Witness Statement Ref. No. 002/2

NAME OF CHILD: Adam Strain

Name: Maurice Savage

Title: Professor

Present position and institution: Consultant Paediatric Nephrologist, Royal Belfast Hospital for Sick Children/Royal Hospitals Trust, and Professor of Paediatrics, Queen's University Belfast

Previous position(s) and institution(s): None
[Since your Witness Statement of 22nd July 2005]

Membership of Advisory Panels and Committees: None
[Identify by date and title all of those since your Witness Statement of 22nd July 2005]

Other Statements, Depositions and Reports: None
[Identify by date and title all those since your Witness Statement of 22nd July 2005]

OFFICIAL USE:
List of previous statements, depositions and reports attached :

Ref:	Date:	
011-001	28.11.1995	Draft Statement
011-015	21.06.1996	Deposition of Witness
002/1	22.07.2005	Witness Statement to the Inquiry on Hyponatraemia
093-006	08.05.2006	Statement to PSNI

IMPORTANT INSTRUCTIONS FOR ANSWERING:
Please identify clearly any document to which you refer or rely upon for your answer. If the document has an Inquiry reference number, e.g. Ref: 049-001-001 which is 'Chart No.1 Old Notes', then please provide that number. If the document does not have such a number then please provide a copy of the document.

I QUERIES ARISING OUT OF YOUR INITIAL WITNESS STATEMENT

With reference to your Witness Statement dated 22nd July 2005, please provide clarification and/or further information in respect of the following:

(1) Response to position and institution: *"Consultant Paediatric Nephrologist, Royal Belfast Hospital for Sick Children and Senior Lecturer in Child Health, Queen's University, Belfast"*

(a) Describe your work commitments to the Royal Belfast Hospital for Sick Children (RBHSC) from the date of your appointment as a Consultant and particularly over the period 26th November to 28th November 1995

The following answers are based on the notes and records of Adam Strain and my recollection in so far as possible given the passage of time, almost 20 years from when I first treated Adam.

Over the period 26-28 November 1995 I was employed jointly at the Royal Belfast Hospital for Sick Children by the NHS and by Queen's University Belfast as a joint clinical appointee. This meant that I had an equal commitment to the Medical School and to the Children's Hospital. Prior to October 1995, I was the only Paediatric Nephrologist in Northern Ireland and so my primary clinical responsibility was to children with kidney disease. On the weekend, including Sunday 26 November, I was the Consultant Paediatric Nephrologist on call. On Monday 27 November I passed care for my clinical patients to my consultant colleague in order to undertake work in the University and because I had been on call over the weekend. On hearing of the unfortunate outcome of Adam Strain's transplant surgery, I returned immediately to the hospital. I remained involved in his care until the time of his death.

(2) State what you considered to be your role in relation to and responsibilities towards Adam from learning on 26th November 1995 of a potential donor kidney for him until 28th November 1995 when ventilatory support was withdrawn, and in particular:

- **From Adam's admission to RBHSC until his arrival in theatre**
- **While Adam was in theatre until his admission to PICU**
- **From admission to PICU until his death**

When I was informed that a potential kidney was available for Adam Strain on 26 November 1995, I identified that the facility to perform the transplant was available in terms of a surgical and anaesthetic team, theatre time and a potential bed in the paediatric intensive care unit post surgery. Then I informed his mother of the offer of the kidney and verified that she was willing to allow the transplant operation. I arranged for Adam to be brought in to hospital, to provide a blood sample for the tissue typing laboratory in order to carry out a tissue cross-match and establish if the kidney was suitable. I also had to assess that Adam was clinically well enough to receive a kidney

transplant and to carry out the requisite checks as laid down in the kidney transplant protocol, to arrange for the appropriate investigations to be made and to communicate Adam's medical history and current clinical condition to the surgical and anaesthetic teams involved. Once the transplant cross-match confirmation was received I discussed the management of Adam in relation to his oral intake and fluid prescription with the consultant anaesthetist. I instructed my junior medical and nursing colleagues on how the patient should be managed until such time as he left for theatre. I obtained written consent for the surgery to proceed from Adam's mother.

I communicated the details of Adam's clinical history to the transplant surgeon and anaesthetist and was involved in discussions as to the optimal time to commence surgery. Once Adam was in theatre, I checked with the consultant anaesthetist that there were no immediate problems and no issues which he needed to further discuss with me in regards to Adam's clinical care. Once the care of our patient was passed to the theatre team, I made it clear that I was available should they need to consult with me or my consultant nephrology colleague who was available whilst I left to undertake University work.

It was only when Adam was admitted to PICU that I was informed that there was a major problem post-operatively. I immediately returned to the PICU to work with the intensive care team and with my other colleagues to ensure that all possible action and treatment was undertaken to achieve his survival.

Sadly I had to communicate the grave situation to his mother who I continued to support up to and after Adam's death.

(3) Answer to Question 1 at p.2

"I was involved in the general medical care of Adam Strain from early infancy"

(a) State the date on which you first become involved in the *"medical care of Adam"*

I first saw Adam Strain at my out-patient clinic at RBHSC on 3 September 1991, when he was aged only one month, at the request of Dr Angela Bell, Consultant Paediatrician at the Ulster Hospital, Dundonald.

(b) Describe your role in the care and treatment of Adam from when you first became involved in the medical care of Adam up to his admission for renal transplant on 26th November 1995, with particular reference to the following periods:

- 26th November 1991 to 17th April 1991
- 8th February 1993
- 23rd August 1994 to 26th August 1994
- 18th October 1995

Adam had been born with bilateral dysplastic kidneys and my advice regarding management was sought from a medical as opposed to a surgical viewpoint. It was surgical relief of obstructed ureters that was initially required at the Ulster Hospital. Unfortunately, following this surgery to relieve this obstruction, Adam developed acute renal failure and was transferred back to my care for a period of peritoneal dialysis at the RBHSC. From that time, I became the nephrologist responsible for Adam's medical care throughout his childhood.

My role in the care of Adam Strain as his Consultant Nephrologist was to co-ordinate his medical

care with the aim of:

a) preserving his renal function as long as possible
b) to provide treatment to mitigate the side effects of renal impairment in a very young child c) to design with the co-operation of dieticians, and on occasions the hospital expert, on total parenteral nutrition, a regimen that would ensure adequate calorie intake, optimal electrolyte balance, nutrition and growth
d) to work with consultant colleagues, particularly Mr Victor Boston and Mr Stephen Brown, in relation to Adam's urological problems, associated with his abnormal kidneys and urinary tract
e) to work with surgical colleagues to ensure intravenous access and access for enteral nutrition via a gastrostomy
f) to treat associated medical problems in relation to his illnesses, including urinary tract infections, vomiting, gastro-oesophageal reflux, blood pressure, renal anaemia and bone disease
g) to help cope with his feeding difficulties, tendency to vomit and the development of a food aversion which required enteral feeding to attain optimal nutrition.

A major part of his management also included repeated surgery on his urinary tract to try to establish good drainage of his kidneys and preserve their function as best as possible. My role was to address his medical problems, including, urinary tract infections, nutrition, fluid and electrolyte balance. In early infancy, vomiting was a major problem and ultimately surgery (fundal plication) was performed to address the recurrent vomiting which made his general management more complex.

During this time I also coordinated dietetic and psychology support for Adam when he became food adverse and achieving adequate fluid and nutritional intake by mouth proved difficult. As a result of this he was initially tube fed and then had a gastrostomy placed so he could be fed through the gastrostomy tube in order to ensure as far as possible that he would grow and thrive.

By March 1994 it became apparent that the only realistic chance for long-term survival for Adam was through renal replacement therapy and this was discussed with his mother. It was agreed that he would start on peritoneal dialysis and that we would seek a kidney for transplantation. My role then extended to managing his peritoneal dialysis and ensuring that his mother was prepared, trained and capable of performing home peritoneal dialysis. This preparation and training involved a renal nurse specialist who undertook the training and assessed the home situation as being suitable for dialysis and signed off Adam's mother's competency in the procedure.

Once renal replacement therapy was required, I established Adam's blood group and tissue type and arranged for him to be put on call for a cadaveric renal transplant. I was responsible for carrying out the appropriate preparatory investigations and explained to his mother what this major surgery involved and confirmed that she was prepared to consent to the procedure.

Between November 1991 and April 1992 I estimate that Adam had up to ten surgical or anaesthetic procedures. During his period of acute renal failure following surgery in November 1991 he became oliguric and as a result became "fluid overloaded". However, this situation was resolved with a period of peritoneal dialysis. Drainage of his kidneys was subsequently achieved via nephrostomies and ultimately, ureterostomies. During this time Adam became extremely ill and septic. On at least one occasion he was hypernatraemic with sodiums rising as high as 156mmol/L, while during his period of acute renal failure he had sodiums as low as 119mmol/L. I was involved in managing fluid and electrolyte problems relating to impaired renal function whereby if he became relatively dehydrated he would have a high serum sodium, but if his fluid balance was too positive he could become hyponatraemic. Vomiting of sodium supplements could also lead to a fall

in serum sodium.

On 8 February 1993, Adam was admitted for a retrograde pyelogram by the paediatric surgical team. This surgical procedure was carried out by Mr Stephen Brown and was not under my supervision. The procedure was unsuccessful, but there were no medical difficulties on that occasion.

Between 23 and 26 August 1994 Adam was again admitted for a surgical procedure; the insertion of a peritoneal dialysis cannula. This was performed by Mr Victor Boston. Immediately post-operatively, there was an episode of hypotension which was corrected with a bolus infusion of HPPF (Human Plasma Protein Fraction). Several cycles of peritoneal dialysis showed that there was blood loss in the peritoneal cavity, possibly the reason for his hypotensive episode due to an associated hypovolaemia. However, this blood cleared by the following day and 48 hours after insertion of the cannula, it was felt that he was stable, comfortable and allowed home (Ref: 057-102-180 to 182). He was readmitted a week later so that his mother could undergo training in the dialysis technique (Ref: 057-102-183 to 185). I note that during this admission when his tube feeds were discontinued because of the abdominal operation on 24 and 25 August 1994 that he received intravenous fluids at N/5 (0.18%) saline in 4% dextrose. His sodium during that period was 131 but on returning to his tube feeds his sodium was 140 on readmission on 3 September. He was at this time polyuric.

Adam's admission on 18 October 1995 was a day procedure for the change of a gastrostomy button. He was fasted from 8.00am before going to theatre and recommenced his tube feeds in mid-afternoon. He also had a left orchidopexy on that occasion. His electrolytes were checked on admission and were satisfactory with a sodium of 142. There were no fluid or other problems recorded during this short admission (Ref: 058-035-129 to 130).

(c) Describe any lessons that were learned about Adam's fluid management over those periods

Adam's fluid management showed that achieving good fluid and electrolyte balance was repeatedly complicated by intercurrent infections, particularly of the urinary tract, the development of polyuria following drainage of the obstructed kidneys, a tendency to vomit, the development of a food aversion and on occasions, diarrhoea.

Adam's ability to alter his urine output and urinary electrolyte losses in response to changes in his clinical condition were limited. The kidneys function in maintaining body homeostasis was severely impaired.

Adam's inability to take food by mouth and the absence of a normal thirst mechanism made managing his fluid balance and nutrition difficult.

His inability to self regulate his body sodium balance and hydration necessitated careful dietary and fluid manipulation.

Adam's serum sodium could vary from 119 (055-054-159) to 152 (050-024-220). He was however generally asymptomatic in relation to these sodium levels, most likely because they developed gradually and were corrected gradually, most often by variations in his enteral feeds. This choice of enteral feed was made in consultation with the renal dietician. Paediatric Nutrison, which we used for his enteral feeds, balanced his sodium loss reasonably consistently, and it also provided high calorie content.

I estimated actual fluid volume requirements based on urine output estimates with additional

allowance for insensible loss, dialysis ultrafiltration and Adam's tendency to vomit.

This approach ensured that he was a well nourished boy with good growth despite his renal impairment.

(d) Over the period when you first became involved in Adam's medical care up to 26th November 1995, describe the plans that were put in place for measuring Adam's:

- fluid output
- urine sodium levels
- serum sodium levels
- urinary creatinine concentration
- plasma creatinine concentration
- urine output
- fractional excretion rates
- glomerular filtration rate
- weight
- volume, content, frequency and process of Adam's peritoneal dialysis
- volume and content of Adam's feeds through his gastrostomy tube

and your role in developing those plans

The measurement of urine output in small incontinent children is best achieved when there is a urinary catheter in situ. Adam underwent many invasive procedures which were upsetting and on occasion frightening. To reduce his distress frequent catheterisation was avoided. The alternative is to measure urine output based on weighed nappies, ie. the difference between dry and wet weight in each nappy would be the urine output. After having established a best estimate of Adam's urine output, subsequently a fluid intake volume was based on this and allowances for other fluid losses, ie. vomiting, insensible loss and dialysis ultrafiltration.

Preliminary urinary sodium and electrolyte measurements were performed at regular intervals to establish that there was no major variation in urinary sodium loss. Glomerular filtration rate was calculated using the Schwartz formula (height in cm x 40 divided by serum creatinine in mmol/L) from serum creatinine when required. Serum urea, creatinine and electrolyte measures were carried out on a regular basis during in-patient admissions and particularly when IV fluids were being employed and at each out-patient follow-up visit.

The plan was therefore to have regular ongoing measurements of renal function and weight. Once it was decided that Adam should start on peritoneal dialysis, this was introduced gradually on an in-patient basis to determine the optimal peritoneal dialysis regimen, ie. the volume, content and frequency, to design a prescription that would produce a stable situation when dialysis was performed at home. Volume content and frequency of the dialysis fluid and cycles were recorded in a dialysis diary, one page for each night's dialysis, including volume of fluid removed or retained and his weight before and after dialysis. Records were kept by Adam's mother and checked by the dialysis nurse specialist and/or myself both in hospital and during home visits. The volume and content of Adam's feed through his gastrostomy tube was based on estimates of his calorie and electrolyte needs and his fluid requirements. The development of these plans was supervised by myself, in consultation with a dietician and other members of the renal team, including nursing staff.

(e) Over the period when you first became involved in Adam's medical care up to 26th November 1995, describe the plans that were put in place for recording Adam's:

- fluid output
- urine sodium levels
- serum sodium levels
- urinary creatinine concentration
- plasma creatinine concentration
- urine output
- fractional excretion rates
- glomerular filtration rate
- weight
- volume, content, frequency and process of Adam's peritoneal dialysis
- volume and content of Adam's feeds through his gastrostomy tube

and your role in developing those plans

As stated in the answer to d) above, these measurements were recorded in Adam's notes in either the in-patient clinical notes, or in the parent-held dialysis record book.

(f) Over the period when you first became involved in Adam's medical care up to 26th November 1995, describe the plans that were put in place for interpreting, assessing and managing Adam's:

- fluid output
- urine sodium levels
- serum sodium levels
- urinary creatinine concentration
- plasma creatinine concentration
- urine output
- insensible losses
- excretion rates
- glomerular filtration rate
- weight
- volume, content, frequency and process of Adam's peritoneal dialysis
- volume and content of Adam's feeds through his gastrostomy tube

and your role in developing those plans

As the only Paediatric Nephrologist (in Northern Ireland) I was involved in Adam's care. I was the key person in developing plans for measuring, recording and interpreting all the measurements listed. In relation to fractional excretion rates, these were not included in any management plan and I believe such measurements were not common practice at that time.

(g) Describe what you did in the light of your assessment of:

- fluid output
- urine sodium levels
- serum sodium levels
- urinary creatinine concentration
- plasma creatinine concentration
- urine output
- insensible losses
- fractional excretion rates
- glomerular filtration rate

- weight
- volume, content, frequency and process of Adam's peritoneal dialysis
- volume and content of Adam's feeds through his gastrostomy tube

I evaluated whether the fluid, nutritional and medical measurements taken needed refinement and determined if we were achieving optimal growth and development for Adam. Sodium supplements (sodium bicarbonate and saline solution) were adjusted to manipulate serum sodium levels. Volume feed intake was increased proportionately to fluid loss and body size as Adam got older. The dialysis regimen was adjusted to achieve satisfactory serum electrolyte and urea levels and fluid balance.

(h)identify the records maintained in relation to Adam's:

- fluid output
- urine sodium levels
- serum sodium levels
- urinary creatinine concentration
- plasma creatinine concentration
- urine output
- fractional excretion rates
- insensible losses
- glomerular filtration rate
- weight
- volume, content, frequency and process of Adam's peritoneal dialysis
- volume and content of Adam's feeds through his gastrostomy tube

Records of electrolyte and urea measures are summarised on investigation summary sheets, for example: 050-016-048, 050-018-051 to 055 and 052-022-043. All laboratory reports were filed in the clinical notes, for example: 055-054-132 to 161. Fluid balance sheets are available under that title in the various files of Adam's case notes. Details of Adam's peritoneal dialysis records are not available as we have not got the parent-held records on file. Weight is recorded at each out-patient and in-patient visit in the clinical notes. Volume and content of Adam's gastrostomy feeds was held by the renal dietician and agreed with me (057-068-128).

(4) Answer to Question 1 at p.2

"I coordinated Adam's care, prescribed and monitored his dialysis treatment with support from a dietician, psychologist, social worker, renal nursing team and of course his mother"

(a) Explain the reasons for what you have described in your Inquest Deposition as Adam's *"potential for a low sodium"* (Ref: 011-015-110)

The reasons for the statement that Adam had a 'potential for a low sodium' were based on the fact that on several occasions he had developed a relatively low serum sodium and was known to lose sodium in his urine based on urinary electrolyte analysis and compensated for by sodium supplements in his nutritional prescription.

(b)State whether the *"potential for low sodium"* that you identified was discussed with Adam's mother and if so describe what was discussed with her including what if any role she was to play in maintaining his sodium concentration at an acceptable level

Adam's mother was meticulous in his care, including undertaking his gastrostomy tube feeds and giving him his medication. In doing so, she would have been aware that he had sodium bicarbonate supplements and on occasions had saline added to his Nutrison tube feeds.

(c) Over the period when you first became involved in Adam's medical care up to 26th November 1995, identify the diet plans that were developed for Adam and explain:

- the reference in the letter dated 13th June 1995 from Janet Mercer Paediatric Dietician (Ref: 057-068-128) to Adam's daily gastrostomy-fed regime 1200 ml of Nutrison and certain supplements made up with water to 1700 mls
- the notes for the dialysis clinic on 9th November 1995 that state Adam's daily fluids as *"3 x 200 bolus 1500 mls overnight"* (Ref: 059-006-021)
- the regime in place at the time of Adam's transplant surgery

Adam's dietary needs and the plan to address these was developed in consultation with the renal dietician. We would have estimated as accurately as possible, his fluid requirement, his electrolyte requirement and his calorie requirement and used this information in designing the volume and nature of his feeds.

The letter dated 13 June 1995 (Ref: 057-068-128) is a record of the type and content of the nutritional tube feeds which had been decided upon at that time. The dietician regularly reviewed Adam's nutritional requirements at out-patient visits and when he was an in-patient. Reference to biochemistry results (057-103-220 and 057-103-218) indicate that his serum sodium was satisfactory at that time on that regime.

A summary note on the day of the dialysis clinic on 9 November 1995 indicate that by that time Adam's total volume intake had been increased to 2100mls given as three day-time boluses of 200mls down his gastrostomy tube and as a continuous drip feed infusion of 1500mls overnight (Ref: 058-035-143). This was the regime in place at the time of Adam's transplant surgery. In the last entry before his transplant admission it can be seen that his gastrostomy tube feeds are recorded as 3 x 200ml boluses and 1500mls overnight (058-035-143). These are the same volumes as have been recorded on the balance charts in 5 July 1995 (057-048-088) when he was an in-patient and it is clear at these times he was receiving a total of 2100mls daily.

(d)State Adam's usual daily sodium intake before 27th November 1995

Adam's usual daily sodium intake before 27 November 1995 was 67mmol. 28mmol came from 1200mls of Paediatric Nutrison, 15mmol came from 100mls of normal saline and added to the Nutrison and 24mmol from his sodium bicarbonate supplement.

(e) State Adam's usual daily sodium loss before 27th November 1995

Adam's usual daily sodium loss before 27 November 1995 would be similar to his sodium intake, estimated at between 40 and 50mmol per litre of urine.

