/1991 which destabilised his function transiently by the mechanisms that I explain in [R16]. This was not managed appropriately at the time, and his fluid infusion with hypotonic saline was maintained at too high a rate. His weight increased and his sodium fell to 111 mmol/l, but did so over 3 days (as opposed to 3 hours during his transplant operation). He required temporary dialysis at the time, but his kidneys then began to work again, until he slid slowly into permanent kidney failure later.

If children are born with even moderate levels of kidney failure, it tends to worsen markedly over the first year or years, as happened with Adam. This is because young children grow, but damaged or badly formed kidneys usually have a very limited growth potential, and kids simply outgrow their kidney function. In addition to this, poorly functioning kidneys are driven to work extremely hard by the body via various mechanisms, and as a result wear out quickly, leaving ever smaller numbers of nephrons to provide function for an ever growing child.

There are several other aspects of having poor kidney function whose mechanisms are not well understood, but which are consistently seen and are clinically important. Many of these are discussed in detail in [R12], and in a paper of mine which I reference in that report in which I undertook a study of all the children treated under the age of 2 years in the UK and Ireland spanning the time that Adam was treated. One major consequence of chronic renal failure in infancy is that very few children with poor kidney function eat normally, or even eat at all in many cases. Instead, most are given their nutrition as a special milk down a naso-gastric tube or gastrostomy until they are transplanted, when feeding typically rapidly normalises. Similarly, most infants with severe kidney failure do not develop normally in their gross motor milestones, and are weaker than normal and sit and stand later, even if their cognitive development is normal, which it is not always.

Children who start off with moderate renal impairment, and then outgrow their kidney function as pre-school children, such as Adam, typically start off feeding and developing normally, and then slowing down. They may then start to require partial or total tube-feeding, and may begin to miss motor milestones. This is exactly what happened to Adam. It is vital that professionals dealing with children with chronic renal failure realise this, otherwise there is a danger that these changes will be misinterpreted as having other causes, such as them having a neurological diagnosis. I believe that Professor Kirkham's evidence and hypothesis about Adam in her report which I respond to in [R12] suffers from this problem. She appears to be postulating rare and complicated reasons for Adam's clinical state, which are in truth absolutely typical features of small children with renal failure.

I only wish to comment about Adam's period on peritoneal dialysis (PD) briefly. He was treated with a PAC-X automated PD system overnight by his Mum, who managed his care with great skill and ability at home. I have read and analysed the diaries that she kept of his progress on PD [R8] which confirm this. They also confirm an observation that I have made in many children, that the volume of fluid removed by overnight PD varies appropriately for the child's requirements. The mechanism by which this happens is not fully understood, but it is a fortunate fact, for it means that if children are a little dehydrated when they start dialysis, less fluid is taken off, and if they are heavier than normal at the start, more fluid is removed. This is clearly so in Adam's case [R8]. It is also the case that most of the fluid removal occurs during the first few cycles. These points are important as it means that children can cope much better than one might otherwise guess if they have a shortened series of cycles overnight, such as happens often if children are unwell, and as happened prior to Adam's transplant.

A final point about Adam's pre-transplant management is that children with renal failure develop anaemia because they lack the hormone erythropoietin (EPO) which is made by the kidneys and drives the bone marrow to make blood cells. In his case, he was commenced on EPO some time prior to his transplant, and this brought his haemoglobin up to the low-normal range. Nowadays we aim to completely correct the levels, but in 1995, the aim was to reach the low-normal range. Giving EPO can generate iron deficiency by using up all the stores, but Adam was managed very carefully in this regard, and had biochemical and haematological evidence showing that he was not iron-deficient.[R12]

There was a great deal of concern in the early literature about the potential complications of EPO treatment, including risks of iron-deficiency anaemia and of thrombocytopenia and excessively high haemoglobin concentrations, which together may promote thrombosis and other events. Dr Kirkham has voiced these as potential risk factors for Adam, in support of a hypothesis that she has put forward to explain Adam's death, in which she suggests that he may have had a cerebral venous thrombosis. I respond to her report in [R12]. I am completely certain that none of these risk factors applies to Adam whose haematological status was ideally managed for a child in 1995, and was maintained stable at that level. The hypothesis also appears unlikely in view of the fact that there was no neuro-radiological or post-mortem evidence of thrombosis either.

Adam's final admission

When Adam was called for a possible transplant, he was essentially a well lad on PD, and typical of a 4 year old requiring a kidney. The decision to accept the offer of the kidney for tissue-typing and proceeding to a transplant if it was a good match was entirely appropriate for him to have in Belfast, with their previous paediatric nephrology and paediatric renal transplant experience.

The role of the paediatric nephrology team was to arrange his admission, to undertake appropriate blood tests (including a test to look at the tissue compatibility of Adam and the donor's blood), to check that he was well, and to ensure that he was in good condition and prepared for a transplant as soon as convenient and safe after the result of the matching was known. This was done entirely appropriately in accordance with their in-house transplant protocol, and involving Dr Savage and his junior medical staff. I have argued that their protocol would have been better if it had included a measurement of the urinary sodium concentration [R16], but their approach was probably the majority view then, and may still be now.