(f) Explain the cause(s) of the serum sodium level of 127mmol/L that was recorded for Adam on 15th February 1994 (Ref: 056-038-097) and the steps taken to address the situation

Due to the passage of time I cannot explain the serum sodium level of 127mmol on 15 February 1994. There is no record in his clinical notes on that date that he was unwell on that occasion or of any action taken. Blood tests taken at monthly intervals afterwards show a rise in his sodium to

132mmol on 22 February 1994 (056-038-095) and subsequently to 135mmol on 24 March 1994 (056-038-094). No note is made of specific treatment advised.

(g) Explain the cause(s) of the serum sodium level of 124mmol/L that was recorded for Adam on 8th June 1995 (Ref: 058-041-197) and the steps taken to address the situation

There is no recorded cause explaining the sodium level of 124mmol on 8 June 1995 (Ref: 058-041-197) nor of steps taken to address the situation. His next serum sodium measurement however on 14 July was normal at 139mmol/L (058-041-195).

(h) Explain in relation to your reference to having *"prescribed and monitored his [Adam's] dialysis treatment"*:

- Adam's usual peritoneal dialysis ultrafiltration rate
- what was discussed with Adam's mother about her maintaining a record of the volume of fluid removed each night through Adam's peritoneal dialysis and his weight before and after the dialysis
- the records that were maintained and by whom in relation to the total volume of fluid removed through Adam's peritoneal dialysis and his weight and electrolytes on commencing and completing dialysis
- Adam's fractional excretion rates, including FEwater and FEsodium and where they are recorded

Adam's usual peritoneal dialysis ultrafiltration rate was approximately 400ml as indicated in a letter dated 8 June 1995 (057-056-114, 115).

Adam's mother was meticulous in maintaining such records in the parent-held dialysis book. The keeping of a record of both the fluid volume removed each night through Adam's peritoneal dialysis and his weight, before and after the dialysis, was part of the standard training for all parents. Its importance was emphasised as on home dialysis, electrolytes are not measured when commencing and completing dialysis. Home peritoneal dialysis training was carried out by the renal dialysis nurse and only when dialysis had been performed satisfactorily without help from nursing staff in the ward unit was the competency of the parent signed off. Initial home dialysis was performed by the parent in their home with a renal dialysis nurse present usually in another room who would be available should any problem arise. There was also ongoing telephone liaison and home visits by the dialysis nurse and checks on the dialysis record and ultrafiltration both by the nurse and at the dialysis clinics in the hospital.

Fractional excretion rates were not measured or recorded.

(5) Answer to Question 2 at p.2

"On the 26th November 1995 we had an offer of a kidney from the UK Transplant Service"

(a) Following Adam's registration for a kidney transplant on 24th November 1994, describe the plans made for renal transplant in the event that a suitable donor kidney became available for Adam, together with:

- the identity of anyone else involved in the formulation of the plans
- your role in their execution

- the information given to Adam's mother about such plans

Following the registration for a kidney transplant on 24 November 1994, plans were made for a transplant in the event that a suitable donor became available for Adam. This included Adam's name, date of birth and tissue type being entered on the list of local patients on call for transplant, along with his tissue type measured in the Tissue Typing Laboratory BCH (Belfast City Hospital).

The names and age of children on call were thus made known to the transplant co-ordinator, and the list circulated to all the nephrologists in Belfast and the transplant surgeons. I had a key role in formulating these plans in conjunction with the multi-disciplinary team of renal nurses, dieticians, psychologists and social workers. I as the Consultant Nephrologist along with the renal dialysis nurse, had regular discussions with Adam's parents (and possibly his grandparents) explaining the system of being on call, the nature of the surgery, the need for a tissue cross-match once a kidney was identified, the fact that the child would be called to the hospital at least six hours before the procedure for a clinical work up, and that depending on the cross-match and the agreement of the surgical team, it would then be decided if the transplant should proceed. All parents of sick children going on call for a renal transplant are given an explanatory booklet. A copy of which has previously been provided to the Inquiry.

(b)State when and who first received the offer of the kidney for Adam

See (5 c) below

(c) State when on 26th November 1995 you first knew about the offer of the kidney for Adam

I first received an offer of a kidney for Adam on the evening of 26 November 1995 by phone from the UK Transplant Service. I do not recollect the exact time, but contacted Adam's mother and he was brought to the ward around 9.30pm. I presume this was the time I was told when the kidney would have been arriving in Belfast.

(d)Following receipt of the offer of the kidney for Adam, describe the process by which it was brought to the RBHSC, including when it was collected and by whom

Following receipt of an offer of a kidney for Adam, I confirmed with UK Transplant that I felt the match was acceptable for the patient and accepted it from the Transplant Service. The kidney would then have been delivered to the renal unit in the Tower Block of the Belfast City Hospital so that samples from the tissue could be cross-matched against Adam's white cells on the BCH site where the tissue typing laboratory is situated. Subsequently, when the decision to proceed with the transplant was confirmed, the kidney was collected by the transplant surgeon and brought to the Children's Hospital.

(e) Describe when you first saw the 'Kidney Donor Information Form' (Ref: 058-009-025) and in what circumstances

I cannot say precisely when I first saw the kidney donor information form. The information on this form is usually checked by the transplant surgeon and the transplant co-ordinator. It is for them to complete. I note this form is signed by the transplant co-ordinator Ms Eleanor Donaghy.

(f) Describe when you first saw the 'Transplant form' (Ref: 057-007-008) and in what circumstances

I have no recollection of when I saw the Transplant Form (Ref: 057-007-008), but most likely following completion of the transplant in the intensive care unit.

(6) Answer to Question 2 at p.3:

"Adam's mother had previously been given information about transplantation. In discussion she was apprehensive in relation to such major surgery"

(a) Describe the information that had *"previously been given ... about transplantation"* to Adam's mother and when that happened

Information regarding renal transplantation was given to Adam's mother prior to Adam being put on call on the national database and before his tissue type was analysed. Patients would not be registered on call for a kidney transplant without the express consent of parents. The nature of the transplant process, the need for the tissue typing, for a cross-match if a kidney was offered and the fact that this was major surgery, including the risks of such surgery and of anaesthetic, would have been explained. Ms Strain was always understandably anxious when Adam required further surgery, bearing in mind, the number of times he had been to theatre. I believe she was apprehensive in relation to such major surgery because of previous experience and because she recognised the potential risk to his life. I am satisfied that she weighed up these risks against the potential of a successful transplant giving Adam a normal life. Whilst I cannot now specify the exact dates when discussions took place, Adam's mother had a close relationship with the renal team and discussions about transplantation took place on many occasions. She would have been provided with a Transplant information book, as was usual practice. A copy has previously been provided to the Inquiry.

(b) Following the offer of the kidney for Adam, state when you first alerted Adam's mother to the offer of a kidney that had been received on 26th November 1995 and:

- what information you gave her about the surgery, its risks and the source of those risks
- when you provided her with that information
- her response

I alerted Adam's mother to the offer of a kidney when I had received this information from the UK Transplant Service. I asked her to bring Adam to the ward as she was willing to proceed with the transplant so that we could initiate the appropriate investigations, including a tissue cross-match. I have not recorded the exact information which I gave to Ms Strain on 26 November 1995. To my recollection I would have informed her that it was an adult kidney which the transplant surgeon planned to use. It is likely I informed her that a paediatric surgeon would also be involved in the surgery who had knowledge of Adam's previous surgery who would therefore be available instantly during the transplantation procedure. I would have explained that we needed to cross-match several units of blood because of the risk of blood loss during surgery so that this could be replaced if necessary. I would have explained the need for the change in his normal overnight feeds so that his stomach was empty at the time he received his anaesthetic and also the plan to give him some intravenous fluids once tube feeds ceased until such time as he got to theatre. I do not remember in what detail I discussed the risk to Adam's life. I believe we both understood there was such a risk and hoped and expected he would come through the procedure successfully. Ms Strain subsequently signed the consent form for us to proceed when we knew the tissue cross-match was satisfactory but understandably was worried about her son undergoing major surgery.

(c) State what information regarding consent was given to Adam's mother and when the form

'Consent by Parent or Guardian Form II Operations on Children' (Ref: 058-039-185) was signed by:

- Adam's mother
- you

The consent form was signed on 27 November 1995. The exact time has not been noted. See (6 b) above.

(7) Answer to Question 2 at p.2: See comment above

"Standard pre-transplant checks were performed including assessment of hydration, temperature, blood pressure, chest examination, blood crossmatch, biochemistry screen, a full blood picture, coagulation screen and a virological check of his blood"

(a) Describe and explain the times at which you were in the RBHSC on 26th and 27th November 1995

I do not remember exactly the times at which I was present in RBHSC on 26 and 27 November 1995. However, I went to the hospital to meet with Adam and his mother around 9.00pm and I believe I was in hospital until the result of the tissue cross-match was available in the early hours of the morning. Again, I do not know the precise time, but expect that it was around 1.00-2.00am. After discussions with the surgical and anaesthetic team, the decision was made to commence Adam's transplant first thing in the morning at 6.00-7.00am. I returned home for a few hours sleep before returning around the time that Adam went to theatre, probably around 6.30am. I believe I was then in the Children's Hospital until my colleague Dr O'Connor relieved me around 9.00am. I remained at the Royal Hospital site at my University office until I was contacted by Dr O'Connor on Adam's return from theatre when it was realised he was extremely ill. I immediately returned to the Children's Intensive Care Unit, and I remained there for the rest of the day.

(b) Explain the reference to *"standard"* in relation to those *"pre-transplant checks"*

The standard pre-transplant checks are those outlined in the transplant protocol which has previously been provided to the Inquiry.

(c) State who requested those *"pre-transplant checks"* and who carried them out

These pre-transplant checks were requested by myself and carried out by Dr Cartmill, and Dr O'Neill, the SHO, who were on duty that evening and overnight.

(d) State the arrangements that existed at the RBHSC at that time for carrying out and receiving the results of laboratory tests 'after hours'

In relation to laboratory tests, blood samples would have been obtained by a doctor and taken to the appropriate laboratory, along with the request forms, by a porter. Results of the tests would be phoned to the ward and recorded by the doctor who received them in the patient's notes.

(e) Explain the arrangements you made to have those *"standard pre-transplant checks"* carried out, including the identity of the person responsible for carrying them out

I provided a copy of the renal transplantation in small children protocol for reference by the junior

doctors involved, Dr Cartmill and Dr O'Neill, and requested that they carry out the appropriate investigations. Subsequently I checked that these had been performed.

(f) State who carried out each of those pre-transplant checks including for Adam's weight

The checks were carried out by myself and the named junior medical staff. Adam's weight was measured by nursing staff and recorded in clinical note (058-035-131).

(g) Explain the source of the weight that you recorded for Adam (21kg) in your note (Ref: 059-006-011)

Adam's weight is recorded on document 057-012-016 as 20.2kg in the weight chart prior to overnight feeds but as 20.9kg in clinical notes on 9 November 1995. Calculation of surface area is based on weight and height measures. The weight of 21kg is an approximate weight used simply to make a calculation of surface area (m^2) from a nomogram. This surface area calculation is then used to determine drug dosage when appropriate.

(h) State when and by what means you received the results of those *"standard pre-transplant checks"* including the serum sodium result

The results of Adam's blood tests are recorded in his notes on 26 November 1995 at 11.00pm (058-035-144). I would have received these investigations at that time or shortly afterwards. I have made a note on the early hours of 27 November 1995 (058-035-133) at the time when the cross-match result became available. On that note I have said his electrolytes were satisfactory but should be repeated first thing in the morning. I would have been aware of the serum sodium result at that time.

(8) Answer to Question 2 at p.3:

"I contacted our operating theatre, the consultant anaesthetist on call and the transplant surgeon on call to alert them to the possibility of a transplant operation and the nature of Adam's condition"

(a) Describe the arrangements that you made in terms of securing an operating theatre for the transplant and putting together the anaesthetic and surgical teams including:

- the identity of each of the persons that you contacted and when you contacted them
- when the teams were agreed of Dr. Robert Taylor and Dr. Terence Montague as anaesthetists and Mr. Patrick Keane and Mr. Victor Brown as surgeons

The arrangements for securing an operating theatre for a transplant involved contacting the senior nurse in theatre and alerting her to the fact that a possible renal transplant might occur in several hours, and from whom the Consultant Anaesthetist would be identified. The Anaesthetist was contacted to alert him again to the possibility of a renal transplant and confirm that he was willing to undertake an anaesthetic for that surgery. On this occasion it was Dr Bob Taylor. From the surgeon on call list for renal transplants held in the Renal Unit in the BCH, the transplant surgeon was identified. On this occasion Mr Patrick Keane confirmed that he was available and willing to carry out a paediatric transplant. Ideally, the presence of a senior paediatric surgeon who could be present and assist with the transplant is required. On this occasion, Mr Stephen Brown agreed to assist Mr Keane. I cannot say exactly what time these arrangements were finalised on the evening of 26 November 1995. I had no part in involving Dr Terence Montague.

(b) Describe the arrangements that existed in the RBHSC at the time for, out of hours, securing

an operating theatre and putting together a team (including nurses) for paediatric renal surgery

The arrangements are essentially as described in (8 a). The theatre sister or charge nurse is informed. The anaesthetist on call is informed, the surgeon on call is informed and a surgical assistant is identified. This team then take forward arrangements for the surgical aspects of the transplant.

(9) Answer to Question 2 at p.3:

"After detailed telephone discussion of the complexity of Adam's case the surgical and anaesthetic team decided that ... a planned transplant operation should commence at 7am, 16 hours after the kidney had been donated.
I was satisfied with his haemoglobin at 10.5g/dl and with his electrolyte status with a sodium of 139 mmol/L and a potassium of 3.6mmol/L. His dialysis was performed as normal although the duration of the dialysis was, of necessity, shorter than usual."

(a) Explain what you meant by the *"complexity of Adam's case"*

Adam was a child who had been ill from immediately after his birth. He had undergone 20 surgical procedures. The anatomy of his urinary tract following these procedures was unusual, for example, one ureter was cross connected to the contralateral ureter with both draining together through the distal part of that ureter into his bladder. He had had several previous urological operations in relation to his bladder and renal tract. He had had several previous intravenous lines inserted via neck veins. He had a gastrostomy for feeding purposes in his abdominal wall, was on peritoneal dialysis with a dialysis tube placed in his abdominal cavity, and was completely tube fed and drank or ate virtually nothing. He had polyuric renal failure and a high urine output but poor urinary concentrating ability and required special feeds to maintain fluid and electrolyte balance. He had suffered recurrent urinary and other infections. His was therefore a complex case.

(b) Describe the matters that were discussed during your *"detailed telephone discussion"* and state when and with whom in the surgical and anaesthetic teams that discussion took place

I do not have a definite memory of the exact time when I had telephone discussions with Dr Bob Taylor, Consultant Anaesthetist, and Mr Patrick Keane, Consultant Surgeon on the late evening and early morning of 26 and 27 December. Discussions with Dr Taylor would have been in relation to Adam's previous medical history and his diagnosis of obstructive uropathy and polyuric renal failure. His previous urological history, his multiple previous anaesthetics and operations and the fact that he was fed by gastrostomy with a high calorie Nutrison feed which was required to be delivered in high volumes of 2.1 litres daily. I would have informed Dr Taylor of Adam's current medical condition, his size, level of nutrition and difficulties with venous access. This discussion led to the development of a plan for his fluid management prior to the surgery, essentially changing from a high density Nutrison feed to clear fluids that would empty from his stomach more rapidly, and the need to discontinue all feeds two hours before surgery (see question 10 a). I would have informed Dr Taylor of his current electrolyte and urea status and agreed the need for a further blood sample immediately before surgery if the transplant operation was delayed overnight.

My discussions with Mr Keane would have been to explain to him the nature of Adam's previous surgery, including the current anatomy of his urinary tract with two ureters draining by a single lower ureter into his bladder and the fact that he had had major urological surgery before. I would have informed him of the situation with a polyuric renal failure, the nature of the tissue type match

and any knowledge I had of the anatomy of the donor kidney from my conversations with the UK Transplant Service. Discussions with Mr Keane also would have involved the choice of time for taking Adam to theatre and arranging for Mr Keane to have a Consultant Paediatric Surgeon to assist him during the operation who had a substantial knowledge of Adam's background surgery and complexity.

(c) Describe what information was available to you on Adam's haemoglobin and electrolyte status at the time of that *"detailed telephone discussion"*

The results of Adam's blood tests following admission, including his haemoglobin and electrolyte status would have been available at the time of the detailed telephone discussion.

(d) Describe your involvement in any of the actions that were taken after Adam's IV cannula tissued at 2.00am on 27th November 1995, including:

- the increase in fluids through his gastrostomy from 180mls/hr to 200mls/hr
- the continuation of fluids through his gastrostomy until 5.00am on 27th November 1995

I was informed by phone that venous access was no longer available to provide intravenous fluids after returning home at 2.00am on 27 November 1995. When repeated attempts failed, the Anaesthetic Senior Registrar (Dr Terence Montague) was contacted for assistance. Adam was very distressed and after consultation with Dr Taylor, the Consultant Anaesthetist, they agreed to make no further attempts (093-037 Witness Statement). I advised an increase of the fluids through his gastrostomy tube to compensate for this. I advised 200mls per hour was the maximum we should deliver in order to avoid vomiting from over-filling Adam's stomach. It had been agreed with the anaesthetist that no fluid should be given through his gastrostomy for 2 hours before going to theatre. I would have communicated this to the ward nursing staff.

(e) Explain when, by whom, and in what circumstances, it was agreed that Adam's surgery would take place at 7.00am as opposed to the 6.00am originally included by you in his records (Ref: 059-006-011)

The decision to postpone Adam's surgery from the time when we knew that his cross-match was suitable to early morning on 27 November 1995 was agreed between the surgical and anaesthetic team. I understand that the rationale for an early morning start was so that surgeons, anaesthetists and nursing staff were fresh starting a day's work rather than finishing a shift. The surgical and anaesthetic consultants believed that this was a safer option for the patient. I do not know why there was a change from 6.00am to 7.00am.

(f) Explain the basis upon which you, the surgical team and anaesthetic team calculated that carrying out Adam's surgery at 7.00am would constitute 16 hours after the kidney had been *"donated"*

I now believe the statement that Adam's surgery would be 16 hours after the kidney was donated is incorrect following my review of his notes recently. It is now clear to me that the kidney was removed at 01:42 on 26 November 1995 as recorded on the Kidney Donor Information Form (Ref: 058-009-027) on 26 November. This is a 24 hour clock recording. In my previous statement I have suggested 16 hours. I had not remembered this detail and assumed the kidney had been donated at 1.42pm.

(g) Describe the changes that were made to his dialysis in the light of it being *"of necessity,*

shorter than usual"

The change made in Adam's dialysis regimen was that he had fewer cycles of the peritoneal dialysis because it was discontinued and his abdomen drained prior to going to theatre. Since peritoneal dialysis is carried out on a daily basis, it slowly alters blood biochemistry and it was not expected to make a major difference to his condition.

(h) State the time when Adam's dialysis was completed

Adam's dialysis was completed before going to theatre. There is no precise time available from his notes.

(10) Answer to Question 2 at p.3:

"I discussed Adam's underlying diagnosis, his past medical history and current management of his condition in terms of dialysis and fluids with Dr. Taylor so that he was aware that Adam normally received 2.1 litres of fluid each day, 1500 ml of which were usually given overnight and that I estimated that his urine output each day was 1200-1500ml"

(a) Describe when you had that discussion with Dr. Taylor and what you told him about *"Adam's underlying diagnosis, his past medical history and current management of his condition in terms of dialysis"* including the concentration of Adam's electrolytes following dialysis

I had a long phone call discussion with Dr Taylor, the precise time of which I do not remember, but was most likely late on the evening of 26 November 1995. I would have discussed his underlying diagnosis of renal failure due to obstructive uropathy, his previous urological history and the fact that he had had multiple previous anaesthetics and operations, both to his renal tract in relation to his gastrostomy feeds, and for central venous access. I would have discussed his current dialysis and fluid regime, including his need for a high fluid intake via gastrostomy each day because of his polyuric state. I would also have discussed the difficulties on occasions with his fluid and sodium balance, and also his history of recurrent urine infection. I would have informed Dr Taylor of his current status in general medical terms and of his size and level of nutrition. Discussion regarding his normal overnight fluids (1.5 litres Nutrison), led to an agreed plan for an alternative pre-anaesthetic regimen.

As far as I remember, I had discussions with the anaesthetic team at the time of Adam's transfer to theatre to include, reviewing his evening electrolyte results, the fluids he had received overnight and the fact that his venous line had tissued so that he had not received some of the intravenous fluids as planned and that it had not been possible to obtain a blood sample so a pre-theatre electrolyte measurement was still outstanding.

(b) State the source of the information that you relied upon in providing that information to Dr. Taylor

Adam's notes was the source of information relied upon to provide information to Dr Taylor in relation to Adam's electrolytes and fluid balance overnight. I was aware from my close involvement with Adam, that he normally received 2.1 litres of fluid each day and this is annotated in his clinical notes and in a summary made by Dr O'Connor on 9 November 1995 (058-035-143). His 11.00pm blood results would have been available to me.

(c) Describe the basis upon which you calculated that *"Adam normally received 2.1 litres of fluid each day"*

See (10 b) above

(d)Describe the basis upon which you estimated that his *"urine output each day was 1200 - 1500mls"*

The estimate of Adam's urine output was based on the fact that he received 2.1 litres daily. Insensible loss was based on the formula 300mls/m²/day. The ultrafiltration loss from his dialysis was around 400mls daily. Therefore, if he received 2.1 litres (2100mls) and lost 700mls by these means, one would estimate that he passed perhaps 1400mls of urine. Also, as on occasions he might vomit or not receive the full 2.1 litres, we estimated a range of urine output between 1200-1500mls.

(11) Answer to Question 2 at p.3:

"In consultation with Dr. Taylor it was decided that he [Adam] should have clear fluids overnight by gastrostomy tube rather than his normal Nutrison feeds ... to stop two hours before going into theatre ... I discussed Adam's underlying diagnosis, his past medical history and the current management of his condition in terms of dialysis and fluids with Dr. Taylor ... It was planned that Adam would receive intravenous fluid (75ml/hr) and have his blood chemistry checked before theatre"

(a) State whether Adam's normal gastrostomy feeds were Nutrison or Nutrizone - see for example: *"His night gastrostomy feeds are normally 1.5l of Nutrizon"* (Ref: 011-015-109)

Adam's normal gastrostomy feeds were with Paediatric Nutrison. 'Nutrizon' is a spelling error.

(b)State when that plan for Adam's pre-operative fluids was decided with Dr. Taylor

The plan for the type of Adam's pre-operative fluids was decided with Dr Taylor during our telephone discussions on the evening prior to his transplant.

(c) Describe in full the plan for Adam's fluid management that you decided with Dr. Taylor and the basis upon which it was formulated, including:

- the precise content of the *"normal Nutrison feeds"*
- the precise content of the *"clear fluids"* that were to be given in substitution for the Nutrison and the total quantity that it was planned Adam would receive prior to the commencement of his surgery
- the basis for the calculation that *"Adam should receive intravenous fluid (75ml/hr)"* after his *"tube feeds"* were discontinued
- the precise content of the 75ml/hr intravenous fluids that he was to receive
- the purpose of administering both the *"clear fluids"* and the *"intravenous fluids"* in terms of hydration and nourishment
- the total amount of all fluid that Adam was to receive prior to his transplant surgery and the matters taken into consideration in determining that total

The precise content of the Paediatric Nutrison feed is given in Appendix 1. The precise composition of Dioralyte is also given in Appendix 1. It was planned to correlate with Adam's overnight intake volume of fluid to most of that which he would normally have received, ie. 1.5 litres. This was the

basis for the calculation of the intravenous fluids at 75mls per hour after the tube feeds were discontinued. Calculating retrospectively as follows: clear fluids by gastrostomy feed for approximately 6 hours at 180mls/hr would give 1080mls. Intravenous fluids at 25mls per hour for 6 hours would give 150mls. When the tube feeds were finished 2 hours of intravenous fluids at 75mls per hour would give another 150mls. Thus, over a 6 hour period Adam would have received 1380mls total fluid.

The precise content of the 75mls per hour intravenous fluid was that it was an N/5 (0.18%) saline in 4% dextrose which was the standard replacement intravenous fluid in use at that time.

The purpose of administering both gastrostomy clear fluids and intravenous fluids was so that his stomach was not over-filled to avoid the possibility of him vomiting some of the fluid and also to ensure that the intravenous line stayed open and was still functional at the time of his transfer to theatre.

(d) In formulating that plan with Dr. Taylor, state:
- what information you had about Adam's clinical condition (including his urine output) and biochemistry
- identify the source of that information
- explain how that information was factored into the plan

The information which was available regarding Adam's clinical condition included the electrolyte measure at 11.00pm and our previous knowledge and calculation of his daily urine output at 1200-1500ml. The electrolyte result at 11.00pm on 26 November 1995 is recorded at 058-035-144. This was factored in and described in 11 c) above.

(e) Explain the effect of Adam receiving 952ml of clear fluid after admission instead of his normal 1.5l Nutrison feed including:

- the effect on his hydration status and electrolyte balance
- whether this meant he was 550ml in deficit
- if so, how quickly such a deficit needed to be restored to keep him safe
- the time difference between IV fluids and oral fluids affecting circulating blood volume or hydration generally

The effect of receiving 952mls of clear fluid after admission rather than the usual 1.5 litre of Nutrison feed and a small volume of intravenous fluids (58mls) meant that Adam was in relative deficit of 500mls compared to previous days. He would therefore have been less well hydrated than usual and it is possible that this may have resulted in some degree of haemoconcentration which would have the possible effect of increasing his serum sodium concentration. In normal circumstances this deficit would have been addressed by replacing the deficit by extending his tube feed at 200mls per hour over 2-3 hours.

My understanding was that once Dr Taylor established IV access in theatre, a blood sample for electrolytes and urea would be drawn and the fluid deficit corrected by IV infusion. Subsequently, a maintenance infusion at 85mls/hr would be required to equate with the normal daily intake of 2.1L.

Clearly, from a surgical viewpoint addressing the deficit was important in order to have good intravascular volume prior to removal of the vascular clamps when a kidney transplant is performed. At that point a volume of blood is lost to the circulation into the transplanted kidney.

This situation is monitored intra-operatively and related decisions taken between the anaesthetist and surgeon. Other measurements taken into account would include the patient's blood pressure and central venous pressure (CVP). Addressing the deficit over 2 hours would seem to be reasonable as it generally takes this length of time at least before vascular clamps are released to initiate perfusion of the kidney. Rapid intravenous fluid corrects circulating blood volume almost immediately. The same volume given orally would be much slower in producing this effect.

(f) Explain your role in ensuring that the agreed plan for Adam's pre-operative fluid management was executed and the extent to which you expected to be informed about any difficulties with its execution

My role in ensuring that the agreed plan for Adam's pre-operative fluid management was executed was to ensure that the fluids were prescribed by junior staff. I always instruct junior staff that if there is any difficulty whatsoever I should be informed immediately.

(g) Explain the reason for and significance of the plan to have Adam's *"blood chemistry checked before theatre"*, including your note in Adam's records *"electrolytes satisfactory - should be repeated first thing in the am"* (Ref: 058-035-133)

There was an instruction to repeat Adam's blood chemistry before going to theatre. This was because there was an alteration in his normal overnight fluid management and I wanted to be sure this had not adversely affected his electrolyte status prior to surgery (Ref: 058-035-133).

(h) State at what time you made the note and on what basis

I have not recorded the time when I made this note but I believe it was after the formulation of the fluid plan and also after the time when we were aware that the cross-match was favourable and therefore probably at 1.00 or 2.00am.

(i) State whether you were advised about any difficulty in implementing that plan and describe what happened, including:

- who contacted you
- when you were contacted
- the nature of the difficulty
- what was to be done about it

I do not remember who contacted me to tell me that the intravenous fluid line had tissued or what precise time that had happened, but I did instruct that the gastrostomy feed volume was increased to compensate for the loss of the intravenous fluid line. I further informed Dr Taylor, the Consultant Anaesthetist, of the difficulty with the intravenous fluids overnight when we met at the time of Adam's transfer to theatre. He had already discussed this situation with Dr Montague, his Senior Registrar overnight (093-037-113).

The plan then agreed with the anaesthetic team was that a blood sample for electrolyte and urea estimation be sent to the laboratory once IV access was established in theatre and the fluid deficit be corrected intravenously.

I was not made aware that a sample was not sent or of the serum sodium of 123mmol/L on the gas machine, which if accurate, indicated a significant fall.

(j) Identify the medical Registrar on duty between 9pm on 26th November and 7am on 27th November 1995

I am unable to do so.

(k) Explain the arrangements in which medical staff (clinicians and nurses) were to inform and/or contact a consultant during the after hours period of either concerns/changes relating to the plan of care or management of a child

Medical staff with any concerns were told to speak to me directly were I still present in the ward, or to telephone me at home so that I could issue instructions or if necessary return to the hospital.

(l) State at what time Adam's preoperative fluids ceased

My understanding is that the venous line was lost at approximately 1.30am. Attempts were made to re-erect the line but these were eventually abandoned due to the difficulty and the upset caused to Adam. This decision was made after the Senior Registrar in Anaesthetics, who was contacted for assistance, discussed the situation with Dr Taylor, the Consultant (093-037-113).

(12) Answer to Question 2 at p.3:

"The total volume he [Adam] received overnight was just under 1 litre"

(a) State the total fluids Adam received pre-operatively from his admission on 26th November 1995, including any fluids administered to provide his normal saline and sodium bicarbonate supplements

Adam received 952mls of oral fluid and 58mls of intravenous fluid pre-operatively from his admission on 26 November 1995. Dioralyte (60mmol/L) contains higher concentration of sodium than Paediatric Nutrison (23mmol/L) to which saline was normally added. The broad calculation was that the volume of clear fluid (Dioralyte) prescribed along with the intravenous $^{N}/_{5}$ (0.18%) saline in 4% dextrose (30mmol/L) would supply approximately the same volume and amount of sodium as he received usually overnight.

(13) Answer to Question 2 at p.3:

"I arranged to return to hospital early the following morning to be available for consultation if required"

(a) Explain what was discussed, when and with whom about you returning to the hospital early in the morning and being available for consultation

I have no recollection of who I told I would return to the hospital the following morning prior to Adam's transfer to theatre, but I would have informed nursing staff, junior medical staff and in particular Dr Bob Taylor, the Consultant Anaesthetist.

(b) Describe what happened on your return the following morning, including:

- the time of your return
- whether a consultation or discussions took place and if so with whom and to what end
- what information did you receive and from what source about Adam's condition and the execution of the plan that had been agreed the previous evening for his fluid management
- what role you had in the plan for Adam's fluid management during the course of his surgery
- whether you met with Adam's mother and if so what you discussed with her about Adam's forthcoming surgery

When I did return the following morning, I had discussions with Dr Taylor regarding Adam's fluid management overnight and the deficit in his fluids compared to a normal 24 hours. I cannot say if I received this precise information from nursing or medical sources but confirmed the exact deficit from reviewing his fluid balance charts. Dr Taylor and I had been informed that inserting a new IV line had been impossible.

I did not have a role in the plan for Adam's fluid management during the course of the surgery, other than to indicate that he was in fluid deficit at the start. Once his care was handed over to the anaesthetic and surgical team and they were aware of the situation as regards fluid balance and the need for further electrolyte estimation, I was not directly involved in fluid management decisions. I cannot be certain that I met with Adam's mother prior to the surgery that morning or what I discussed with her. It would have been my habit to talk to parents at this stage and inform them that I would be in contact with the procedures in theatre and update them on how the surgery was progressing over the next number of hours.

(14) Answer to Question 2 at p.3:

"On the morning of the 27th November I made myself available in theatre for consultation and understood there were no early problems during the transplantation procedure. I reassured Ms. Strain of this before undertaking some university duties and my colleague, Dr. Mary O'Connor, then made herself available for consultation."

(a) Explain what is meant by your reference to *"made myself available in theatre"* including whether you were scrubbed, gowned and in the operating theatre

While it was not normal practice for a nephrologist to be present during a renal transplant, since we are physicians rather than surgeons or anaesthetists, it was my habit to observe the procedure intermittently and always be present close to the theatre for consultation should information be required by the transplant team. I would have been changed into theatre scrubs but would not have been gowned as an observer. Up until 9.00am at any time when I was in theatre, there were no problems with Adam about which I was made aware or consulted. When I handed over to my colleague Dr O'Connor and left theatre, I spoke to Ms Strain to let her know the epidural was in place and that things were proceeding slowly with no problems at that stage.

(b) Describe what happened whilst you were in theatre, including:

- when you arrived in theatre and when you left
- what consultation took place, which whom and to what end, including in respect of Adam's fluid management during the course of his surgery
- who was present in theatre

I cannot say when exactly I arrived in theatre and when I left. I was not in theatre again after 9.00am. Any consultation in relation to Adam's fluid management during the course of his surgery was, most likely, between the anaesthetic staff. My involvement was prior to the surgery to alert the anaesthetic team of the need for electrolyte estimation and the calculated deficit in his normal fluid provision overnight. I cannot say who was in theatre other than my senior colleagues, ie. Mr Patrick Keane, the Transplant Surgeon, Mr Stephen Brown, the Paediatric Surgeon, Dr Bob Taylor, the Paediatric Consultant Anaesthetist, although I was aware there was another senior Registrar Anaesthetist present as well as the nursing staff, whose names I do not know.

(c) State whether you were in the theatre at 9.32am when Adam's serum sodium level was recorded on a blood gas machine at 123mmol, and if so describe what action, if any, was taken in consequence of that reading

I was not in theatre at 9.32am to the best of my knowledge and I was not made aware of a serum sodium level on a blood gas machine of 123mmol.

(d) Describe the progress of the surgery at the time you left theatre and from which you concluded that *"there were no early problems"*

To the best of my knowledge when I say there were no early problems when I left theatre at around 9.00am, this was on the basis of communication with the anaesthetic team and the surgeons present.

(e) State when you spoke to Adam's mother and describe what you told her as part of reassuring her of the progress of Adam's operation

I spoke to Adam's mother shortly after leaving theatre around 9.00am and reassured her that there were no problems at that time which was the position then. It is worth stating that the first hour or so in theatre is generally taken up with preparing the patient for surgery, including the positioning of the epidural to provide anaesthesia, and establishment of appropriate arterial and venous lines.

(f) Describe the discussions you had with Dr. O'Connor about Adam's condition and the transplant before leaving to undertake some university duties

My discussions with Dr O'Connor were to be sure that she was aware of the details of Adam's condition. I was aware that she had summarised his past history a few weeks before for her own information. I informed her of the fluid situation overnight and the fact that things seemed to be progressing slowly but satisfactorily in theatre.

(g) Explain your opinion at the time as to why an x-ray of Adam's chest showed signs of pulmonary oedema postoperatively

My opinion at the time was that this indicated significant fluid overload. Signs of pulmonary oedema following transplant surgery generally indicate that the patient is significantly fluid overloaded. Of itself, this is a manageable problem, particularly in a patient who is being ventilated, as the pulmonary oedema initially interferes with respiratory function and can be compensated for mechanically and corrected with careful manipulation of post-operative fluids.

(15) Answer to Question 2 at p.4:

"Following the events surrounding Adam's death Dr O'Connor and I revised the Renal Transplant

Protocol to state that normal saline, plasma or blood should be used in theatre to raise central venous pressure prior to releasing vascular clamps to perfuse the kidney"

(a) Explain the function of the Renal Transplant Protocol at the RBHSC

The function of the Renal Transplant Protocol at RBHSC is to provide guidance for all medical and nursing staff involved with the care of children undergoing renal transplantation. The checklist on admission provides an aid memoire for the information and investigations required prior to the transplant. There is a section giving appropriate doses of immunosuppressive drugs and detailed information relating to post-operative management, including the management of fluids, drug treatment and rejection. A copy of the transplant guidelines are placed with the notes of every child undergoing a transplant so that they are available to anyone involved in their care.

(b)Explain the particular *'events surrounding Adam's death'* that led to you and Dr. O'Connor revising the Renal Transplant Protocol dated September 1990

The events around Adam Strain's death, and particularly the finding that this was caused by dilutional hyponatraemia, led us to review our Protocol to see if there was any guidance that we could introduce to prevent this happening again. We expanded the Protocol with more detailed guidance and included a nursing checklist for transplantation and a theatre checklist. Transplant management and protocols evolve with experience, both within a Unit and as shared experience nationally and internationally. In revising the protocol, we consulted protocols from other centres in the UK. We wanted to ensure that our guidelines were up-to-date or improved to be consistent with best current practice. We wanted to ensure that electrolytes were regularly monitored and that there was some move towards the use of fluids with a higher sodium content perioperatively. The aim of the revision was to improve patient safety.

(c) Describe the differences between the Renal Transplant Protocol of September 1990 and the revised Renal Transplant Protocol of September 1996 and explain the reasons for them

The differences between the 1990 and 1996 Protocols include, listing in the history which central lines have previously been placed in the patient. In the investigation section, the BCH Tissue Typing Laboratory's phone number is included. A coagulation screen has been added to the list of investigations. The detail of the virological screen to be performed is defined. Urine analysis for electrolytes and urea has been added, as has an ECG if the patient is on anti-hypertensives.

In the pre-operative plan, at that stage Vancomycin was to be added to the peritoneal dialysis fluid to reduce the risk of infection. Recommendations regarding the use of intravenous fluids during pre-operative fasting are given, and there is a requirement that if the serum sodium is less than 133 the Consultant Nephrologist should be informed and also a requirement for a repeat serum electrolyte and urea measurement at the time of going to theatre.

The theatre checklist sheet which was added also includes a space to record the pre-theatre electrolyte and urea level, full blood picture and the results of the coagulation screen. In the theatre section, recommendations include an assessment of hydration and a need for electrolytes and arterial blood gasses to be performed 2-hourly during the procedure. There are recommendations for the use of antibiotics and anticoagulants to reduce the risk of infection and thrombosis, the need for a triple lumen central CVP line is defined, and also the need for an intra-arterial line. A dose of Dopamine to improve renal blood flow is given, and the use of normal saline, plasma or blood in order for the CVP to achieve a level of 8-10mmHg prior to the removal of vascular clamps is given. In the post-operative management section, it is recommended that half normal saline with 2.5%

dextrose is used as standard replacement therapy instead of the 0.18% saline with 4% dextrose ($^{N}/_{5}$ saline with dextrose) that had previously been recommended.

Also recommended is the use of normal saline or HPPF (which has a similar sodium content) or used as bolus fluids to maintain or raise CVP and blood pressure.

In the observation section, recommendations for monitoring the CVP, blood pressure and urine output are now described.

In the drug section, revised details of the immunosuppressive drugs dosage and administration are given. Details of prophylactic drugs to maximise renal blood flow to prevent clotting and gastric irritation due to steroid treatment are given. The use of epidural anaesthesia as well as morphine is suggested in the analgesia section.

In the post-operative investigation recommendations, the use of daily renal Doppler ultrasounds to assess blood flow in the transplant kidney has been added. Daily urine U&E has been added as a daily test. The Rejection Protocol has no major changes. The nursing and theatre checklists are provided as appendices which list the need for a pre-operative serum U&E before going to theatre and the need for a urine collection and urinary electrolytes.

(d)Explain the process of and mechanism for the revision of such protocols at the RBHSC

These protocols are essentially guidelines since practice evolves with experience and the sharing of best practice, for instance, when new drugs become available. When the consultant team believe there has been a significant shift in practice or new information needs to be added, a revised protocol is produced. This usually occurs every five years. In preparing revisions, practice in other centres and published advice, for example: NICE Guidelines for Immunosupressive Therapy for Renal Transplantation in Children and Adolescents (www.nice.org.uk/TA099), are taken into account. Generally, we would have access to recent protocols from other major centres for comparison and indeed keep such protocols for cross reference.

(e) Identify the current Renal Transplant Protocol

The current Renal Transplant Protocol dated February 2011 on page 9 is provided in Appendix 2.