The role of the transplant surgeon during this time is first to discuss the particulars of Adam's medical case with the paediatric nephrologist and to consider all of the known factors, such as the age and size of the donor, the anatomical information about the kidney, the time that it was retrieved, the degree of tissue mis-match, and any prior surgery or particular problems the recipient may have had (many will have had more than 1 previous laparotomies, as Adam did). The decision to accept and proceed with a transplant has to be one that both the surgeons and nephrologists are happy with – this appears to have been the case here. The plan to dialyse him overnight, and to start fresh the following morning was entirely sensible.

In 2012, it is a requirement that the person that is going to undertake the surgery must obtain informed written consent from the parent. In 1995 this was not so prescribed, and it had to be "an appropriate person". In Adam's case, Dr Savage obtained consent. I think that this was entirely acceptable and appropriate as he would know Adam better than any other doctor, and would know, understand and convey the risks of the procedure as thoroughly as a transplant surgeon could. In fact, the process of informing and agreeing consent begins a long time before the family is called in for a kidney. From the moment that kidney replacement is discussed, Adam's Mum will have been given appropriate information over a long period, which is far easier to fully assimilate. In my view, our practice in Newcastle of the family jointly meeting the paediatric nephrology team and the transplant surgeons prior to putting the child on call has many advantages. We also have regular professionals meetings between the nephrology and surgical teams to review the particulars of each child who is waiting for a graft, the minutes of which are readily available in case a different consultant surgeon is on-call that night. I would recommend this practice. Although this was not done in Belfast at the time, I am sure that their management in this regard was entirely appropriate.

Another role of the paediatric nephrologist at this time is to arrange and liaise with an anaesthetist for the operation. I would expect the paediatric nephrologist to discuss the details of the case with that anaesthetist. This discussion would include the case background, including previous anaesthetic problems, venous access difficulties, his plan for overnight fluids and PD management, and the child's normal biochemical and fluid volume status, including an assessment of his usual urine output when stable (about 1.5 litres per day, or about 62 ml/hour in Adam's case).

I would also expect the paediatric nephrologist to confirm their general management requirements, unless they had previously managed a transplant jointly with that particular anaesthetist before. Thus, I would check that they were aware that we would want him to have his CVP monitored, and to aim to fill him with fluids prior to the clamps being released, connecting the graft to the child's circulation. I would inform him of the likely (or in our case, measured) urinary sodium concentration to guide him which fluids to replace them with. I would not, however, expect to have to address questions about which fluids the anaesthetist would use to fill the child's circulation, as I would expect them to already understand the basics of physiology and medicine, and thus to know that these would have to be physiological with respect to their sodium concentration. I would not expect to have to ask them to catheterise the child for the operation as in my experience this is always a routine procedure when transplanting non-anuric children.

Having delivered the child to theatre in good clinical condition, I would endeavour to visit during the procedure in order to keep the parents informed of progress, or ask for a colleague to deputise for me in that role if I had other commitments, and if they had the time to do that. This is exactly what happened.

Frequently in paediatrics, management has to be adjusted to what is practical and what children can tolerate. Given that Adam's plasma sodium was virtually normal on arrival, and given the plans for sodium-containing clear fluid to be administered overnight instead of milk in parallel with a shortened dialysis programme, and knowing how stable Adam generally was on PD, I would have regarded it as an ideal but not essential to repeat his plasma biochemistry tests before theatre in the morning. However, as Adam's veins were difficult to sample from, and after discussion with a member of the anaesthetic team during the night as blood was not easy to obtain, I would have considered that I had arranged for the anaesthetists to collect and test a blood sample urgently while they were accessing his central line in theatre.[R2]

I would expect the anaesthetist to meet the child and parent on the ward before the transplant to familiarise themself with their case, to plan the details of the procedure, and to answer the families' questions. I cannot remember a single case where the consultant or his deputy did not meet the family on the ward in advance, whatever the time of day or night. I do not think it acceptable to first meet them in the anaesthetic room where both mother and child are likely to be very anxious and be unable to provide or take in information easily.

It is the anaesthetist's role in theatre to take responsibility for the child's medical management and welfare during surgery, as well as administering the actual anaesthetic agents to render them unconscious, pain-free, and with relaxed abdominal muscles. They take on managing their monitoring, including for their fluid treatment. For a child undergoing a kidney transplant, the monitoring would include setting up a CVP line that they were confident recorded the child's atrial pressure. For a child such as Adam, who had a regular significant urine output, it would also include them catheterising the bladder, or arranging for somebody else to do this, so that urine output could be monitored to ensure that its replacement rate was maintained correctly.

It has to be appreciated that these requirements of anaesthetists are not extra-ordinary ones that only rarely apply, such as during a child's kidney transplant. That is not the case. Instead, these elements of management apply to every small child who is ill and unable to regulate their own fluid intakes for a whole range of common reasons. For example, a baby presenting very sick with meningitis may become drowsy or even unconscious, may be too ill to feed, and may become dehydrated. This can lead to them developing pre-renal or established renal failure. In such a case, CVP monitoring, bladder catheterisation, intravenous fluid infusion or total parenteral nutrition and continuous monitoring of vital signs are all part of routine care. Almost every child on a paediatric intensive care unit (PICU) either has these requirements, or is at risk of doing so. PICUs are primarily staffed by paediatric anaesthetists and paediatric intensivists, many of whom have trained initially as anaesthetists. This is their bread and butter. A consultant paediatric anaesthetist would be expected to cope with all of these events, and to know to call for back up and assistance if special problems arose.

Central venous access and pressure monitoring

Adam required to have a central venous line inserted to provide adequate venous access for blood sampling and for the administration of fluids and to provide CVP pressure monitoring.[R10] This procedure is often technically demanding in small children, especially in ones who have had previous multiple central venous access lines. This situation is, however, common in children who have had renal failure from early in life because central venous access is often required repeatedly for procedures that are needed prior to transplantation. Dr Taylor presents his difficulty with obtaining central access as an indication that Adam was dehydrated on arrival in theatre, confirming his prior assumption based upon his mistaken belief that Adam had lost 400 ml of urine in the previous 2 hours, after his nasogastric fluids had been stopped. This is a false argument. Apart from the fact that the evidence points to Adam having been adequately hydrated at that point, it is commonly tricky to cannulate a central vein in a child, let alone one who had had previous access.

The process of inserting a central venous line involves the operator testing its patency by putting a syringe onto the end connection and sampling blood into it, often washing it back and forth repeatedly to test how freely it flows. This would have been an ideal opportunity for Dr Taylor to obtain a blood sample to measure Adam's starting biochemistry values had he wanted to. Given that this had been discussed between his team and the ward staff overnight, one would have expected him to do this. All he would have needed to do would have been to hand the syringe to a medical, nursing, or theatre technician colleague, so that they could add the blood to a sample bottle and organise for it to be sent

to the laboratory. He would have had to do it this way rather than to add it to the sample bottle himself as he would have been scrubbed to insert the line and would not have wanted either to touch a non-sterile bottle, or to leave the syringe on his sterile towel until later as it would have clotted in that interval.

In his earlier testimonies Dr Taylor repeatedly provided multiple reasons why he did not collect a blood sample at this stage, but has recently admitted that these were not valid reasons. He is correct that they were not valid reasons. It is worth considering them now, however, as they may illustrate principles that apply to other aspects of Adam's management.

First, the argument that everybody was under a time pressure to complete the transplant because the kidney had been harvested many hours earlier does not stand up.[R8] Although it is true that a shorter interval is statistically associated with a better outcome for kidney transplants, this evidence relates to a large number of hours of delay, and has to be balanced against the dangers of cutting corners in other ways which may only contribute minor time savings. For example, it was decided to wait several hours (overnight) to transplant Adam because of the advantage of having fresh staff operating – a reasonable decision. In relation to sampling blood, this omission would at most have saved a couple of minutes, which would have produced no significant advantage.

His second group of arguments were based on the lack of theatre staff time available to deal with sending the blood sample. All that was required immediately was for the blood to be taken and put into a sample bottle – it could have been dispatched to the lab several minutes later if there really was too much else to do at that precise moment. If he was implying that there were too few theatre staff to deal with it even then, he would also be implying that the theatre was not one that was adequately staffed to carry out transplant surgery safely; that it was not fit for purpose.

His third reasons related to his allegations about the laboratory service having a too slow turn-round time to allow an acute sample to be processed in time to still be relevant or useful. Again, if this had been the case (which I don't accept), it would have not been a safe hospital to undertake PICU or major paediatric surgery of any kind in, and to anaesthetise a child under these circumstances would in itself be irresponsible.

Having said that Dr Taylor's (later withdrawn) arguments for not taking this sample were not valid, I personally do not think that a sample taken at 07:00 would have been likely to have produced results that would have led to concern.[R1,2,3&4]

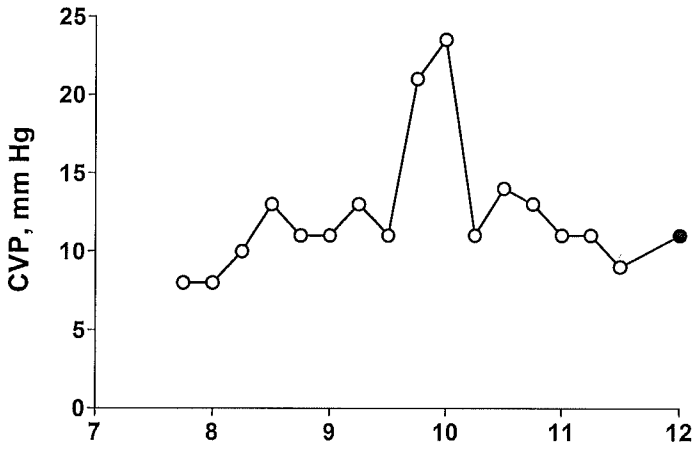
The value of CVP pressure monitoring is that it is a valuable way of assessing whether there is too little, the right amount, or too little fluid circulating in the child's blood stream. It is extremely important in paediatric transplantation for that reason. Kidneys require approximately 20-times more blood flow than the average body tissues do, so when a child's heart has to suddenly perfuse an adult sized kidney as well as the child's body, it really needs all the help it can get. Thus, when the surgeons have sewn the new kidney in place and are ready to open the clamps on its artery and vein, it is essential that the child has a slightly over-filled blood stream, otherwise there is a significant risk that the new kidney will not receive a sufficient blood flow, and may just clot as a consequence.