(f) Explain the basis upon which you revised the guidelines to include; *"D/W Consultant if Na<133. Repeat U/E at time of going to Theatre"* (Ref: 002/1. Page.5)

The revised guideline is in relation to alerting consultants to sodium levels less than 133 is to ensure that this is not overlooked, but is analysed and investigated and the transplant team alerted. The consultant would be concerned to identify whether there were any symptoms associated with this level of sodium, whether it was a major variation in the serum sodium level and whether or not there had been any rapid change. Repeat U&E recommendation at the time of theatre is to ensure that the pre-operative fast and IV fluids have not significantly altered fluid or electrolyte balance.

II QUERIES ARISING OUT OF YOUR DEPOSITION

With reference to your Deposition to the Coroner taken on 21st June 1996, please provide

clarification and/or further information in respect of the following:

(16) State what is written in the handwritten amendment on the penultimate line of the first page of your deposition to the Coroner (Ref: 011-015-109), and the basis upon which that amendment to your deposition was made

The amendment on the penultimate line of the first page is not in my handwriting. I do not remember why this change was made. I believe it says '$^{N}/_{5}$ saline dextrose'. This is the intravenous solution which Adam was receiving on that evening.

(17) *"He [Adam] had a potential for a low sodium which was being managed."*

(a) Describe and explain how Adam's potential for *"a low sodium"* manifested itself throughout the period between 26 November 1991 and 27 November 1995 when Adam was in your care

Adam's potential for a low sodium on occasions during his life did not manifest with any significant symptoms but was detected on routine blood tests. These are identified in his clinical notes on several occasions in summary flow sheets of his serum electrolytes. See answers under 3 c), 4 f) and 4 g).

(b) Describe in what way the potential for *"a low sodium"* was being managed during that period

The potential for a low sodium managed by dietary means and supplements included saline solution added to feeds, sodium bicarbonate supplements and was addressed with minor alterations in his tube feeding regime and by attention to intercurrent illnesses such as urinary tract infection and other causes of vomiting.

(18) *"The majority of children with renal failure have similar problems concerning electrolyte levels. Since Adam's death these would be measured more frequently. I have discovered that in the UK there have been 9 other deaths from an apparently similar cause though these have not been published ...The information about the 9 other deaths was told to me verbally later – it was not published. "*(Ref: 011-015-113)

(a) State when and in what circumstances you *"discovered that in the UK there have been 9 other deaths from an apparently similar cause though these have not been published "* and identify the person(s) who verbally told you of them

The death of Adam Strain was devastating to all of us in the renal team who had looked after him. As a result of this I discussed his case with many colleagues in the UK and indeed possibly further afield at Nephrology meetings. On one of these occasions, a colleague told me that they believed there had been nine or ten other deaths from a similar cause. After these many years, I do not remember who the individual was who informed me of this belief. Subsequently, although there have been publications related to death from hyponatraemia related to renal transplantation, and most recently one from the Hospital for Sick Children in Great Ormond Street (Cansick et al, Pediatric Nephrology (2009) 24:1231-34), I have been unable to find any publication that identifies this number of deaths from dilutional hyponatraemia. It is possible this was a figure relating to European transplants as there were only 15-30 renal transplants per year in small children at that time across the UK.

(b) State in detail what you discovered in relation to the *"9 other deaths from an apparently similar cause"* including the date of each death

This was an anecdotal comment quoted at the Inquest. I was unable to substantiate this and consequently I am unable to give details such as you request.

(c) Describe and explain any actions you took in relation to this "discovery"

As I have said, I endeavored to establish if indeed there were nine other similar deaths and was unable to establish that this was the case and certainly not to my current knowledge in the UK.

(d) Document reference 060-018-036 states *"... a number of renal transplants complicated by hyponatraemia leading to death in 10 (reported in May 1996)..."*

- State whether you provided the information relating to *"a number of renal transplants complicated by hyponatraemia leading to death in 10 (reported in May 1996)"*
- If so, state to whom did you provide that information
- State when you provided that information
- State the reasons why you provided that information
- Describe fully the circumstances and details of the *"number of renal transplants complicated by hyponatraemia leading to death in 10 (reported in May 1996)"* including the date of each death

With reference to the document 060-018-036, I presume this refers to the handwritten addition to the statement in my deposition to the Coroner mentioned under 18 b) above and I can only say that this was anecdotal evidence.

III ADDITIONAL INFORMATION

(19) You stated in a letter dated 7th June 1996 to Dr. G. Murnaghan *"Information regarding the Child's Urinary Output Prior to Surgery... Urine output in incontinent children in nappies can only be measured by inserting a urinary catheter"* (Ref: 059-003-005)

(a) Specify the basis of that statement

Accurate measurement of urinary output in incontinent children can be best measured by inserting a urinary catheter if this is deemed necessary. Measuring it by other means will be subject to error. In recent years, we have made attempts to get a reasonably accurate measure of urine output in these situations by measuring the weight of a dry nappy and then the same nappy when wet. With accurate scales, a reasonable estimate of the urine passed into the nappy is possible. We also use daily patient weights with accurate scales not to specifically measure urine output, but to detect significant shifts in weight in relation to fluid therapy. Urine output might be estimated over a 24 hour period when weight remains static by calculating insensible loss based on a child's surface area and subtracting this and any other losses, such as that from ultrafiltration on dialysis from the measured fluid volume input. I believe what I meant by this statement is that accurate urine output without the insertion of a urinary catheter is difficult.

(20) Describe in detail the education and training that you received in fluid management (in particular hyponatraemia) and record keeping through the following, providing dates and names of the institutions/bodies:

(a) Undergraduate education

This is a virtually impossible question to answer. My undergraduate education was over 40 years ago at Queen's University Belfast and to describe in detail the training I would have received in fluid management, and in particular hyponatraemia, dates etc is not feasible.

(b) Postgraduate education and training

My postgraduate education and training as a junior doctor took place in Northern Ireland between 1971 when I first qualified and 1976, during which time I was awarded the Diploma in Child Health in 1973 and was successful in the examinations for Membership of the Royal College of Physicians (London) in 1976. During that period and in studying for these higher professional examinations, I would have received teaching and undertaken study in the management of fluid balance and prescription, particularly for children, as all of my postgraduate training except for one year, was in Medical Paediatrics. During that time I would also have received instruction and advice on record keeping. Having become a member of the Royal College of Physicians, I continued my postgraduate training at the Hospital for Sick Children at Great Ormond Street, where I was attached to the Renal Unit. The following year, I moved to the Royal Manchester Children's Hospital Renal Unit for further experience and training in dialysis and transplantation. I was given a full accreditation as a Specialist in Paediatrics in 1980 and in Paediatric Nephrology in 1981 by the Joint Committee on Higher Medical Training. In 1989 I became a Fellow of the Royal College of Physicians of London and in 1996, a Fellow of the Royal College of Paediatrics and Child Health. I was appointed Consultant Paediatric Nephrologist and Senior Lecturer in Paediatrics in 1981.

(c) Hospital induction programmes

In the 1970s when I was undergoing postgraduate training in various hospitals in the UK, there were generally no formal induction programmes.

(d) Continuous professional development

There were however regular weekly postgraduate training sessions and workplace education and training when I gained knowledge and experience of managing fluid and electrolyte problems. Since becoming a Consultant, I have regularly kept up my continuous professional development, attending national meetings of the Royal College of Paediatrics, the British Association for Paediatric Nephrology (of which I have been President), Paediatric Nephrology update courses at the Institute for Child Health, University College London, and most years have attended scientific meetings of the European Society for Paediatric Nephrology or the International Paediatric Nephrology Association to ensure that my knowledge and understanding of my subject is current. I regularly attend weekly clinical update meetings in the Royal Belfast Hospital for Sick Children. I subscribe to and regularly read the British Medical Journal, The Archives of Disease in Childhood and the international journal Pediatric Nephrology.

(21) Prior to 26th November 1995, describe in detail your experience of children :

(a) With hyponatraemia, including:

- the estimated total number of such cases, together with the dates and where they took place
- the number of the children who were aged less than 6 years old
- the nature of your involvement

- the outcome for the children

I cannot give any realistic estimate of the total number of cases of children with hyponatraemia in whose treatment I was involved before November 1995. No records which would enable me to give such information exist. Undoubtedly I did look after children with hyponatraemia, possibly at Great Ormond Street Children's Hospital and at the Royal Hospital for Sick Children in Manchester, and at the Royal Belfast Hospital for Sick Children. It is likely that I would have been involved in management of such children in an advisory capacity, and to the best of my knowledge, I do not know of any children whom I treated who did not recover.

(b)Undergoing renal transplants, including:

- the number of all such transplants, together with the date of each and where they took place
- the number of the children who were aged less than 6 years old
- the nature of your involvement

My experience with paediatric renal transplantation prior to November 1995 includes 22 children who were transplanted at the Belfast City Hospital on the following dates: 12 November 1982, 15 July 1984, 20 May 1985, 21 September 1985, 4 December 1985, 6 April 1986, 24 June 1986, 14 August 1986, 27 October 1986, 10 December 1986, 29 April 1987, 6 February 1988, 30 August 1988, 7 December 1989, 12 December 1989, 25 December 1989, 20 April 1990, 19 September 1990, 27 April 1991, 8 July 1991, 3 February 1992 and 17 July 1993.

I was also involved in the management of renal transplantations in a further 9 children at RBHSC on: 16 June 1990, 31 October 1990, 19 December 1990, 30 December 1991, 12 November 1992, 14 May 1993, 7 October 1993, 18 July 1994 and 9 April 1995.

This is a total of 31 transplants prior to November 1995. Only four of these children were aged below 6 years. I was the named Consultant in charge of the management of all these children. When the transplants occurred in the Belfast City Hospital, surgery was carried out by adult transplant surgeons. On some occasions, a Paediatric surgeon was also present. The day-to-day care for the children pre and post transplant was my responsibility, although on occasions I did receive cross cover from the adult Nephrologists while the children were in-patients in the adult renal transplant unit. Only four of these children were under the age of 6 years as it would neither have been appropriate nor feasible to transplant very small children in the adult unit and this was the stimulus for commencing renal transplants at RBHSC.

(22) Identify any 'Protocols' and/or 'Guidelines' which governed Adam's renal transplant surgery

The Protocols and Guidelines which governed Adam's renal transplant surgery have been provided in Appendices 3, 4 & 5. The protocol in Appendix 3 is the RBHSC Protocol at that time. The protocols in Appendices 4&5 were available for consultation.

(23) Identify and describe any standards or guidelines governing dialysis that were operating at the time of Adam's dialysis on 26th November 1995 and those currently in operation

I have been unable to locate dialysis guidelines from 1995. The standards and guidelines governing dialysis are provided in Appendix 6.

(24) Identify precisely on Adam's medical notes and records the entries that you made or which

were made on your direction and state below:

(a) When each of the identified entries was made

As the single Consultant with overall responsibility for Adam Strain's medical treatment and management during the five years of his life, all the medical record entries made in his notes during hospital admissions and at out-patient visits were made either by me or under my direction by one of my junior colleagues. The exceptions to this will be entries made by members of the surgical team, bearing in mind that he had 20 operations, and which are listed in a separate document provided by the Belfast Trust. There are therefore many hundred entries spread across 10 sets of clinical notes.

(b) The source of the information recorded in the entry

See (24 a) above

(25) Provide any further points and comments that you wish to make, together with any documents, in relation to:

(a) The care and treatment of Adam from his admission for the renal transplant surgery on 26th November 1995 to his death on 28th November 1995

(b) Record keeping

(c) Communications with Adam's family about his care and treatment in respect of the renal transplant surgery

(d) Lessons learned from Adam's death and how that has affected your practice

(e) Current 'protocols' and procedures

(f) Any other relevant matter

Adam had episodes of hyponatraemia prior to the events of 25-27 November 1995. These developed and were resolved relatively slowly, usually by receiving oral tube feeds with added sodium supplements. On such occasions he was asymptomatic and came to no harm.

Neurological complications of hyponatraemia generally occur when this develops acutely during intravenous fluid treatment and when the serum sodium falls quickly and to an extremely low level (Friedman and Ray, Pediatric Nephrology (2008) 23: 677-680).

The standard and accepted maintenance of intravenous fluid for children in 1990-1995 and for a long time subsequently, was N/5 (0.18%) saline in dextrose (Kannan et al, Pediatric Nephrology (2010) 25: 2303-2309).

The paper published by Arieff (British Medical Journal (1992), 304, 1218-1222) alerting the medical profession to the possibility of hyponatraemia and death in healthy children receiving hypotonic intravenous fluids perioperatively, eventually stimulated a reconsideration of IV fluid management recommendations in children, which were developed 40 years before (Holliday and Segar (1957) Pediatrics, 18, 823-832). None of the children in this paper had renal disease.

Some children can only produce dilute urine because of renal disease including renal dysplasia; most such children will maintain a normal plasma sodium on N/5 (0.18%) saline in dextrose (Coulthard, Archives of Disease in Childhood 2008: 93:335-340, pp 336). Adam was born with dysplastic obstructive kidneys, and like many of today's hospitalised patients, was complex.

Even with the developments since Adam's case, these patients remain extremely difficult to manage and fatalities still occur even in the best Centres (Cansick et al, Pediatric Nephrology (2009) 24:1231-1234).

Debate and discussion around the best intravenous fluids for managing children, including clinical trial studies (Kannan et al, Pediatric Nephrology (2010) 25:2303-2309) continues. The intense debate resulted in the discontinuation of the use of hypotonic solutions such as N/5 (0.18%) saline in dextrose in Northern Ireland, the UK and further afield (National Patient Safety Agency Alert, NHS 2007).

The renal team at the Royal Belfast Hospital for Sick Children uses only normal saline for intravenous replacement of fluid deficit and N/2 saline in 2.5% dextrose for maintenance therapy. We relate IV fluid choice to accurate fluid loss and urine electrolyte measurement. The choice, volume and rate of fluid replacement is individually tailored using both scientific and clinical judgment. We monitor the speed of change in serum sodium and electrolyte levels frequently, as we have recognized this is as important a factor as the choice of fluid. Such frequent measures are adopted both in the perioperative period and during transplant surgery.

Adam Strain's death had a devastating effect on his mother Debra and her parents. When I explained to her that Adam would not survive, she asked even in the midst of her distress about the possibility of organ donation. She had always been concerned that another child should not be lost in similar circumstances.

Adam's death had a profound effect on me and the team who had looked after him in the Children's Hospital in Belfast. The lessons gained from reviewing Adam's care have now been incorporated into our management of other children with renal failure.

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

Signed: Maurice Savage Dated: 14/4/11

APPENDIX 1

Nutrison Paediatric Standard

Gemiddeld gehalte per 100 ml:

Energie	**420 kJ/100 kcal**	
Eiwit (11 En%)	**2,8**	**g**
– caseïne	2,8	g
Koolhydraten (49 En%)	**12,2**	**g**
– glucose	0,2	g
– lactose	< 0,01	g
– maltose	0,7	g
– polysacchariden	11,1	g
– overige	0,1	g
Vet (40 En%)	**4,5**	**g**
– verzadigd vet	0,3	g
– enkelv. onverz. vet	2,7	g
– meerv. onverz. vet	1,4	g
(linolzuur	1,16	g)
(α-linoleenzuur	0,23	g)
Mineralen:		
– Na	53	mg
– K	93	mg
– Cl	93	mg
– Ca	50	mg
– P	39	mg
– Mg	11	mg
Spoorelementen:		
– Fe	0,73	mg
– Zn	0,60	mg
– Cu	0,09	mg
– Mn	0,13	mg
– F	0,12	mg
– Mo	3,3	µg
– Se	2,3	µg
– Cr	1,9	µg
– I	8,7	µg
Vitamines:		
– vit. A	47	µg RE
– vit. D	0,83	µg
– vit. E	0,60	mg α-TE
– vit. K	1,3	µg
– thiamine	0,07	mg
– riboflavine	0,09	mg
– niacine	1,1	mg NE
– pantotheenzuur	0,33	mg
– vit. B6	0,09	mg
– foliumzuur	11	µg
– vit. B12	0,17	µg
– biotine	4,2	µg
– vit. C	4,0	mg
Overige:		
– carnitine	2,0	mg
– choline	10	mg
Osmolariteit	210 mOsmol/l	
N:(niet-eiwit)energie ratio	1:210	

Omschrijving:

Nutrison Paediatric Standard is een volledige kindersondevoeding op melkeiwitbasis (1 kcal/4,2 kJ per ml) en is lactose-arm en residu-arm. Deze sondevoeding is speciaal aangepast aan de voedingsbehoefte van kinderen van 1 tot 10 jaar.

Ingrediënten:

Water, dextrine-maltose, plantaardige vetten, caseïnaten, mineralen, emulgator (soja-lecithine (E322)), vitamines, spoorelementen.

Indikatie:

Kinderen tussen 1 en 10 jaar die niet (of niet voldoende) kunnen, mogen of willen eten en drinken.

Bereiding:

Zie pag. 15.

Gebruik:

Te gebruiken op advies van arts of diëtist.
De hoeveelheid sondevoeding is afhankelijk van geslacht, leeftijd, lengte, gewicht en ziektebeeld van het kind.

Houdbaarheid en bewaaradvies:

Zie pag. 15.

Verpakking en kodenummer:

Glazen flessen:
Fles à 200 ml.
Tray à 12 flessen.
Kodenummer 03209.

Nutrison Paediatric Energy

Gemiddeld gehalte per 100 ml:

Energie	**630 kJ/150 kcal**	
Eiwit (9 En%)	**3,4**	**g**
– caseïne	3,4	g
Koolhydraten (50 En%)	**18,8**	**g**
– glucose	0,4	g
– lactose	< 0,01	g
– maltose	1,1	g
– polysacchariden	17,1	g
– overige	0,2	g
Vet (41 En%)	**6,8**	**g**
– verzadigd vet	0,5	g
– enkelv. onverz. vet	4,2	g
– meerv. onverz. vet	2,1	g
(linolzuur	1,76	g)
(α-linoleenzuur	0,35	g)
Mineralen:		
– Na	80	mg
– K	140	mg
– Cl	140	mg
– Ca	75	mg
– P	58	mg
– Mg	16	mg
Spoorelementen:		
– Fe	1,1	mg
– Zn	0,90	mg
– Cu	0,13	mg
– Mn	0,20	mg
– F	0,18	mg
– Mo	5,0	µg
– Se	3,5	µg
– Cr	2,9	µg
– I	13	µg
Vitamines:		
– vit. A	70	µg RE
– vit. D	1,3	µg
– vit. E	0,90	mg α-TE
– vit. K	2,0	µg
– thiamine	0,10	mg
– riboflavine	0,13	mg
– niacine	1,6	mg NE
– pantotheenzuur	0,50	mg
– vit. B6	0,13	mg
– foliumzuur	16	µg
– vit. B12	0,25	µg
– biotine	6,3	µg
– vit. C	6,0	mg
Overige:		
– carnitine	3,0	mg
– choline	15	mg
Osmolariteit	290 mOsmol/l	
N:(niet-eiwit)energie ratio	1:256	

Omschrijving:

Nutrison Paediatric Energy is een volledige geconcentreerde kindersondevoeding op melkeiwitbasis (1,5 kcal/6,3 kJ per ml) en is lactose-arm en residu-arm. Deze sondevoeding is speciaal aangepast aan de voedingsbehoefte van kinderen van 1 tot 10 jaar.

Ingrediënten:

Water, dextrine-maltose, plantaardige vetten, caseïnaten, mineralen, emulgator (soja-lecithine (E322)), vitamines, spoorelementen.

Indikatie:

Kinderen tussen 1 en 10 jaar die niet (of niet voldoende) kunnen, mogen of willen eten en drinken.

Bereiding:

Zie pag. 15.

Gebruik:

Te gebruiken op advies van arts of diëtist.
De hoeveelheid sondevoeding is afhankelijk van geslacht, leeftijd, lengte, gewicht en ziektebeeld van het kind.

Houdbaarheid en bewaaradvies:

Zie pag. 15.

Verpakking en kodenummer:

Glazen flessen:
Fles à 500 ml.
Tray à 12 flessen.
Kodenummer 03213.

ORAL REHYDRATION SALTS (ORS) (*continued*)

Child 1–12 years 200 mL after every loose motion

Child 12–18 years 200–400 mL after every loose motion

UK formulations

Note After reconstitution any unused solution should be discarded no later than 1 hour after preparation unless stored in a refrigerator when it may be kept for up to 24 hours.