When Dr Taylor discovered that the first CVP reading was extremely high at 17 mm Hg, he correctly recognised that this level could not be a true measure of Adam's pressure. This is because a value of 17 would indicate that Adam's blood stream was markedly over-filled, and would imply that he had a large excess of fluid on board, whereas the rest of his clinical history, examination and vital signs contradicted that. In my opinion, Adam was likely to have been about normally hydrated and would have had a normal CVP, and I note that Dr Taylor believed him to be fluid depleted and would have expected him to have a low value.

However, Dr Taylor did not manage the situation correctly. The logical sequence of trouble-shooting this problem is first to look at the dynamic CVP trace to see if it had pressure waves transmitted from the emptying and refilling of the right atrium (cardiac pulses in time with the heart beat) and pressure waves due to the lungs being ventilated (respiratory traces in time with his breathing). If no cardiac or respiratory pulses are seen it means that the tip of the venous line is not in fluid continuity with the large central veins in the chest and implies that it may be clotted (easily tested with a syringe) or that the tip is blocked by being jammed into a small vein lumen, or against its wall. If, on the other hand, cardiac and respiratory waves are seen, then it is in fluid continuity with those veins, and **is** reflecting central venous pressure. Dr Taylor states clearly that these traces were present.

Thus, since the evidence that we have is that these traces were present, there is no way that the CVP line could have been clotted or blocked. All further discussion in Dr Taylor's and others' statements about where the tip of the line was, or might have been, and whether a vein had previously been tied off or not, are therefore all irrelevant. The fact that the intra-thoracic pressure waves are measured means that it was functioning properly. For interest, in my experience (and I have put in many central lines myself for acute dialysis or plasmapheresis treatments) about 50% of subclavian vein lines in children go up into the neck as Adam's did, and this was certainly true for several successfully functioning ones that anaesthetists had inserted for transplanted children under my care).

Given the combination of a functioning line and a physiologically implausible CVP recording, the operator should then swap the electronic equipment (pressure transducer and recorder devices) to ensure that they were functioning normally. If that doesn't solve the problem, then there must be a problem with the zeroing procedure, and this should be critically checked. This is explained in a separate report [R14]. In summary, the correct calibration is achieved by briefly opening the transducer device to atmospheric (zero) pressure while it is held at the level of the correct anatomical point on the child's chest. The transducer then has to remain fixed at that same height to give correct readings. In practice, this can be tricky because the transducer may be fixed on a stand some distance from the child's chest, and the horizontal alignment has to be determined using a spirit level. Errors such as the operator at the chest end of the level aligning the top edge of the device to the correct anatomical height, while the operator adjusting the transducer level to its lower edge, would introduce a consistent false-positive pressure error. A meter-long builder's spirit level that was 12 cm high in its operating position would cause the CVP to over-read by 9 mm Hg. If this sum is subtracted from all of Adam's readings in theatre (open circles in the graph below), but not from the PICU one (filled dot) where zeroing is much easier as it can usually be done right by the child, it converts Adam's problematic clinical chart to the one below, which makes good clinical sense:



Thus, I believe that the CVP readings were all about 8 – 10 mm Hg too high in theatre, due to a zeroing mistake. None of the other suggestions that I have heard makes complete sense of all of the facts available.

Dr Taylor's conclusion that the line was blocked by being jammed into the vein, and his initial decision to disbelieve the absolute readings, but to use the trace as a guide to the trend, makes no logical sense. His later clinical actions of then disregarding the trace altogether and to decide that Adam was seriously dehydrated when he clearly was not, in the face of an apparent rise in the trend he was observing, was also wrong. His correct action would have been to delay surgery until he had a satisfactory, plausible CVP reading. If necessary he should have sought the assistance of another anaesthetic colleague to deal with this. The excuse offered for not doing so, of further prolonging the waiting time for the kidney, is no more valid in this case than it was for omitting to take the blood sample.

If Dr Taylor had taken the time to zero the CVP properly, he would have had a reliable measure of Adam's vascular fullness, and would thus have been alerted to the fact that he did not need any more extra fluid, at the point that he decided to infuse him with a large volume of hypotonic fluid to counteract his presumed hypovolaemia.

Adam's fluid regimen

The principles of fluid management in small children with non-anuric renal failure whilst undergoing a kidney transplant are no different from the principles applied to any anaesthetised dependent child. Though there is a danger of them appearing complex, and despite the great attention to detail that is required to manage it well, the principles and the practicalities of maintaining both salt and water balance in such a child are simple. Safety is guaranteed if good practices are adhered to.