Dioralyte® (Sanofi-Aventis)
Oral powder, sodium chloride 470 mg, potassium chloride 300 mg, disodium hydrogen citrate 530 mg, glucose 3.56 g/sachet, net price 6-sachet pack = £2.11, 20-sachet pack (black currant- or citrus-flavoured or natural) = £6.99

Note Reconstitute 1 sachet with 200 mL of water (freshly boiled and cooled for infants); 5 sachets reconstituted with 1 litre of water provide Na^+ 60 mmol, K^+ 20 mmol, Cl^- 60 mmol, citrate 10 mmol, and glucose 90 mmol

Dioralyte® Relief (Sanofi-Aventis)
Oral powder, sodium chloride 350 mg, potassium chloride 300 mg, sodium citrate 580 mg, cooked rice powder 6 g/sachet, net price 6-sachet pack (apricot-, black currant- or raspberry-flavoured) = £2.35, 20-sachet pack (apricot-flavoured) = £7.42

Note Reconstitute 1 sachet with 200 mL of water (freshly boiled and cooled for infants); 5 sachets when reconstituted with 1 litre of water provide Na^+ 60 mmol, K^+ 20 mmol, Cl^- 50 mmol and citrate 10 mmol; contains aspartame (section 9.4.1)

Electrolade® (Actavis)
Oral powder, sodium chloride 236 mg, potassium chloride 300 mg, sodium bicarbonate 500 mg, anhydrous glucose 4 g/sachet (banana-, blackcurrant-, lemon and lime-, or orange-flavoured). Net price 6-sachet (plain or multiflavoured) pack = £1.33, 20-sachet (single- or multiflavoured) pack = £4.99

Note Reconstitute 1 sachet with 200 mL of water (freshly boiled and cooled for infants); 5 sachets when reconstituted with 1 litre of water provide Na^+ 50 mmol; K^+ 20 mmol, Cl^- 40 mmol, HCO_3^- 30 mmol, and glucose 111 mmol

WHO formulation

Oral Rehydration Salts (Non-proprietary)
Oral powder, sodium chloride 2.6 g, potassium chloride 1.5 g, sodium citrate 2.9 g, anhydrous glucose 13.5 g. To be dissolved in sufficient water to produce 1 litre (providing Na^+ 75 mmol, K^+ 20 mmol, Cl^- 65 mmol, citrate, 10 mmol, glucose 75 mmol/litre)

Note Recommended by the WHO and the United Nations Children's Fund but not commonly used in the UK

9.2.1.3 Oral bicarbonate

Sodium bicarbonate is given by mouth for *chronic acidotic states* such as uraemic acidosis or renal tubular acidosis. The dose for correction of metabolic acidosis is not predictable and the response must be assessed. For *severe metabolic acidosis* sodium bicarbonate can be given intravenously (section 9.2.2).

Sodium supplements may increase blood pressure or cause fluid retention and pulmonary oedema in those at risk; hypokalaemia may be exacerbated.

Sodium bicarbonate may affect the stability or absorption of other drugs if administered at the same time. If possible, allow 1–2 hours before administering other drugs orally.

Where *hyperchloraemic acidosis* is associated with potassium deficiency, as in some renal tubular and gastro-intestinal disorders it may be appropriate to give oral potassium bicarbonate, although acute or severe deficiency should be managed by intravenous therapy.

SODIUM BICARBONATE

Cautions see notes above; avoid in respiratory acidosis; **Interactions:** Appendix 1 (antacids)

Indication and dose

Renal acidosis (see also notes above)

By mouth

Child 1 month–18 years initially 1–2 mmol/kg daily in divided doses, adjusted according to response

Renal hyperkalaemia section 9.2.2.1

Sodium Bicarbonate (Non-proprietary)
Capsules, sodium bicarbonate 500 mg (approx. 6 mmol each of Na^+ and HCO_3^-), net price 56-cap pack = £13.07

Tablets, sodium bicarbonate 600 mg, net price 100 tabs = £2.48

Important Oral solutions of sodium bicarbonate are required occasionally; these need to be obtained from 'special-order' manufacturers or specialist importing companies, see p. 943, and the strength of sodium bicarbonate should be stated on the prescription

POTASSIUM BICARBONATE

Cautions cardiac disease; **Interactions:** Appendix 1 (potassium salts)

Renal impairment close monitoring required—high risk of hyperkalaemia; avoid in severe impairment

Contra-indications hypochloraemia; plasma-potassium concentration above 5 mmol/litre

Side-effects nausea and vomiting

Potassium Tablets, Effervescent (Non-proprietary)
Effervescent tablets, potassium bicarbonate 500 mg, potassium acid tartrate 300 mg, each tablet providing 6.5 mmol of K^+. To be dissolved in water before administration. Net price 56 = £28.20. Label: 13, 21

Note These tablets do not contain chloride; for effervescent tablets containing potassium and chloride, see under Potassium Chloride, section 9.2.1.1

9.2.2 Parenteral preparations for fluid and electrolyte imbalance

9.2.2.1 Electrolytes and water

Solutions of electrolytes are given intravenously, to meet normal fluid and electrolyte requirements or to replenish substantial deficits or continuing losses when it is not possible or desirable to use the oral route. When intravenous administration is not possible, fluid (as sodium chloride 0.9% or glucose 5%) can also be given subcutaneously by hypodermoclysis.

In an individual patient the nature and severity of the electrolyte imbalance must be assessed from the history and clinical and biochemical examination. Sodium, potassium, chloride, magnesium, phosphate, and water depletion can occur singly and in combination with or without disturbances of acid-base balance; for reference to the use of magnesium and phosphates, see section 9.5.

Isotonic solutions may be infused safely into a peripheral vein. Solutions more concentrated than plasma, for example 15% glucose, are best given through an indwelling catheter positioned in a large vein.

Maintenance fluid requirements in children are usually derived from the relationship that exists between body-weight and metabolic rate; the figures in the table below may be used as a guide outside the neonatal period. The glucose requirement is that needed to minimise gluconeogenesis from amino acids obtained as substrate from muscle breakdown. Maintenance fluids are intended only to provide hydration for a short period until enteral or parenteral nutrition can be established.

It is usual to meet these requirements by using a standard solution of sodium chloride and glucose. Solutions containing 20 mmol/litre of potassium chloride meet usual potassium requirements when given in the suggested volumes; adjustments may be needed if there is an inability to excrete fluids or electrolytes, excessive renal loss or continuing extra-renal losses. The exact requirements depend upon the nature of the clinical situation and types of losses incurred; see Caution on dilutional hyponatraemia below.

Fluid requirements for children over 1 month:

Body-weight	24-hour fluid requirement
Under 10 kg	100 mL/kg
10–20 kg	100 mL/kg for the first 10 kg + 50 mL/kg for each 1 kg body-weight over 10 kg
Over 20 kg	100 mL/kg for the first 10 kg + 50 mL/kg for each 1 kg body-weight between 10–20 kg + 20 mL/kg for each 1 kg body-weight over 20 kg (max. 2 litres in females, 2.5 litres in males)

Important The baseline fluid requirements shown in the table above should be adjusted to take account of

APPENDIX 2

RBHSC RENAL TRANSPLANT GUIDELINES

UKT will phone the on-call Consultant Nephrologist with kidney offer (call will go to Barbour Ward - 028 90636621 or 028 90633398).

Consultant will ring parents (phone nos in dialysis room red box).
Recipient co-ordinators available office hrs - office 028 90263846, bleep 07623 652169 via BCH switch. (Dolores Elliot, Sharon McCarron, Pamela Stronge).

Kidney will arrive to Ward 11T (Transplant) Belfast City Hospital (028 90263652). Transport organised via UKT and BCH Transplant Ward (Consultant may need to liaise).

CHECK LIST ON ADMISSION

A) HISTORY

Wt = Ht =

BSA (see nomogram) =

Pre transplant urine output mls / 24hours

Pre transplant fluid allowance mls / 24hours

Underlying diagnosis
Urological problems
Bladder Function
Recent contact with infectious diseases
When last dialysed
Vaccination history
CMV status donor/recipient
Cytotoxic antibody status
Tube feeds - what and how much
What central line sites used previously
List drugs (consultant will probably stop anti-hypertensives and non essential drugs such as Alfacalcidol and phosphate binders)

B) EXAMINATION

Clinical examination to establish fit for surgery
State of nutrition
State of hydration
BP
Catheter exit site appearance

C) **INVESTIGATIONS** (insert peripheral cannula at same time)

Clotted sample - 5ml by Hospital transport 7111-6402 (come to dialysis room at back of Barbour Ward) to Ward 11T (Transplant), BCH for tissue typing X-match (tissue type lab 028 90263846 or via BCH switchboard 028 90329241).

FBP, DWCC, coagulation screen
U/E, creatinine, Ca, albumin
Group and X-match 4 units CMV -ve blood
Virology for up to date CMV and EBV (IgG). Check notes for other virology
Skin swabs -nasal, perineum or groin, exit sites e.g. gastrostomy or dialysis line (for LRD should already be performed-check result. May need decolonisation)
PD fluid and urine for culture
Urine for U and E
CXR
ECG if on anti-hypertensives

PLAN:-

1. Fast and consent
2. Shower
3. Dialysis if k+>5 mmol/L
4. Fluid management to be determined by Consultant Nephrologist
5. If prolonged fast - maintenance IV fluids (give insensible losses (= 300 ml/m^2/day) and output usually as 2.5% dextrose 0.45% sodium chloride solution
   D/W consultant if Na < 133. Repeat U/E at time of going to Theatre
6. CHECK CMV Ig G STATUS and order Valganciclovir if indicated (for post-op use).

DONOR	RECIPIENT	ACTION
positive	negative	valganciclovir
positive	positive	valganciclovir
negative	positive	valganciclovir
negative	negative	No treatment

Valganciclovir should be taken with food. The dose is calculated as below (Vaudry et al, 2009). The dose should be administered orally once daily and therapy should begin within 10 days of transplantation and continue until day 100 post-transplantation.
Formulation: 250 mg in 5 mls, 450 mg tablets.

Dose (mg) = 7 x BSA x GFR (Schwartz formula) - Maximum dose 900mg daily.

GFR = Height (cms) x40 / creatinine.

IMMUNOSUPPRESSION PRE OP

1. TACROLIMUS

0.15 mg/kg as a single oral dose 1-4 hrs pre-operatively.
For LRD dose 20.00 hrs night before and 08.00 on day of transplant.

2. MYCOPHENOLATE MOFETIL (MMF)

day 1 - 14	**600 mg/m^2** twice daily orally or iv (max adult dose 1000 mg twice daily)
after day 15	**300 mg/m^2** twice daily orally

Single oral dose 1-4 hrs pre-operatively. For LRD dose 20.00 hrs and 08.00.

3. BASILIXIMAB

2nd TRANSPLANTS, THOSE AT HIGH RISK OF REJECTION OR BARDET-BIEDL SYNDROME PATIENTS MAY RECIEVE ON CONSULTANT DECISION BASILIXIMAB

Basiliximab (Simulect)

Dose: patients will be given two infusions of Basiliximab.
< 35kg: 10mg infused on Day 0 within 2 hours prior to surgery and on Day 4 after transplantation
> 35kg: 20mg infused on Day 0 within 2 hours prior to surgery and on Day 4 after transplantation

Reconstitution & Administration
Simulect is provided as a vial containing 20mg Basiliximab powder + ampoule of water for injections.
Add 5ml water for injection to the vial containing 20mg Basiliximab powder.
Shake the vial gently to dissolve the powder. After reconstitution the solution should be used immediately (at least within 24hours if stored in a refrigerator).
The reconstituted solution is isotonic and must be further diluted:
10mg dose must be diluted to at least 25 mls (20mg to at least 50 mls) with sodium chloride 0.9% or glucose 5%, infuse over 20-30minutes.

IN THEATRE

Assess hydration, check electrolytes and ABG x 2 hourly
IV Co-Amoxiclav 30 mg/kg on induction
S/C Heparin with Surgeons consent after induction

- Tinzaparin (Innohep®) 50 I.U. s/c per kg post vascular anastamosis, and 24hrly.
- Multidose vial 10,000 I.U. per ml -2 people to check dose.

Triple lumen CVP catheter
IA line in small children
Start Dopamine 2 - 3 µg/kg/min
Use N saline, 4.5% albumin or blood (as appropriate) to raise CVP to 8-12 mmHg prior to removal of vascular clamps.
Blood Transfusion can result in sensitisation, therefore **transfuse only if actively bleeding or Hb <8 g/dl.**
Use CMV negative blood.

10 - 15 MINS PRIOR TO RELEASE OF CLAMPS

- 0.5 g/kg (2.5 ml/kg) 20% Mannitol
  (alternative 4 mg/kg Frusemide)

- 10 mg/kg Methylprednisolone (max 500 mg)

POST-OPERATIVE

1. FLUIDS

Replace urine output and insensible losses (300 ml/m^2/day) EACH HOUR as 0.45% saline 2.5% dextrose (subtract volume of infusions).

Anticipate hypovolaemia (low peripheral temp., low CVP, tachycardia, low BP).

Boluses of N saline or 4.5 % albumin (5 - 10 ml/kg) over 20 mins to maintain CVP and BP.

2. OBSERVATIONS

a. CVP between 8 - 10 mmHg

b. BP decided on individual basis

c. Optimal urine output to be decided on an individual basis
In polyuric patients this will be around 4 ml/kg/hr initially falling to 2 ml/kg/hr when stable. In previously anuric patients far lower outputs may be acceptable if ATN has occurred. Check transplant troubleshooter for management guidelines on output and BP.

3. DRUGS POST OP

a. TACROLIMUS (Prograf®)

0.3 mg/kg divided into 2 doses (0.15 mg/Kg each) to be given orally and started within 24 hours of transplant.
I/V tacrolimus dose is 1/5 of total oral dose i.e. 0.06mg/kg/day given as continuous infusion over 24 hours in N saline or 5% Dextrose via non PVC giving set or syringe and tubing and change daily.
Infusion concentration in range 0.004 - 0.1 mg/ml

Capsules sizes available 0.5 mg 1 mg 5 mg
Suspension available as non-licensed special of 5.0mg in 5mls

b. METHYLPREDNISOLONE

60mg/m^2/day as bd dose for first 5 days and then reduce (see separate sheet).

c. MYCOPHENOLATE MOFETIL (MMF or Cellcept).

day 1 - 14	**600 mg/m^2** twice daily orally or iv (max adult dose 1000 mg twice daily)
after day 15	**300 mg/m^2** twice daily orally

Side effects (mostly diarrhoea) could be lessened by dividing the same daily dose in to 3 or 4 doses.
Give same iv/oral dose.
Dose reductions will be needed if low WBC, PLT or haemoglobin.
Available in liquid 1000 mg/5mls, 250 mg capsules or 500mg tablets

d. DOPAMINE - 2 -3 µg/kg/min

e. RANITIDINE 1 mg/kg/bd IV oral 2 mg/kg bd (until minimum steroid dose achieved) 150 mg tablets or syrup 75mg in 5 mls).

f. CO-TRIMOXAZOLE as pneumocystis prophylaxis.120-480 mg (450mg/ m^2orally) Mon, Wed, Fri bd for 3 - 6 months

g. TINZAPARIN (Innohep®) 50 I.U per kg given sub cut following vascular anastamosis, and then 24hrly for 1 week or until fully ambulant.
Multidose vial contains 10,000 I.U. per ml -2 people to check dose.
In children < 20 kg consider following this with Aspirin 37.5 mg once daily for 6 months.

h. VALGANCICLOVIR if CMV +ve donor or recipient (see above).

i. ANALGESIA

Epidural OR Morphine 10 - 20 µg/kg/hr infusion (half BW (kg) in mg in 50 ml at 1 - 2ml/hr)

3. DRUGS POST OP

a. TACROLIMUS (Prograf®)

0.3 mg/kg divided into 2 doses (0.15 mg/Kg each) to be given orally and started within 24 hours of transplant.
I/V tacrolimus dose is 1/5 of total oral dose i.e. 0.06mg/kg/day given as continuous infusion over 24 hours in N saline or 5% Dextrose via non PVC giving set or syringe and tubing and change daily.
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i. ANALGESIA

Epidural OR Morphine 10 - 20 µg/kg/hr infusion (half BW (kg) in mg in 50 ml at 1 - 2ml/hr)

TRANSPLANT TROUBLESHOOTER

The following is a guide to what measures need to be taken when vital signs fall outside the pr values.

	TEMP GAP	CVP	BP	
1	↑	↓	↓	**Consider Volume**
2	↑/N	↑/N	↑	**Consider Vasodilator**
3	↑/N	↑/N	↓	**Consider Dobutamine**

Volume:

5-10 mls/kg/stat N saline or 5% albumin (max bolus of 500 mls) & reassess.

- **Extreme caution where patient is 0_2 dependent - may indicate evolving Pulmonary oedema**

Vasodilators:

Hydralazine: 0.2 to 1.0 mg/kg/IV stat then hourly infusion at same dose. Nicardipine: 0.5-2□g/kg/h more potent vasodilator than hydralazine.

Dobutamine:

10-20 ug/kg/min for hypotension/low cardiac output

INVESTIGATIONS

1. U/E, creatinine, glucose, Ca x 6 hourly for 48 hours
   x 12 hourly next 48 hours
   x daily, thereafter if situation is stable
2. Doppler renal USS post-op and repeat daily
3. FBP, DWCC, (and CD3 count if on ATG) daily.
4. Chest X-ray initially for CVP line position and daily for 2 -3 days.
5. Urine - culture, U/E and creatinine daily.
6. Twice daily weight.
7. Tacrolimus levels analysed daily Mon-Fri (BCH). When on oral drugs send daily for 10 days and thereafter Tue and Fri.
8. CMV AND EBV PCR (EDTA purple top to virology) Mondays from Day 14.
9. Tissue type bloods at 2,4,6,8 weeks -8mls (red top clotted to BCH tissue type lab).
10. DMSA scan at 1 month.

IMMUNOSUPPRESSION POST TRANSPLANT

1. STEROIDS

Day 1-5 Methylprednisolone 60 mg/m^2/day as bd dosage x 5 days (may be changed to same dose oral Prednisolone as soon as tolerated)

Day 6 Prednisolone 30 mg/m^2/day as 2 divided doses

Day 14 Prednisolone 20 mg/m^2/day as 2 divided doses

Day 21 Prednisolone 10 mg/m^2/day as 2 divided doses

Week 4-8 Prednisolone 10 mg/m^2 DAILY as one dose

Week 8-12 Prednisolone 5 mg /m^2 DAILY

Week 12+ Prednisolone 10 mg/m^2 alternate days

2. MYCOPHENOLATE MOFETIL (MMF)

day 1 - 14	**600 mg/m^2** twice daily orally or iv (max adult dose 1000 mg twice daily)
after day 15	**300 mg/m^2** twice daily orally

3. TACROLIMUS

0.3 mg/kg divided into 2 doses (each of 0.15mg/Kg) to be given orally and started within 24 hours of transplant. Observe precautions of using non PVC giving sets and syringes and flushing N/G and G tubes with water after administration:

Levels Initial target range 10 - 15 ng/ml. After six months range 5-10 ng/ml

FOLLOW UP

After discharge	- alternate days x 1 week
Until week 6	- twice weekly
Week 6 - 10	- weekly
Week 10 - 12	- fortnightly
> 3 months	- monthly
> 1 year	- 6 - 8 weekly

NB See within 4 days of any DOSE CHANGES

REJECTION

ASSESSMENT OF REJECTION

> 10% rise in serum creatinine is a significant change. It could be due to:-

1. Laboratory error.
2. Rejection
3. Tacrolimus toxicity
4. Other drug toxicity
5. Infection (especially UTI)
6. Obstruction - exclude with renal USS/MAG 3 renogram.

All such rises in creatinine should be reported to the consultant and repeated **immediately.** If a 10% rise is confirmed and rejection suspected then initial treatment would be:

Methylprednisolone 15 mg/kg/IV for 3 days (maximum 500 mg)

This should only be prescribed after discussion with Consultant.

Other causes of a rise in creatinine should be excluded and diagnosis confirmed whenever possible with a renal biopsy (need coagulation screen and Group and Hold, inform Path technician x 32534).

For patients who have received renal transplant > 1 month previously, oral Prednisolone 3 mg/kg/day is given for 3 days (maximum 150 mg).

ANTI-THYMOCYTE GLOBULIN (MERIEUX-RABBIT)

Given for steroid resistant rejection or as prophylaxis when recipient > 75% cytotoxic antibodies or second transplant when first graft lost early with rejection

Test dose: 0.1 ml (0.5 mg) in 10 ml N. Saline over 1 hour via central line

Therapeutic dose ATG

< 30 kg - 2.5 mg/kg/day

>30 kg - 1.25 - 2.5 mg/kg/day

Diluted in 100 ml saline central line over 8 hours. Chills, fevers and arthralgia common.

ANAPHYLAXIS treated with:

Hydrocortisone 100 mg IV
Chlorpheniramine 5 - 10 mg IV

Adrenaline (0.01 ml/kg of 1 in 1000, 1 m)

Prior to therapeutic dose give Chlorpheniramine IV and Hydrocortisone IV

ATG Monitoring

Aim absolute lymphocyte count 200 - 400 (omit if < 200).

CD3 count daily

(send 0.5 ml EDTA blood to RVH immunology, arrange with X 32689, ask for lymphocyte markers profile 1 which includes CD3)

Aim level 100 - 300 (omit if < 100).

Updated February 2011 Drs McKeever and O'Connor and Professor Savage

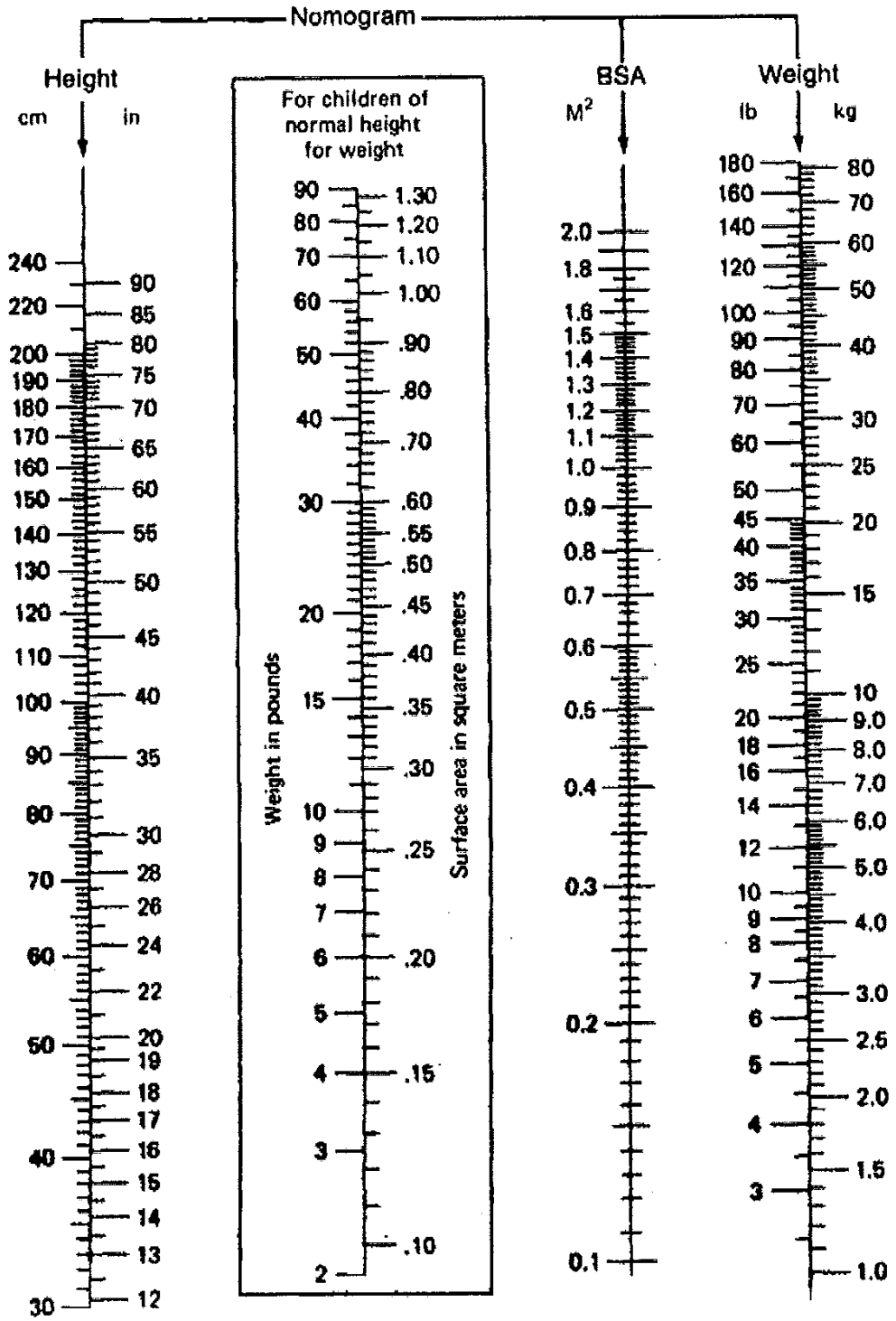

Figure 3–1. West Nomogram (for Estimation of BSA). The BSA is indicated where a straight line connecting the height and weight intersects the BSA column or, if the patient is roughly of normal proportion, from the weight alone (enclosed area). (Nomogram modified from data of E. Boyd by C. D. West; from Vaughan, V. C., and R. J. McKay, eds., *Nelson Textbook of Pediatrics*, 12th ed., Philadelphia: Saunders, 1983.)

NURSING PRE-TRANSPLANT CHECK LIST

NAME:

Height	
Weight	
BP	
MSU and urine U/E sent	
Skin swabs and Shower	
PD sample for microscopy , DWCC and culture	
Drain PD fluid	

Drug	**Given**	**Time**
Tacrolimus		
Mycophenolate Mofetil		
Basiliximab		

Does Valganciclovir need ordered according to CMV status?

Have immunosuppressive drugs and Innohep® heparin been labelled for transfer to ICU?

THEATRE CHECK LIST FOR TRANSPLANT PATIENT

NAME:

Height	
Weight	
SA	

	Donor	**Recipient**
CMV status		
EBV status		
Blood Group		

Pre theatre bloods - record time most recent serum electrolytes taken = _____

Na	Hb	PT	Urine Na
K	WCC	PTTK	
Urea	Plats		
Creat		Is blood available in theatre ?	Usual 24 hr urine output =
Ca			
Albumin			

Drugs in ward pre-transplant	**Dose**	**Given**	**Time**
Tacrolimus			
Mycophenolate Mofetil			
Basiliximab			

Prescribe drugs for use in theatre

Co-amoxiclav (on induction) (30mg/kg, max 1.2g)	
Methylprednisolone (10mg/kg, max 500mg)	
Mannitol 20% (0.5 g/kg = 2.5ml/kg)	
Heparin Tinzaparin (Innohep®) 50 I.U./kg.	

APPENDIX 3

RENAL TRANSPLANT PROTOCOL

RBHSC

1990-1995

Renal Transplantation in small children

ADMISSION PROTOCOL

History on Admission

Note
residual renal function + urine output
recent infections UTI peritonitis etc.
recent contact with infectious diseases
type of dialysis
drug therapy - inform anaesthetist of anti-hypertensives
check transplant/on call list

Examination on Admission

Note
state of nutrition and hydration
blood pressure
height and weight
catheter exit site condition

Investigations on Admission

10 mls clotted blood to BCH Typing Lab.
Group and cross match 4 units blood
FBP WCC platelet count
MSU
CXR
CAPD fluid culture
U + E and total protein
10 mls for virology

Obtain written consent from parents

Arrange haemodialysis if indicated
Assess degree of fluid restriction caused by pre-op fasting
Ensure parents have transplant booklet
Contact Transplant Surgeon, Paediatric Surgeon, Anaesthetist, Theatre, ICU

INTRA-OPERATIVE FLUIDS

CAPD patients may be relatively hypovolaemic and hypo-albuminaemic. Blood, PPF or N/2 Saline may be required before unclamping the artery to ensure a good intravascular volume. This is determined by reference to BP and CVP levels.

enal Transplantation in Small Children

IMMUNOSUPPRESSION

Intra-operative

Hydrocortisone 5 mg/kg i/v Stat.
Azothioprine 5 mg/kg i/v Stat. if wcc >4000

Post-operative

STEROID

1. First 24 hours hydrocortisone 5 mg/kg i/v QDS.

2. Daily subsequently for 5 days

Prednisolone 1 mg/kg orally or equivalent dose hydrocortisone (4 mg/kg) i/v in 2 divided doses

3. Then Prednisolone 0.5 mg/kg/day in a single morning dose for 1/12

4. Then 1 mg/kg alternate days tapering.

AZOTHIOPRINE

1. Daily 1.5 mg/kg/day until GFR 1/3rd normal for age then increase to 3 mg/kg/day if wcc >4000.

CYCLOSPORIN A

To be introduced once graft function is stable.

Renal Transplantation in Small Children

POST-OPERATIVE MANAGEMENT

After transplantation patient will return initially to ICU

Lines required
(i) arterial line for BP
(ii) Multiple lumen central venous line for CVP and i/v fluids
(iii) urinary catheter

ANALGESIA Morphine infusion 10÷20 micrograms/kg/hr

Fluids

Arterial line - 0.9% saline with 1 unit/ml heparin running at 1 ml/hr

CVP
(a) 0.18% saline 4% dextrose (n/5 saline) with 1 unit/ml heparin
(b) morphine infusion PRN 0.025 mg/kg/hr in N/5 saline at 1 ml/hr volume
(c) n/2 or N/5 saline to replace insensible loss + output.

Rate of fluid input is set to maintain

(i) CVP at 4-8 cm H_2O
(ii) BP appropriate for size of child
(iii) urine output 2-4 mls/kg/hour
(iv) N/2 saline is usually required to maintain plasma Na

CVP	BP	Rx
↑ ↓		
N or ↓	↓ or N	Volume expansion
N	↓	Dopamine infusion
↑	↑	Reduce i/v fluids ? hydrallazine or frusemide

URINE OUTPUT

If urine output is poor after correcting vital signs ? try one dose of Frusemide 2 mg/kg i/v stat.

If urine output falls in association with haematuria consider renal vein thrombosis.

Hypertension

Common in the immediate post-operative period and best managed i/v hydrallazine or labetalol.

Renal Transplantation in Small Children

Post-operative Investigations

(i) 4-6 hourly initially

blood gases

U + E, Ca^{++}

glucose

Hb

Urine output volume + dipstick testing for blood and urine

(ii) Daily

U + E Creatinine

24 hr urine collection of protein and creatinine clearance

Albumen + total protein

FBP DWCC Platelets

? coagulation

CXR

Fluid input/output

(iii) Twice weekly

MSU

24 hr urine for protein and creatinine clearance

DTPA ± Doppler USS of renal transplant vessels.

SMAC

M. Savage
September 1990

APPENDIX 4

RENAL TRANSPLANT PROTOCOL

BELFAST CITY HOSPITAL

1995

DO NOT REMOVE FROM WARD

[redacted]

Renal Transplantation Protocol Belfast City Hospital

Admission process for the potential renal transplant patient.

a. Laboratory Investigations

1. FBP with differential
2. Group and cross match 2 units packed cells
3. Coagulation screen
4. Biochemistry screen U&E, Creatinine, Bone profile, LFTs
5. Tissue typing samples (whether recent sample for cross matching is necessary is at the discretion of the consultant on call).

6. MSSU

b. ECG

c. Chest X-ray

d. Patient's weight

e. Intravenous line to be inserted in peripheral vein. Central line to be placed at the time of surgery by the anaesthetist.

f. The patient's CMV status to be recorded.

g. The donor's CMV status to be recorded.

h. ~~Patient's PRA titre to be recorded.~~

I. Immunosuppression Induction:

a. Standard Patient:

Preoperatively

1. Insert venflon and commence slow infusion of saline. (500mls)
   The giving set should have a biuret on-line.

2. Hydrocortisone 200 mg IV in 50ml of saline administered over a period of 5 minutes. Slowly

   Imuran.

3. Azathioprine 5mg/Kg IV in 50 ml of saline administered over a period of 5 minutes.

   250

→ fill Buret/c 50mls + add Hydrocortisone & infuse refill buret 50mls NaCl + add Imuran & infuse.

Run NaCl Slowly T.K.V.O. Pre-op.

4. Hydrocortisone 200mg IV to be administered 6 hours, 12 hours and 18 hours after the initial dose.

b. Highly Sensitized Patient:

Preoperatively

1. Follow standard protocol as above, steps 1 - 3.

2. Commence vasodilator Nifedipine Retard 20mg BD or equivalent calcium antagonist.

3. Allow at least one hour to elapse before commencing intravenous Cyclosporin. Total dose 3mg/Kg in two divided doses in the first 24 Hours. Each infusion should be of 6 hours duration. At the discretion of the consultant supervising the case, oral cyclosporine may be administered, in a dose of 8mg/Kg per day in divided doses, starting preoperatively. Nifedipine should be administered prior to the first dose.

II. Maintenance Immunosuppression

a. Post operatively

1. Standard Patient:

The routine immunosuppression for a standard patient is:

a. Prednisolone 20mg/day

b. Azathioprine 1.5mg/Kg if Creatinine clearance < 30ml/min
Increasing to:
Azathioprine 3.0mg/Kg if creatinine clearance > 30ml/min
If the WCC falls below 4.0 Azathioprine is withdrawn. It is reintroduced at reduced dosage when the WCC is greater than 4X 10^3again .

c. Cyclosporin is not introduced until the transplanted kidneyis functioning. Function is recognised by a rising urinary output and improving renal function tests. The standard introductory dose is 8mg/Kg in two divided oral doses. (The initial dose of Cya may be reduced at the discretion of the consultant in charge of the case.) The Cya level is adjusted to remain in the therapeutic range of 100 - 250ng/l.

N.B. It is the policy of the unit that Cya should not be started until the patient has commenced on a Calcium channel antagonist e.g.

Nifedipine Retard 20mg BD or equivalent. The calcium channel blocker should be administered roughly 12 hours prior to commencement of Cya.

2. Highly Sensitized Patient:

a. As described above the highly sensitized patient is commenced on Cya at the time of surgery.

b. Prednisolone and Azathioprine are administered as for the standard patient.

c. Cya is continued in low dosage - 5mg/Kg in two divided doses until graft function is established at which time the dose is increased to achieve therapeutic levels.

Intravenous Cyclosporin:

In general patients are given oral Cya. If the patient has an ileus or has malabsorption the drug may be administered intravenously. The bioavailability of the drug given intravenously is roughly three times that of orally administered drug. The intravenous dose of the drug is therefore one third that of oral dose.

III. Anti-rejection Therapy:

Clinically acute rejection is manifest by:

Deteriorating renal function
Swollen, painful graft
Pyrexia

Before initiating anti-rejection therapy it is essential that other conditions which may have similar signs and symptoms are excluded.

Then when acute rejection is believed to be present the standard treatment protocol is:

Prednisolone 200mg/day in divided doses for 3 days.
The dose is reduced by 50 mg per day at 3 day intervals.

200 D1
150 D4
100 D7

Whilst the standard protocol is as described above, the dosage schedule may be altered for example if the patient is of small stature or if there is evidence of osteoporosis, the dosage of prednisolone may be decreased at a faster rate e.g. in 2 day steps.

To definitively diagnose rejection it is necessary to perform a renal biopsy. The first course of anti-rejection therapy is frequently administered on the basis of a clinical diagnosis of rejection. The consultant in charge of the case may however elect to perform a biopsy prior to commencement of anti-rejection therapy. If there is a poor response to anti-rejection therapy or if a second course of anti-

rejection therapy is contemplated, a percutaneous biopsy would normally be performed.

An alternative anti-rejection regime involving intravenous the daily administration of intravenious Methyl prednisolone may be used at the discretion of the consultant in charge of the case.

Patients responding to steroid therapy usually do so rapidly indicated by improved renal function, decreased graft swelling and decreased temperature. If the patient fails to respond promptly to steroid or if there is evidence of recurrence of rejection soon after the discontinuation of antirejection therapy, if a biopsy has not previously been performed, it will be done at that time.

If steroid resistant rejection is confirmed then in the absence of a contraindication, Anti-thymocyte Globulin (ATG), will be introduced. ATG acts by selectively binding to T-lymphocytes, it is therefore intensely immunosuppressant and is not used if there is any suspician of infection.

ATG is administered by slow intravenous infusion (over a period of 12 hours). It is very irritant and should only be infused via a central vein. The drug dose is 1.5 - 2.5mg/Kg/day. Side effects associated with the administration of ATG include rigors and flushing. An antihistamine - e.g. Piriton should be given prior to administration. The drug frequently induces severe leucopaenia. Azathioprine is withdrawn while ATG is being administered. It is not normally given if the WCC is less than $4X10^3$. Infusions of ATG are administered on a daily basis for a total of 10 days. If the patient becomes leucopaenic, the dose is adjusted down appropriately to avoid leucopaenia.

4. Fluid Balance:

Early Post-operative Management

In the immediate postoperative period it is essential that monitoring of fluid balance begun in the operating room is continued. There is evidence that hypotension and hypovolaemia occurring in an ischaemic kidney may lead to more prolonged acute tubular necrosis on a vascular basis. It has therefore been our policy to monitor central venous pressure, blood pressure and urinary output intensively in the postoperative period to ensure optimum hydration and blood pressure.

A central venous catheter is inserted at the time of surgery and the CVP is maintained between 5 and 12 cm H_2O. Urinary output is measured hourly and fluid administered according to the CVP and the previous hour's urinary output. The standard regime is to administer the previous hour's output + 30ml if the CVP lies within the normal range. If the CVP is below 5cm H_2O the previous hour's output + 50ml (or sufficient to raise the CVP to within the normal range) is administered. If the CVP is greater than 12 cm H_2O then the previous hour's output is administered with no supplement. If the

patient has evidence of pulmonary oedema then fluid intake is decreased and if there is evidence of renal function a loop diuretic is administered.

The fluids administered are usually normal, 0.9% saline and 5% dextrose in roughly equal proportions, although if the patient has diabetes or severe acidosis this regime may be altered accordingly.

Hourly measurement of the urinary output and appropriate replacement with intravenous fluids is continued for 24 hours post operatively. At that time, if the patient has normal bowel sounds oral fluids may be administered. Urinary output is measured on a 12 hourly basis and fluids prescribed appropriately. Central venous pressure is monitored for a 24 hour period at that time, unless there is concern about the patient's haemodynamic status, the central line is withdrawn.

5. CMV Prophylaxis:

In many units it is policy not to transplant organs from CMV positive donors into CMV negative recipients because of the risk of overwhelming CMV infection particularly CMV pneumonitis. It has been our policy to accept CMV positive grafts for CMV negative recipients however we administer Acyclovir prophylactically to sero-negative recipients receiving sero-positive grafts for a period of one month post transplantation. The standard dosage is 800mg daily in a divided dose.

NB IF CMV STATUS OF DONOR UNKNOWN
— This should be treated AS +ve
AND PATIENT COMM. ON Acyclovir
Treatment AS above. (PP Dr. Doherty)
23/1/92.

APPENDIX 5

TRANSPLANT PROTOCOL FROM BRISTOL 1995

GUIDELINES FOR MANAGEMENT OF CHILDREN (IE ALL PATIENTS FROM JOHN MILTON/ VICTOR MEALE) UNDERGOING RENAL TRANSPLANTATION

UK Transplant or the transplant co-ordinator will phone with the offer of a kidney. Often the Consultant Paediatrician is consulted directly. If the call comes to a junior medical member of staff then it is important to talk to Dr McGrav, Dr Chambers, Dr Tizard or the Senior Registrar immediately as usually only half an hour is available to accept the kidney.

ONCE KIDNEY IS ACCEPTED

Inform transplant co-ordinator if he/she has not already been informed.