The concept is simple. If a child starts off in sodium and water balance, they will stay in balance if all of their salt and water losses are replaced with similar quantities of salt and water. All that is needed is to:

a) Measure or estimate the volumes of the various losses
b) Measure or estimate the sodium concentrations of the various losses
c) Infuse IV fluids to balance these losses as closely as is possible, or at least as closely as is it is reasonable to achieve in practice.

You need to give fluids (containing sodium or not) under 3 different circumstances during surgery.

(i) To replace losses that you know about but cannot measure (insensible)
(ii) To replace losses that you can measure
(iii) To be retained as extra – for example if you think their volume is too low for some reason, or if you need to give them a drug or similar in liquid IV form.

There is no need for complex calculations to be done to work this out.

To replace the insensible losses from the skin and respiratory tract and evaporation from the open wound you simply need to have a simple formula to do this, based on a per kg or per body surface-area rate, and to replace this volume as free water (as these losses are mostly of water without salt).

Measured losses can include a range of bodily fluids, but in most cases, including Adam's, the major one is urine. If the child has healthy kidneys all you need to do is give about the approximate volume of fluid that the child is expected to drink on average each hour, with some sodium in it, and they will adjust their urine output of both sodium and water it the exact quantity chosen is not precisely right. This approach will not do for a child whose kidneys are not able to respond in this way, and is therefore never good enough during paediatric transplantation. I will deal with this below.

Another measured fluid loss during surgery is blood. Since the sodium concentration of the blood is (by definition) that of normal plasma sodium, it needs to be replaced with the same. If the blood losses are only moderate it may not be necessary to replace them with blood itself, but if a clear fluid is used it should be of similar sodium concentration to plasma, so normal saline or a solution such as Hartmann's can be used, or even plasma. If the losses are sufficient to potentially cause the child to become significantly anaemic, they may need to be given whole blood, or packed red blood cells plus plasma or clear fluid with a normal sodium concentration.

If any other fluids need to be given over and above that to replace kidney and other losses, such as to provide clotting factors or platelets, or to carry a drug, or in the case of a kidney transplant to ensure that the circulating blood volume is relatively large prior to opening the vascular clamps, it is self-evident that it must be assumed that in the short-term, those fluids will be retained within the child's body. It is therefore obvious that they must have a sodium concentration close to that of plasma, otherwise it is inevitable that by being added to and mixing with the body's fluids, they will dilute the plasma. This is simple, and obvious.

Dr Taylor deviated from these simple principles, and thereby made major mistakes when he anaesthetised Adam which resulted in him being given very large volumes of inappropriately dilute intravenous fluids.

His first error, which he now admits to,[R11] was to conclude that Adam usually passed 200 ml of urine each hour, with the possibility of being able to increase that further if given more water to drive his urine production up. It has never been clear where this figure came from. In his various statements[R5], Dr Taylor has implied that it was from his case-notes (which he did not look at until

after Adam was in the anaesthetic room), or from a discussion with Dr Savage when being briefed about Adam on the telephone, or from a knowledge of his fluid intakes and urine volumes in the past, or from his experience of having anaesthetised him before (one of which times he also caused hyponatraemia by a different mechanism). Suffice to say that Dr Savage's repeated estimates of Adam's daily urine output based on his known fluid intakes, documented more than once in the notes, was about 1.5 litres, which is an average of 62.5 ml/hour. Thus, his decision to deliver 200 ml/hour of urine-replacement fluid meant he gave 3-times the correct amount, or an extra 137 ml each hour.

His second error was to assume that the sodium concentration of the urine was likely to be as low as it had been when measured in the past, rather than since Adam had moved on to develop end-stage kidney failure. As a result, he judged it would be best balanced by using 0.18% saline + 4% dextrose, a solution with a sodium concentration of 31 mmol/l (hereafter called N/5 saline, as its sodium concentration is one-fifth that of physiological 0.9% saline, or Normal saline). I have argued that it would be sensible to measure the urinary sodium routinely in children undergoing transplantation who still have a native urine output, and the responsibility for not doing that has to be shared with Dr Savage. In the absence of that, the best assumption is that the urine concentration is likely to be close to 0.45% saline, or half-normal, N/2 saline, which has a concentration of 77 mmol/l.[R3&4]

Assuming that 77 would have been correct, giving a solution with a concentration of 31 would mean that for each litre of urine replaced, Adam's body would become sodium depleted by 46 mmol of sodium.

A third error was not to measure Adam's urine output. My experience of kidney transplantation is that it has always been routine to catheterise the child's bladder at the beginning of the operation. Apart from providing drainage and monitoring for the urine volume during the operation, these children always have to have a catheter inserted at some point anyway to drain the urine and decompress the bladder after the operation when the new kidney makes urine. This was an important mistake.[R8] Again, arguments about time-pressure would be misplaced.