Other individuals to be informed are as follows. The transplant co-ordinator may do this although it is important for the member of the junior medical staff to establish exactly who is to make which phone calls.

i Phone UK Transplant and arrange for kidney to be sent to Bristol if harvested from elsewhere.

ii Phone the patient and arrange for them to arrive as soon as possible.

iii Check with tissue typing if a recent serum is available for cross-matching. If there is a very recent specimen and the patient has not been transfused since, this specimen may be used for the direct cross-match which may then commence as soon as the kidney arrives. If a fresh sample is needed from the patient it is vital to take this immediately he/she arrives as the cross-match takes eight hours and delay postpones the operation.

iv Inform also:

a Ward and nursing staff

b Transplant surgeon

c Theatre and make provisional booking

d First on-call anaesthetist and ask him/her to contact Senior Registrar and/or Consultant on-call anaesthetist

ONCE PATIENT ARRIVES

1 Take blood samples before anything else. It is important that the 5 mls of clotted blood for tissue typing (and any other specimens the tissue typing laboratory require) are sent immediately on arrival of the patient.

In addition bloods need to be taken for full blood count, coagulation screen, renal SMAC (with U&E, creatinine, calcium and albumin to be available at the time of transplantation. Other results may be available later), serum for virology (baseline CMV titres) and cross-match 4 units of blood (2 packed cells 2 whole blood).

2.....

2 Complete paediatric check list pre-transplant. All aspects must be filled in. Note in particular the need to record target weight, blood pressure and normal urine output and body surface area. This check list must go with patient to theatre.

3 Set up intravenous infusion at maintenance fluids appropriate for size of patient and replacing any deficit on assessing difference between current and target weight.

4 Institute other investigations including chest X-ray, ECG, FB culture, urine culture.

5 If history of hyperkalaemia or potassium of greater than 5 mmol/l

a Fast cycle if on PD

b Give calcium resonium 1 gm/Kg PR if on haemodialysis and discuss with consultant if haemodialysis needed in view of chemistry

6 Talk to parents and obtain consent.

7 Write up immunosuppression to be given in the theatre. For all patients this will be Methylprednisolone 10 mg/kg I.v. 5-10 minutes before vascular clamps are released.

8 Write up instructions for intra-operative blood transfusion on checklist once haemoglobin is known. This will be the number of mls of packed cells required to bring the patients haemoglobin up to 10 gms/dl.

9 Write up appropriate Mannitol dose on checklist (0.5 g/Kg 20% Mannitol ie 2.5 ml/Kg).

10. Write up induction dose of antibiotics iv Augmentin 30 mg/kg (max 1.2g).

IN THEATRE

1. Insert CVP and arterial line.

2. Use normal saline, plasma or blood, (as appropriate) to raise CVP to + 8-10 cm H20 (6-8 mm Hg) before the vascular clamps are removed from the donor kidney. Aim to keep CVP at this level for the remainder of the operation. Please always take into account actual and target weights and overall hydration state.

3. Give intra-operative blood transfusion as per checklist instructions.

4. Give intra-operative immunosuppression as per checklist 10 minutes prior to the vascular anastimosis together with Mannitol see checklist for dose).

5. Start dopamine 2-3 ug/kg/min via central line

3.....

IMMEDIATE POST-OPERATIVE CARE

1 Allow nurses to make patient comfortable and connect up the monitoring equipment and lines, which will be as follows:

i Weigh bed

ii Rectal and toe temperature probes

iii Hewlett-Packard ECG, BP and CVP monitor or equivalent connected to CVP and arterial lines

iv Peripheral intravenous infusion(s)

v Urethral catheter

vi Ureteric catheter (in some cases only)

vii PD catheter spigotted and empty (if appropriate)

2 Write up the following drugs:

a Morphine 0.01-0.02 mg/kg/hour (half the patients weight in kg = mg in 50 mls at 2 mls/hour) or

Papaveretum 0.02 to 0.04 mg/kg/hour or fentanyl as per selection protocol

b Methylprednisolone 10 mg/metre^2/day as b.d. dosage. First dose to be given 12 hours post-operatively

c Cyclosporin 6 mg/kg/24 hours written up as continuous infusion 3 mg/kg/12 hourly. This will be converted to Cyclosporin 14 mg/kg/day orally given as b.d. dosage when the patient is tolerating oral fluids

d Ranitidine 2 to 4 mg/kg/day orally (as bd dose)

e Dopamine 2 micrograms/kg/minute - see drug infusion protocol

f Anti-thymocyte globulin (Fresenius) for those on high risk protocol only (ie previous graft or high cytoxic antibodies) 4 mg/kg/day iv. Need to give test dose intravenously first.

g Other drugs such as Hydralazine or Frusemide may be written up when required

h Further antibiotic therapy is discretionary and would be used only if there was a history of recent infectin in either the patient or the donor, or the recipient is known to have vesicoureteric reflux into their native kidneys. This should be discussed with the consultant.

4.....

i Acyclovir Post Renal Transplant

Check CMV status donor and recipient. If donor and recipient negative, no Acyclovir given. If donor positive course given for 12 weeks regardless of recipient status. If donor negative and recipient positive, course given for six weeks.

Dosage * 800 mg po 2-6 hours pre op
* 800 mg po 24 hours post op
Thereafter according to GFR:

> 25 ml/m	6 hourly	* 800 mg po
10-25 ml/m	8 hourly	* 800 mg po
< 10 ml/m	daily	* 800 mg po
dialysis dependent	12 hourly	* 800 mg po

* half dose in under 2 years old

OBSERVATIONS

Pulse, blood pressure, core and peripheral temperature, CVP and urine output should be measured hourly. One should aim to maintain:

i CVP between 8 and 12 cm H20 (6-9 mm Hg)

ii Temperature gap less than or equal to 2 degrees centigrade

iii Blood pressure to be decided on an individual basis within that patients normal target blood pressure guidelines

iv The patient should be weighed daily. It is important to note that weigh bed weights may differ markedly from pre-operative weights and that whilst changes in weigh bed weights are important no significance can be attached to the difference between weights made on different scales

v Optimal urine output to be decided on an individual basis. In polyuric patients this will be around 4 ml/Kg/hour initially falling to 2 ml/Kg/hour when stable. In previously anuric patients far lower urine outputs may be acceptable if A.T.N. has occurred Check transplant troubleshooter for management guidelines on response to falling urine outputs. Otherwise aim for at least 2ml/Kg/hour

FLUIDS

Arterial line 0.9% Heparinised saline at 3 mls/hour with a pressurised bag or 1-3 mls/hour heparinised 0.45% saline with a syringe pump. Take care not to confuse the 3 ml/hr flush device used with a pressurised bag with the 30 ml/hr device used with a syringe pump.

Central line half normal saline/2.5% dextrose plus or minus KCL at rate to replace all losses (sodium and potassium content to be adjusted according to urine electrolytes)

Peripheral line at insensible loss and containing drug infusions

5.....

INVESTIGATIONS

U & E (urine and plasma, glucose and calcium) (6 hourly for 24 hours, 12 hourly for next 24 hours and thereafter 24 hourly)

Full blood count, renal SMAC daily and chest X-ray daily for first two or three days

Urine cytology daily

Cyclosporin levels, urine culture, magnesium, 24 hour urine, creatinine and protein clearance twice weekly. Urine and saliva for CMV once weekly

A doppler ultrasound renal scan should be performed early if there are doubts about initial function and thereafter if there are concerns about deterioration in renal function. The decision for a scan should be made by the Paediatric Consultant and timing discussed with Dr Howarth.

Comments/corrections in writing to

Dr ME McGrav - Consultant Paediatrician and Nephrologist
or
DR D E Holland - Consultant Anaesthetist/Intensive Care

Updated January 1995 ref: A/rglines

APPENDIX 6

BAPN PD guidelines as available at

<< http://www.bapn.org/clinical_standards.html>>

Peritoneal dialysis clinical practice guidelines for children and adolescents

Note that the current version is DRAFT number 1, 7/2/07.

This document has been adapted for paediatric patients from the Renal Association Standards for Peritoneal Dialysis in Adults (www.renal.org/guidelines/index.html) which was written by Prof Simon Davies. Although the large majority of standards for adults also apply to children, there are some areas that differ significantly. There are also some important areas not covered in the adult standards, such as the specific requirements of the growing child and the need for a structured process for transfer of

adolescents to adult services. For this reason, the renal association adult guidelines have been adapted where necessary. All standards that are taken directly from the adult

guidelines are shown in regular font and paediatric guidelines are in red italics.

The lead author of this paediatric guideline was Dr Lesley Rees, along with Dr Sally Feather and Dr Rukshana Shroff. Please send feedback to L.Rees@ich.ucl.ac.uk

CONTENTS

Summary of Clinical Practice Guidelines for Peritoneal Dialysis

1. Equipment and Resources

1.1 The dialysis unit should have sufficient specialist support staff to fulfil the criteria listed by the Renal Workforce Planning Group 2002.

Paediatric standard 1

PD for children should take place in specialised paediatric centres able to provide
multidisciplinary support
1.2 Access to other paediatric sub-speciality services should be easily available.
1.3 Adolescents need to be prepared for transfer to adult services. It is important that the process is begun in good time, and that there is an appropriate transfer policy that is agreed by both the referring and receiving centres.
Paediatric standard 2
A transfer process for adolescents must be in place and agreed by referring and
receiving units
1.4 Peritoneal dialysis should be delivered in the context of a comprehensive and integrated service for renal replacement therapies, including haemodialysis (including
temporary backup facilities), transplantation and conservative care. Both continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD), in all
its forms should be available. Dedicated PD nursing staff (1 W.T.E. per 20 patients) should be part of the multidisciplinary team
1.5 All equipment used in the delivery and monitoring of therapies should comply with
the relevant standards for medical electrical equipment [BS-EN 60601-2-39:1999, BS5724-2-39:1998, IEC 60601-2-39:1998, Particular requirements for the safety . specification for peritoneal dialysis equipment]. Tubing sets and catheters should carry
the .CE. mark to indicate that the item conforms to the essential requirements of the Medical Devices Directive (93/42/EEC) and that its conformity has been assessed in accordance with the directive.
1.6 Fluids for peritoneal dialysis are required to satisfy the current European quality standards as indicated in the European good manufacturing practice and the European
Pharmacopoeia Monograph .Solutions for Peritoneal Dialysis.. Manufacturing facilities are required to meet the relevant standards (ISO 9001/2 and EN 46001/2). Product registration files must be submitted to and product approval given by the Medicines Control Agency.
1.7 The use of disconnect systems should be standard unless clinically contraindicated.
1.8 Biocompatible PD solutions (normal pH, low concentrations of glucose degradation products) should be used in patients experiencing infusion pain. *Also, they*
should be considered in patients who are likely to remain on PD for a significant period of time, (e.g. those who do not have a suitable living related donor and poor matchability scores, thus anticipating a longer than usual wait for a deceased donor kidney).
2. Preparation for Peritoneal Dialysis
2.1 All patients should, where possible, be adequately prepared for renal replacement
therapy and this should include receiving information and education about PD treatment, delivered by experienced members of the MDT *who have paediatric renal training.* Patients commencing RRF in an unplanned fashion for whatever reason

should receive this information once appropriate.
2.2 Where possible, timing of PD catheter insertion should be planned to accommodate
patient convenience, commencement of training between 10 days and 6 weeks and before RRT is essential to enable correction of early catheter-related problems without
the need for temporary haemodialysis.
2.3 Dialysis centres should have a dedicated team approach to catheter insertion. This
is more important than the type of catheter or the implantation technique used. *In children, the most important thing is that the surgeon undertaking the procedure is appropriately trained and skilled.*

Paediatric standard 3
Peritoneal dialysis catheter insertion should be undertaken by appropriately trained
and skilled staff.

2.4 Peri-operative catheter care and catheter complications (leaks, hernias, obstruction) should be managed according to the International Society of Peritoneal Dialysis guidelines

3. Solute Clearance

3.1 Both residual urine and peritoneal dialysis components of small solute clearance should be measured at least six monthly or more frequently if clinically indicated. Both
urea and/or creatinine clearances can be used to monitor dialysis adequacy and should
be interpreted within the limits of the methods.
3.2 A combined urinary and peritoneal Kt/Vurea of 1.7/week or a creatinine clearance
of 50L/week/1.73m2 should be considered as minimal treatment doses. The dose should be increased in patients experiencing uraemic symptoms.

Paediatric standard 4
A Kt/Vurea of 1.7/week and creatinine clearance 50L/week/1.73m$_2$ should be the minimum for children.

4. Ultrafiltration and fluid management

4.1 Peritoneal membrane function should be monitored regularly (6 weeks after commencing treatment and at least annually or when clinically indicated) using a peritoneal equilibration test (PET) or equivalent. Daily urine and peritoneal ultrafiltration volumes, with appropriate correction for overfill, should be monitored at least six-monthly.
4.2 Dialysis regimens resulting in fluid re-absorption should be avoided. Patients with high or high average solute transport, at greatest risk of this problem, should be considered for APD and icodextrin use.
4.3 Dialysis regimens resulting in routine utilisation of hypertonic (3.86%) glucose exchanges should be avoided. Where appropriate this should be achieved by using icodextrin or diuretics.
4.4 Treatment strategies that favour preservation of renal function should be adopted where possible. These include avoidance of episodes of dehydration, and the use of diuretics, ACEi and ARBs.
4.5 Anuric patients who consistently achieve a daily ultrafiltration of less than 750

ml/1.73m2 should be closely monitored and the benefits of modality switch considered.

5. Infectious complications

1. Prevention Strategies

5.1.1 PD units should undertake regular audit of their peritonitis and exit-site infection rates, including causative organism, treatment and outcomes. They should enter into active dialogue with their microbiology department and infection control team to develop optimal local treatment and prevention protocols.

Paediatric standard 5

All units should collect and audit data on the incidence of exit site infection.

Paediatric standard 6

All units should collect and audit data on the incidence of peritonitis.

5.1.2 Flush-before-fill dialysis delivery systems should be used.

5.1.3 Patients should undergo regular revision of their technique and receive intensified training if this is below standard.

5.1.4 Initial catheter insertion should be accompanied by antibiotic prophylaxis.

5.1.5 Invasive procedures should be accompanied by antibiotic prophylaxis and emptying the abdomen of dialysis fluid for a period commensurate with the procedure.

5.1.6 Topical antibiotic administration should be used to reduce the frequency of *Staph. aureus* and Gram negative exit-site infection and peritonitis.

2. Treatment

5.2.1 Exit site infection is suggested by pain, swelling, crusting, erythema and serous discharge; purulent discharge always indicates infection. Swabs should be taken for culture and initial empiric therapy should be with oral antibiotics that will cover *S. aureus and P. aeruginosa. If there is pain and redness that is tracking along the tunnel, particularly if associated with an exit site infection, a tunnel infection should be suspected. An exit site swab should be taken and the PD fluid sent for microscopy and culture. An ultrasound of the tunnel may show evidence of inflammation. A tunnel infection that fails to respond to antibiotics is an indication for removal of the PD catheter.*

5.2.2 Methicillin resistant organisms (MRSA) will require systemic treatment (e.g vancomycin) and will need to comply with local infection control policies.

5.2.3 Initial treatment regimens for peritonitis should include cover for bacterial Gram positive and Gram negative organisms until result of culture and antibiotic sensitivities are obtained.

6. Metabolic Factors

6.1 Standard strategies to optimise diabetic control should be used; these should be complemented by dialysis prescription regimens that minimise glucose, including glucose free solutions (icodextrin and amino-acids), where possible.

6.2 Central obesity can worsen or develop in some PD patients. The risk of this problem, and associated metabolic complications, notably increased atherogenicity of lipid profiles and insulin resistance, can be reduced by avoiding excessive glucose prescription and using icodextrin.

6.3 Awareness of the effects of Icodextrin on assays for estimation of amylase and glucose (using glucose dehydrogenase) should be disseminated to patients, relatives,
laboratory and clinical staff.

7. Laboratory and clinical indices

7.1 Monitoring of biochemical and haematological parameters should be performed monthly or at each clinic visit if less often than monthly

7.2 Serum bicarbonate concentrations should be between 20 and 26mmol/l.

7.3 Serum potassium should be between 3.5 and 6.5mmol/l.

7.4 Serum phosphate should be within, and preferably nearer to the 50th centile, for the age appropriate normal range (appendix, page 37).

7.5 Serum calcium, adjusted for serum albumin, should be within the age appropriate normal range.

7.6 Serum albumin corrected calcium x phosphate product should be less than *<4.5 mmol2/L2 (K/DOQI guidelines) or <5 mmol2/L2 (European PD working group advice).*

7.7 The optimum range for serum PTH levels is controversial. There is emerging evidence that levels should be maintained at less than twice the upper limit of normal for the intact PTH assay used.

7.8 *Although aluminium is not a recommended phosphate binding agent in children, the* serum aluminium concentration should be measured every three months in all patients receiving oral aluminium hydroxide. No patient whose ferritin level is <100 µg/l should have a serum aluminium concentration >60 µg/l (2.2 µmol/l).

7.9 Pre-dialysis haemoglobin concentration should be greater than the lower limit of the age appropriate normal range.

7.10 Ferritin levels should be between 100 and 800mcg/L. However, given the increased risk of thrombotic events with higher ferritin levels that have been shown in recent trials, the revised K/DOQI guidelines for the management of anaemia recommend that the serum ferritin levels should be maintained between 100 . 500mcg/L in adults. In the absence of paediatric studies, in patients at risk of thrombosis (e.g. those with heavy proteinuria, arteriovenous fistulae or synthetic grafts), serum ferritin levels above 500mcg/L should be avoided.

7.11 Height and head circumference (in those under 2 years of age) should be measured monthly, and the rate of growth checked against normal centiles. Dry weight should be estimated regularly, at least monthly or every 2 weeks in infants. Pubertal stage should be assessed every 3 months in those over 10 years of age, or sooner if clinically indicated.

Paediatric standard 7

Growth and development should be measured regularly as part of the assessment of
dialysis adequacy

Paediatric standard 8

Dry weight needs regular reassessment in the growing child

7.12 An assessment of school progress, both in the hospital and locally, should be made annually.

7.13 Blood pressure should be maintained within the age appropriate normal range.

8. Access to and withdrawal from dialysis

8.1 All children with chronic kidney disease should be considered for renal replacement therapy by stage 4

CKD should be suspected in children with: bilateral renal anomalies on antenatal scans (many children with CKD are now diagnosed antenatally); a creatinine above

the normal age appropriate range; bilateral renal defects on scans e.g. for UTI; a family history of CKD; persistent proteinuria; or after an episode of acute renal failure. All such children should be referred to a paediatric nephrologist. Early referral provides the opportunity for delaying the progression of CKD by treating hypertension and proteinuria, for optimising growth and preventing renal bone disease. Importantly, it also allows for timely forward planning for renal replacement therapy.

8.2 If there is no medical contraindication the choice of initial dialysis modality should be based on patient choice. However, although patient choice is paramount, guidance from unit staff is necessary: venous access can be difficult to achieve and maintain in those less than 5 years of age, and needling of a fistula can be particularly difficult in an uncooperative patient. Also, PD is likely to preserve residual renal function for longer. For these reasons, as well as social ones, PD is recommended in young children.

8.3 After full education and counselling a small proportion of families may opt for active non-dialytic management of advanced chronic kidney disease, including nutritional, medical and psychological support, rather than plan to initiate dialysis. *This decision may need to be discussed with an independent ethics advisor if a consensus on further management is not reached amongst members of the medical and nursing teams or amongst the parents and medical teams.* The numbers of patients not taken on to dialysis and the reasons for this decision should be subject to audit.

8.4 Renal replacement therapy should commence when a patient with an eGFR < 15ml/min/1.73m$_2$ has symptoms or signs of uraemia, fluid overload, malnutrition *and/or growth failure* in spite of medical therapy or before an asymptomatic patient has an eGFR < 6ml/min/1.73m$_2$.

8.5 Any decision to discontinue dialysis should be made jointly by the patient (when age appropriate) and their carers and the responsible consultant nephrologist and renal team and the family practitioner. The decision, and the reasons for it, must be recorded in the patient.s notes. Renal units should develop guidelines for palliative care of such patients, including liaison with community services.