Dr Taylor's now agreed mistake that Adam's urine output was likely to be at least 200 ml/hour would hardly have mattered if he had been catheterised. It would have been abundantly clear that his urine bag was not draining anywhere near that quantity of urine, and his ongoing fluid assessment would have been reviewed and altered. I have already made the point earlier, that there is always a need to monitor the ongoing urine production carefully in children with end-stage kidneys, as their urine production may suddenly switch off in the face of stresses such as a general anaesthetic.[R15] The volume of urine measured at the end of Adam's entire 5 hours in theatre was not the 5 x 200 = 1,000 ml which Dr Taylor predicted and aimed to replace, but just 49 ml. This indicates that Adam did indeed cease producing urine during this time, probably between 7am and 8am since he did not even produce 1 hours' worth of his average urine output.

At several points in his reports, Dr Taylor refers to his repeated thorough re-assessments of Adam's fluid status throughout surgery which allowed him to make adjustments to his fluids and allow recalculations to be done. Given that he did not rely on the CVP measurement as he disbelieved the readings, and that he did not measure the 'out' component of the 'in-out' equation, it is difficult to know how he was making his reassessments.

Dr Taylor's fourth error was to consider it appropriate to use N/5 saline as fluid to be retained (category (iii) above). Thus, at the start of surgery, he assumed (incorrectly) that Adam would have been dehydrated to the extent of 400 ml or so because he imagined that he had made urine at that rate during the 2 hours immediately prior to entering theatre, when his oral fluids had been stopped, and deliberately planned to 'top him back up' urgently using N/5. Similarly, and perhaps even more bizarrely, he actively chose to use N/5 a little later to expand Adam's blood volume prior to the clamps being released.

Altogether, by these mechanisms, the result was that Adam was given 1.5 litres of N/5 saline during a 3 hour period that he didn't need, half of it during the first hour. Most of this was retained in his body, and inevitably reduced his body salt concentration considerably, and dramatically fast. This is what killed him.

The water in the body is distributed into 3 main compartments; outside the body's cells it is present (1) in the blood plasma and (2) in-between the individual cells and in lymph, and then (3) there is the water that is inside the cells which all the organs of our body are made up from. The distribution of water between these compartments is controlled by physical forces of concentrations of chemicals.

The chemical which regulates the distribution of water inside and outside the cells is the sodium.[R1] If its concentration falls in the plasma, water shifts into the inside of cells, and makes them swell. Later, when the body sorts out the plasma sodium concentration, the water comes back out again, and the cells shrink back. Within limits, this does not matter too much for most of the body's cells – if the liver gets a bit heavier and then lighter again it does not stop it from doing its job. However, the brain is housed with very little spare room inside the bony case of the skull, and if it swells suddenly the pressure can increase inside the skull and prevent the body from being able to pump blood in to nourish the brain. This brain swelling is called cerebral oedema.

Cerebral oedema is the inevitable consequence of a child having their plasma sodium concentration suddenly fall. The impact is the same if it falls from a stable high value towards normal (as is seen fairly commonly in certain babies whose breast feeding does not commence from birth [R15]), or if it falls from normal to sub-normal, the common factor is it falling. Sometimes the oedema is not severe enough to cause any symptoms before it resolves. Sometimes it can progress to cause symptoms but can be reversed by an infusion of mannitol among other treatments. Sometimes it is so fast and extreme that the child's brain-stem (which controls basic functions such as breathing) dies, and this is irreversible brain death. This is what happened to Adam.

Lots of medical conditions can lead to cerebral oedema and brain death. The inadvertent or accidental infusion of a large volume of free water (just water alone, without accompanying sodium at body levels) is a very rare cause. This means that when a case such as Adam's is reviewed, there are not a huge number of previous cases of this sort to compare it with. This leads to doctors of various specialities speculating whether the findings in the child being reviewed were caused simply by that explanation, or if other causes or other aggravating factors may have been present to explain their outcome. Adam's case review has led to a number of such questions being raised. I do not think any of them is likely to be relevant, but instead that the infusion of this amount of fluid into him was sufficient to explain all of the events that occurred. Indeed, I consider that the fluid insult his body received would be guaranteed to make any normal child extremely ill, and would have a very high chance of killing them.

A final error that Dr Taylor made which contributed to this unfortunate series of events is that he did not measure the plasma sodium concentration in the laboratory at all during the operation, despite the fact that a reading made by the nearby blood gas machine indicated an alarmingly low level. Dr Taylor has on one hand justified his decision to ignore this reading of 123 mmol/l on the grounds that it was not necessarily reliable, and at the same time has claimed to have responded to it by changing his treatment as a consequence. Neither statement appears to reflect what actually occurred.

I agree that less credence should be given to the precision of plasma sodium results produced on equipment sited in clinical areas than ones measured in laboratories.[R3,4&8] However, near-patient devices are not necessarily intended to provide such precision, but are an additional screening test to help the medical staff. Dr Taylor should have immediately taken a blood sample from Adam to send urgently for laboratory analysis, and at the same time should have stopped all hypotonic fluid infusions while awaiting the lab confirmation. None of the reasons he gives for failing to do so is justified. This was a wasted opportunity to attempt to correct Adam's condition.

How extreme was the fluid insult?

I have approached this question from 2 angles. I have looked at the rates at which it is thought that high plasma sodium concentrations can be safely reduced towards normal, and I have tabulated the few published values that are available about other children who have been accidentally treated in this way.

High sodium concentrations may develop in some babies by about 10 days of age due to feeding complications. When this is diagnosed and they are rehydrated, the plasma sodium concentration will fall. Clinical experience has shown that some of these babies die of cerebral oedema during the time that the sodium is falling, and retrospective analyses have indicated that the risk of this complication is much higher if the sodium falls quickly. This clinical data has suggested that a rate of fall of 3 mmol/l each hour or more is much more likely to lead to death than slower rates. Similar estimates have been made for other groups of children whose plasma sodium falls rapidly. Compared to this, Adam's sodium fell very rapidly during the early part of his anaesthesia.

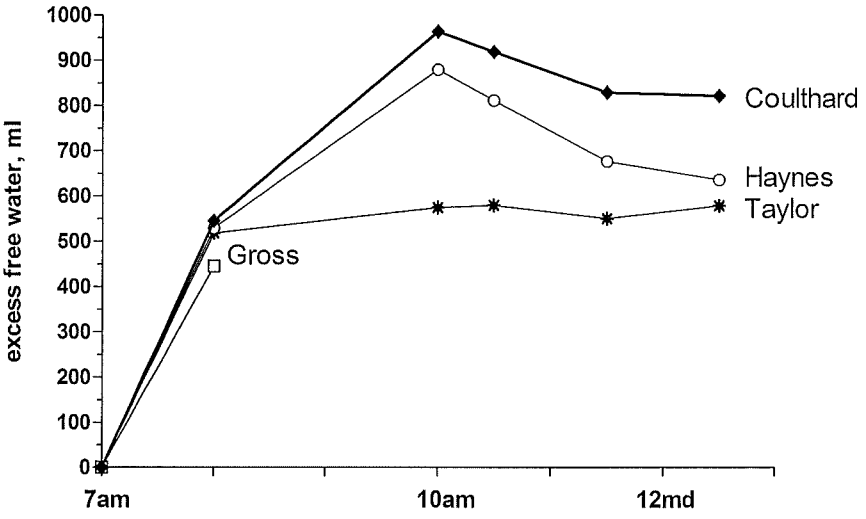
I have tabulated the 8 reported cases of children developing hyponatraemia following an infusion of hypotonic fluids that the Inquiry was able to identify from 3 publications, including their outcomes, and the rates of infusion of free water.[R13] Incidentally, all of them had the benefit of having normal kidneys which will have given them a degree of protection compared to Adam. Adam's rate of free water infusion in the hour from 7am to 8am was 31.6 ml per kg, which was twice the rate ever described in any other case. Three of the children died as a result of cerebral oedema consequent on their fluid infusions, and these were administered it at rates of just 3.2,6.5 and 6.7 ml/kg hourly, a fraction of the rate that Adam was given.

There are no compensatory mechanisms in the body that can come into play anywhere quickly enough to prevent brain swelling in the face of such an inappropriate and massive perturbation.

Is the calculation of his infusion rate in doubt?

The Inquiry Team asked me and 2 other experts, Professor Gross and Dr Haynes, to give our own closest possible estimates of Adam's sodium and water losses and gains during his admission, and to work out the resulting balances. I have tabulated and graphed them in 1 of my reports [R11], and have added the calculations that Dr Taylor now considers to be the case, after having recognised some of his earlier mistakes. Below is a graph of Adam's estimated accumulation of excess free water as a result of all the fluids given and lost from the start of the transplant operation at 7 am until he arrived in PICU after mid-day.[R15]

The lines are all slightly different because of the slightly different assumptions we have made in our calculations, but the striking thing is that all 4 of us conclude that he took on board about 0.5 litre of free water by 8am. Prof Gross' figures after 8am were not available to me at the time I drew this graph, but he has assured me since that his 10am values are virtually identical to Dr Haynes' figure.



This degree of agreement or certainty about the water retained by Adam indicates that he definitely did receive a huge infusion very rapidly.

Dr Taylor's graph differs from the 3 experts' lines after 8 am because he calculates his figures as if he had administered the second half of the 1.5 litre N/5 saline solution over the whole of the rest of the operation, even though his earlier testimonies and the case records clearly indicate that this was not the case, and that it had been completed by 10am.

I believe that Adam's brain-stem died somewhere between 7am and 10am, and that it was probably before 8am in response to the most dramatically fast component in his fall in plasma sodium. Once that happened, the situation for him was irretrievable. How his kidney transplant did or did not perfuse or function is not relevant to this. The administration of mannitol after he could not be woken was entirely appropriate management,[R8] but in reality was all too late.

Did he have another neurological condition, or PRES?

Professor Kirkham, a children's neurology specialist, noted that the post-mortem appearances of Adam's brain were strikingly more affected by cerebral oedema posteriorly than in the rest of his brain, especially his cerebellum. As a consequence of this, and of his early clinical and developmental history, she gave extensive consideration to the possibility that Adam had a prior neurological condition, and then developed either a condition known as PRES, or developed cerebral thrombosis (blood clotting) as a primary cause of brain death, with the hyponatraemia only playing a minor or secondary role.

I completely reject all of these speculations.[R12]

The evidence of Adam's prior neurological abnormalities were his feeding difficulties and developmental delay which I recognise as being an absolutely predictable accompaniment of having chronic renal failure from early in life. I would go as far as to describe these features in him as absolutely typical of children of his age with his kidney condition, and much milder than we have often seen.

I do not accept that PRES is a true diagnosis as discussed by some paediatric neurologists in the literature, but instead is the neuro-radiological manifestation of children affected by an acute rise in blood pressure that has caused a hypertensive encephalopathy. It is said to be characterised by symptoms that could not be checked in Adam during anaesthesia (such as headache, blindness), and a sharp rise in blood pressure (which he did not have) and posterior brain involvement. In a nutshell, the only point in favour of this condition is that Adam's brain showed more changes posteriorly than elsewhere. Finally, I have since noted that the brain scan and post-mortem changes are described for one of the 3 children I have mentioned above who died from an accidental water overload. She also had generalised oedema with striking engorgement of the cerebellum.[R13] This suggests to me that a fatal acute water overload may lead to this pattern. I have suggested that the authors of this case should be approached to compare cases in more detail, if possible [R15], and also that an animal model might usefully be developed to study the impact of hypotonic infusions on the pattern of cerebral oedema it causes.

There was absolutely no gross post-mortem nor histological evidence to support the presence of cerebral thrombosis. Nor did I understand the rationale that had led to it being suggested as a diagnostic possibility, but that is not my specialist area.

Final comment

Adam's death was an avoidable tragedy.

I am pleased that Dr Taylor has recently been able to recognise that his decision to infuse a massive volume of hypotonic into Adam was a mistake, as it may now finally allow important lessons to be learned and shared.

Any tragedy should be used to learn from, so we may be able to build ways of doing better in the future, and avoid repeating mistakes in other children. It is a shame that it has taken so many years for the lessons to be learnt in this case.

Expert Witness Declaration

I Malcolm Coulthard DECLARE THAT:

1) I understand that my duty in providing written reports and giving evidence is to help the Court, and that this duty overrides any obligation to the party by whom I am engaged or the person who has paid or is liable to pay me. I confirm that I have complied and will continue to comply with my duty.
2) I confirm that I have not entered into any arrangement where the amount or payment of my fees is in any way dependent on the outcome of the case.
3) I know of no conflict of interest of any kind, other than any which I have disclosed in my report.
4) I do not consider that any interest which I have disclosed affects my suitability as an expert witness on any issues on which I have given evidence.
5) I will advise the party by whom I am instructed if, between the date of my report and the trial, there is any change in circumstances which affect my answers to points 3 and 4 above.
6) I have shown the sources of all information I have used.
7) I have exercised reasonable care and skill in order to be accurate and complete in preparing this report.
8) I have endeavoured to include in my report those matt ers, of which I have knowledge or of which I have been made aware, that might adversely affect the validity of my opinion. I have clearly stated any qualifications to my opinion.
9) I have not, without forming an independent view, included or excluded anything which has been suggested to me by others, including my instructing lawyers.
10) I will notify those instructing me immediately and confirm in writing if, for any reason, my existing report requires any correction or qualification.
11) I understand that;

- 11.1) my report will form the evidence to be given under oath or affirmation;
- 11.2) questions may be put to me in writing for the purposes of clarifying my report and that my answers shall be treated as part of my report and covered by my statement of truth;
- 11.3) the court may at any stage direct a discussion to take place between experts for the purpose of identifying and discussing the expert issues in the proceedings, where possible reaching an agreed opinion on those issues and identifying what action, if any, may be taken to resolve any of the outstanding issues between the parties;
- 11.4) the court may direct that following a discussion between the experts that a statement should be prepared showing those issues which are agreed, and those issues which are not agreed, together with a summary of the reasons for disagreeing;
- 11.5) I may be required to attend court to be cross-examined on my report by a cross-examiner assisted by an expert;
- 11.6) I am likely to be the subject of public adverse criticism by the judge if the Court concludes that I have not taken reasonable care in trying to meet the standards set out above.

12) I have read Part 35 of the Civil Procedure Rules and the accompanying practice direction including the "Protocol for Instruction of Experts to give Evidence in Civil Claims" and I have complied with their requirements.
13) I am aware of the practice direction on pre-action conduct. I have acted in accordance with the Code of Practice for Experts.

Statement of Truth

I confirm that I have made clear which facts and matters referred to in this report 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 they refer.

Signed _____ Dr Malcolm Coulthard

Dated 17/8/12 17/03/2012

Dr Malcolm Coulthard, BSc, MB BS, DCH, FRCP, FRCPCH, PhD