9. Summary of the most important paediatric clinical practice guidelines

Paediatric standard 1
PD for children should take place in specialised paediatric centres able to provide multidisciplinary support (good practice)

Paediatric standard 2
A transfer process for adolescents must be in place and agreed by referring and receiving units (good practice)

Paediatric standard 3
Peritoneal dialysis catheter insertion should be undertaken by appropriately trained and skilled staff (good practice)

Paediatric standard 4
A Kt/Vurea of 1.7/week and creatinine clearance 50L/week/1.73m$_2$ should be the minimum for children (good practice)

Paediatric standard 5
All units should collect and audit data on the incidence of exit site infection (good

practice)
Paediatric standard 6
All units should collect and audit data on the incidence of peritonitis (good practice)
Paediatric standard 7
Growth and development should be measured regularly as part of the assessment of dialysis adequacy (good practice)
Paediatric standard 8
Dry weight needs regular reassessment in the growing child (good practice). A paediatric renal dietician should regularly review patients and provide guidelines on the nutritional requirement in each case.

Summary of Audit Measures for Peritoneal Dialysis

1. Adequacy of staffing levels (medical, surgical, radiological, anaesthetic, nursing, dietetic, play therapists, psychosocial, pharmacy, and schooling)
2. Presence of a transfer process for adolescents that is agreed by referring and receiving units
3. Availability of modality choice
4. Monitoring of modality switching
5. Systems in place to check medical equipment
6. Systems in place to ensure purchase of dialysis fluid fulfil legal requirements
7. Use of non-standard systems with documentation of clinical indication
8. Use of biocompatible solutions and indication for use
9. Audit of care pathway for dialysis preparation to include information given, when and who delivers it.
10. Audit of care pathway for catheter insertion to include timeliness and need for temporary haemodialysis
11. Catheter complications and their resolution
12. Frequency of solute clearance (residual and peritoneal) estimation
13. Cumulative frequency curves for the total solute clearance
14. Frequency of measurement of membrane function, residual urine and peritoneal ultrafiltration volume
15. Identify patients with fluid reabsorption in long dwell
16. Routine annual audit of infection prevention strategies
17. Routine annual audit of infection outcomes (exit site and peritonitis rates)
18. Cumulative frequency curves of plasma bicarbonate
19. Processes in place to increase awareness of interference of assays by icodextrin metabolites
20. Cumulative frequency curves of pre-dialysis serum calcium, phosphate calcium x phosphate product and PTH concentration
21. Cumulative frequency curves of pre-dialysis haemoglobin concentration
22. Height, weight, head circumference and pubertal progression
23. School attendance
24. Cumulative frequency curves of BP predialysis
25. An audit of cases where PD was refused or withdrawn and the indications for this.

Rationale for clinical practice guidelines for paediatric patients on peritoneal dialysis

Introduction

In the UK peritoneal dialysis is usually the first choice dialysis modality because it

interferes less with the child.s day-to-day life, particularly in those who may live a long way from their paediatric renal unit. The ratio of children on peritoneal dialysis compared to haemodialysis is approximately 2:1; of the 173 children who received dialysis in the UK in 2003, 62% were on peritoneal dialysis (Report of the Paediatric Renal Registry, Seventh Annual Report of the UK Renal Registry, December 2004). The National Service Framework Part 1: Dialysis and Transplantation is a document that is applicable to both adult and paediatric services (1). It stresses the importance of a family-centred approach to the care of children. It also stresses the importance of the team needed to provide such services i.e. medical, surgical, anaesthesiology, radiology, nursing, dietetic, play therapy, psychological, social work and pharmacists, all of whom need the special skills necessary to treat such children. However, this document was not designed to set standards for clinical care. Owing to the small numbers of children with CKD stage 5, and, in particular, the very small numbers on dialysis, there are very few analyses to help in the management of paediatric patients, and paediatric nephrologists have to rely on extrapolation of data from adult studies. Clinical practice guidelines for adults on peritoneal dialysis have been developed in Australasia, Canada, Europe and the USA as well as the UK (2-11). Guidelines for children on peritoneal dialysis have also been published (12-17). These guidelines serve to identify and promote best practice in the delivery of haemodialysis and have set clinical standards to allow comparative audit of the key aspects of the haemodialysis prescription, laboratory data and patient outcomes. The reports of the UK Renal Registry, Scottish Renal Registry and NHS Quality Improvement Scotland have demonstrated the benefits of performing regular audit to improve clinical standards in haemodialysis (2-4).

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1. Equipment and Resources

1.1 Peritoneal Dialysis should be delivered in the context of a comprehensive and integrated service for renal replacement therapies, including haemodialysis (including temporary backup facilities), transplantation and conservative care. Both continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD), in all its forms should be available. Dedicated PD nursing staff (1 W.T.E. per 20 patients) should be part of the multidisciplinary team (Good Practice)

Evidence from observational studies or registry data, with all its limitations, indicates that peritoneal dialysis (PD) used in the context of an integrated dialysis programme is associated with good clinical outcomes, certainly comparable to haemodialysis in the medium term (HD) (1-5). The only randomised study (NECOSAD), comparing HD to PD as a first treatment showed no differences in 2 year quality adjusted life years or 5 year mortality, but the number randomised was insufficient to generalize this observation; notably, most patients in this national study had sufficient life-style preferences related to one modality to decline randomisation (6). PD has a significant technique failure rate however, so patients need to be able to switch treatment modality (to either temporary or permanent HD) in a timely manner, which has implications for HD capacity.

PD modalities (CAPD v. APD) have a different impact on life-style; one randomised study found that APD creates more time for the patient to spend with family or continue employment but is associated with reduced quality of sleep (7). APD is the preferred modality for children. There are medical indications for APD (see sections 2, 3 and 4), but generally modality choice is a lifestyle issue.

The success of a PD programme is dependent upon specialized nurses with appropriate
skills in assessing and training patients for PD, monitoring of treatment and with sufficient resources to provide continued care in the community. A recent randomised
trial of more intensive training has shown that this reduces peritonitis risk (8) (see section 5). Several studies have documented the benefits of home visits in identifying
new problems, reducing peritonitis and non-compliance (9-11). It is usually possible for a WTE PD nurse to deliver this quality of care with a case load of 20 PD patients (see recommendations of the National Renal Workforce Planning Group, 2002).

Audit measure 1 - Adequacy of staffing levels (medical, surgical, radiological, anaesthetic, nursing, dietetic, play therapists, psychosocial, pharmacy, and schooling)

***Audit measure 2 - Presence of a transfer process for adolescents that is agreed by
referring and receiving units***

Audit measure 3 - Availability of modality choice

Audit measure 4 - Monitoring of modality switching

1. Fenton SSA, Schaubel DE, Desmeules M, et al. Hemodialysis versus peritoneal dialysis: a comparison of adjusted mortality rates. *American Journal of Kidney Diseases* 1997;30(3):334-42.
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3. Heaf JG, Lokkegaard H, Madsen M. Initial survival advantage of peritoneal dialysis relative to haemodialysis. *Nephrol Dial Transplant* 2002;17(1):112-7.
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6. Korevaar JC, Feith GW, Dekker FW, et al. Effect of starting with hemodialysis compared with peritoneal dialysis in patients new on dialysis treatment: a randomized controlled trial. *Kidney Int* 2003;64(6):2222-8.
7. Bro S, Bjorner JB, Tofte-Jensen P, et al. A prospective, randomized multicenter study comparing APD and CAPD treatment. *Perit Dial Int* 1999;19(6):526-33.
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9. Lewis NM, Pickering KR. Establishment of a formalized CAPD retraining program. *Perit Dial Int* 1995;15:S58.
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11. Ponferrada L, Prowant BF, Schmidt LM, Burrows LM, Satalowich RJ, Bartelt C. Home visit effectiveness for peritoneal dialysis patients. *Anna J* 1993;20(3):333-6.

1.2 All equipment used in the delivery and monitoring of therapies should comply with the relevant standards for medical electrical equipment [BS-EN 60601-2-39:1999, BS5724-2-39:1998, IEC 60601-2-39:1998, Particular requirements for the safety . specification for peritoneal dialysis equipment]. Tubing sets and catheters should carry the .CE. mark to indicate that the item conforms to the essential requirements of the Medical Devices Directive (93/42/EEC) and that its conformity has been assessed in accordance with the directive.

Audit Measure 5 - Systems in place to check medical equipment

This is a legal requirement

1.3 Fluids for peritoneal dialysis are required to satisfy the current European quality standards as indicated in the European good manufacturing practice and the European Pharmacopoeia Monograph .Solutions for Peritoneal
Dialysis.. Manufacturing facilities are required to meet the relevant standards (ISO 9001/2 and EN 46001/2). Product registration files must be submitted to and product approval given by the Medicines Control Agency.
Audit Measure 6 - Systems in place to ensure purchase of dialysis fluid fulfil legal
requirements.
1.4 The use of disconnect systems should be standard unless clinically contraindicated (evidence).
Audit Measure 7 - Use of non-standard systems with documentation of clinical indication
Disconnect systems have been shown through randomised trials to be associated with a
lower peritonitis risk, especially in infections due to touch contamination (1)
1. MacLeod A, Grant A, Donaldson C, et al. Effectiveness and efficiency of methods of dialysis therapy for end-stage renal disease: systematic reviews. *Health Technol Assess* 1998;2(5):1-166.
1.5 Biocompatible PD solutions (normal pH, low concentrations of glucose degradation products) should be used in patients experiencing infusion pain (evidence).
Also, they should be considered in patients who are likely to remain on PD for a significant period of time (those who do not have a suitable living related donor and poor matchability scores, thus anticipating a longer than usual wait for a deceased donor kidney).
Audit Measure 8 - Use of biocompatible solutions and indication for use
A minority of patients commencing PD will experience infusion pain, often severe enough to consider discontinuing the therapy. A double blind randomised study demonstrated that pain could be prevented by using a normal pH, bicarbonate-lactate
buffered dialysis fluid (Physioneal) (1). Subsequent clinical experience has found that
the benefit of this more biocompatible solution on infusion pain results in immediate and sustained benefit, and is probably applicable to other biocompatible solutions.
The evidence of clinical benefit from the routine use of biocompatible solutions is more
controversial. Standard solutions are clearly bio-incompatible, with low pH (~5.2), lactate rather than bicarbonate buffer, high osmolality and high concentrations of glucose which also result in high concentrations of glucose degradation products (GDPs). Many *in vitro* and *ex vivo* studies have demonstrated the relative toxicity of these solutions, with all of the biocompatible features playing their part (2-7). There is
also strong observational evidence that (a) detrimental functional changes to the membrane occur with time on treatment, which are more exaggerated in patients using
solutions with high glucose concentration early in their time on therapy (8, 9) and (b) morphological changes occur that are related to time on treatment which include membrane thickening and vascular scarring (10). Time on treatment is also the greatest

risk factor for encapsulating peritoneal sclerosis (EPS) (11, 12).
These observations have led all the main dialysis companies to develop and market .biocompatible. solutions, with normalization of pH, reduction of GDPs and a variable approach to buffering. In randomised clinical trials these solutions have been shown to
improve the dialysate concentrations of biomarkers considered to be indicators of mesothelial cell and possibly membrane health (13-16). Systemic benefits possibly include reduced circulating advanced glycation end-products (16) and better glycaemic
control in diabetics (17). *However, the long-term effects of metabolic alkalosis on the developing skeleton are not known, and an alkaline pH can predispose to soft tissue calcification.* Data is currently lacking on hard clinical endpoints such as technique failure, functional membrane change or patient survival. One non-randomised study has
found an improved patient but not technique survival; patients in this study using biocompatible solutions were younger, suggesting a selection bias that may not be fully
adjusted for, so caution should be exercised in the interpretation of this study (18).
Currently there is insufficient evidence to recommend that all patients should be treated
with biocompatible solutions, especially as this may have a significant cost implication.
A selective approach to their use should be considered. Working on the assumption that the primary benefit of biocompatible solutions is membrane protection then there is evidence indicating that function membrane changes become more significant at 4 years of treatment, even in patients commencing PD with good residual renal function
and low use of hypertonic exchanges (9). Likewise the incidence of EPS is rare before
this period of time on treatment. This issue remains controversial at this stage and further studies are required.
An area of difference between paediatric and adult PD is that fill volumes vary with size. Surface area is preferable to body weight, which may underestimate the optimal
fill volume in younger children, and should be between 1200 and 1400ml dialysate/m2
body surface area (19).

1. Mactier RA, Sprosen TS, Gokal R, et al. Bicarbonate and bicarbonate/lactate peritoneal dialysis solutions for the treatment of infusion pain. *Kidney Int* 1998;53(4):1061-7.
2. Liberek T, Topley N, Jorres A, et al. Peritoneal dialysis fluid inhibition of polymorphonuclear leukocyte respiratory burst activation is related to the lowering of intracellular pH. *Nephron* 1993;65(2):260-5.
3. Jorres A, Bender TO, Finn A, et al. Biocompatibility and buffers: effect of bicarbonate-buffered peritoneal dialysis fluids on peritoneal cell function. *Kidney Int* 1998;54(6):2184-93.
4. Jörres A, Topley N, Steenweg L, Müller C, Köttgen E, Gahl GM. Inhibition of cytokine synthesis by peritoneal dialysate persists throughout the CAPD cycle. *Am J Nephrol* 1992;12(1-2):80-5.
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solute transport with time on Peritoneal Dialysis. *J Am Soc Nephrol* 2001;12(5):1046-51.
9. Davies SJ. Longitudinal relationship between solute transport and ultrafiltration capacity in peritoneal dialysis patients. *Kidney Int* 2004;66:2437-45.
10. Williams JD, Craig KJ, Topley N, et al. Morphologic changes in the peritoneal membrane of patients with renal disease. *J Am Soc Nephrol* 2002;13(2):470-9.
11. Rigby RJ, Hawley CM. Sclerosing peritonitis: the experience in Australia. *Nephrol Dial Transplant.* 1998;13(1):154-9.
12. Lee HY, Kim BS, Choi HY, et al. Sclerosing encapsulating peritonitis as a complication of longterm
continuous ambulatory peritoneal dialysis in Korea. *Nephrology (Carlton).* 2003;8(Suppl):S33-9.
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16. Williams JD, Topley N, Craig KJ, et al. The Euro-Balance Trial: the effect of a new biocompatible peritoneal dialysis fluid (balance) on the peritoneal membrane. *Kidney Int* 2004;66(1):408-18.
17. Marshall J, Jennings P, Scott A, Fluck RJ, McIntyre CW. Glycemic control in diabetic CAPD patients assessed by continuous glucose monitoring system (CGMS). *Kidney Int* 2003;64(4):1480-6.
18. Lee HY, Park HC, Seo BJ, et al. Superior patient survival for continuous ambulatory peritoneal dialysis patients treated with a peritoneal dialysis fluid with neutral pH and low glucose degradation product concentration (Balance). *Perit Dial Int.* 2005;25(3):248-55.
19. White CT, Gowrishankar M, Feber J, Yiu V; Canadian Association of Pediatric Nephrologists (CAPN); Peritoneal Dialysis Working Group. Clinical practice guidelines for pediatric peritoneal dialysis. Pediatr Nephrol. 2006 Aug;21(8):1059-66

2. Preparation for Peritoneal Dialysis

2.1 All patients should, where possible, be adequately prepared for renal replacement therapy and this should include receiving information and education about PD treatment, delivered by an experienced member of the MDT. Patients commencing RRF in an unplanned fashion for whatever reason should receive this information once appropriate. (Good practice)

Audit Measure 9: Audit of care pathway for dialysis preparation to include information given, when and who delivers it.

The arguments and rationale for this guideline relate to the National Service Framework for Renal Services, Part 1. The reader is referred to standard 2, Preparation and Choice pp. 21-23.

2.2 Where possible, timing of PD catheter insertion should be planned to accommodate patient convenience, commencement of training between 10 days
and 6 weeks, (unless using the Moncrief catheter) and before RRT is essential to
enable correction of early catheter-related problems without the need for temporary haemodialysis. (Good practice)

Audit Measure 10: Audit of care pathway for catheter insertion to include timeliness and need for temporary haemodialysis

The arguments and rationale for this guideline relate to the National Service Framework for Renal Services, Part 1. The reader is referred to standard 3, Elective Dialysis Access Surgery, pp. 24-26. The Moncrief catheter is buried subcutaneously and is designed to be left in this position, where it can remain for many months, until required (1). *If the catheter needs to be used within 7 days of insertion, fill volumes should start at 500ml/m$_2$ body surface area in order to reduce the chances of*

dialysate leak, with its associated risk of tunnel and peritoneal infection.

1. Gokal R, Alexander S, Ash S, et al. Peritoneal catheters and exit-site practices toward optimum peritoneal access: 1998 update. (Official report from the International Society for Peritoneal Dialysis). *Perit Dial Int* 1998;18(1):11-33.

2. White CT, Gowrishankar M, Feber J, Yiu V; Canadian Association of Pediatric Nephrologists (CAPN); Peritoneal Dialysis Working Group. Clinical practice guidelines for pediatric peritoneal dialysis. Pediatr Nephrol. 2006 Aug;21(8):1059-66

2.3 Dialysis centres should have a dedicated team approach to catheter insertion. This is more important than the type of catheter or the implantation technique used. (Good practice)

An experienced team approach to catheter insertion is recommended by all available guidelines; in the case of the European guidelines this is given a level A evidence although no randomised trial has been published comparing *ad hoc* arrangements with
those of a dedicated experienced team (1). This approach should be combined with regular audit of outcomes. Several randomised trials have been performed comparing
different catheter designs and insertion techniques. These are fully reviewed elsewhere
(1-4). Whilst there are theoretical advantages in choosing different catheters, e.g. double *v.* single cuff to reduce leakage, coiled *v.* straight to reduce catheter migration,
when put to the test in randomised trials no significant benefit of one over another has
been demonstrated. Equally, there may be clear logistic benefits of one approach to catheter insertion over another, e.g. laparoscopic *v.* open surgical *v.* Seldinger that reflect local expertise and facilities but no studies have demonstrated a clear benefit. Evidence would suggest that a downwards-directed exit site is associated with less infection and a caudally directed angle of the catheter in the deep tunnel, especially if
this is made through the rectus muscle, is associated with reduced likelihood of catheter migration (5).

Similarly for children, there is no evidence showing any difference in the incidence of complications and the number of cuffs. However, in young children care is necessary to avoid placement of the distal cuff too near the exit site as cuff extrusion can occur. For this reason, it is recommended that there should be at least a 2cm distance between the distal cuff and the exit site. There is also no evidence to support the use of swan necked in comparison to straight catheters or a coiled in comparison to a straight intraperitoneal segment. However, downward or lateral pointing exit sites have been shown to be associated with a decreased incidence of peritonitis in 2 studies (6). Furthermore, there is no evidence in the paediatric literature to demonstrate any benefit of omentectomy, although there is some evidence in adults. The most important issue, therefore, is that the catheter is inserted by experienced staff who are aware of these issues.

Paediatric standard 3

Peritoneal dialysis catheter insertion should be undertaken by appropriately trained and skilled staff (good practice)

1. Dombros N, Dratwa M, Feriani M, et al. European best practice guidelines for peritoneal dialysis. 3 Peritoneal access. *Nephrol Dial Transplant.* 2005;20(Suppl 9):ix8-ix12.

2. Gokal R, Alexander S, Ash S, et al. Peritoneal catheters and exit-site practices toward optimum peritoneal access: 1998 update. (Official report from the International Society for Peritoneal Dialysis). *Perit Dial Int* 1998;18(1):11-33.

3. Canadian Guidelines for treatment wth peritoneal dialysis. *J Am Soc Nephrol* 1999;Suppl 13.
4. Flanigan M, Gokal R. Peritoneal catheters and exit-site practices toward optimum peritoneal access: a review of current developments. *Perit Dial Int.* 2005;25(2):132-9.
5. Crabtree JH, Burchette RJ, Siddiqi NA. Optimal peritoneal dialysis catheter type and exit site location: an anthropometric analysis. *ASAIO J.* 2005;51(6):743-7.
6. White CT, Gowrishankar M, Feber J, Yiu V; Canadian Association of Pediatric Nephrologists (CAPN); Peritoneal Dialysis Working Group. Clinical practice guidelines for pediatric peritoneal dialysis. Pediatr Nephrol. 2006 Aug;21(8):1059-66

2.4 Peri-operative catheter care and catheter complications (leaks, hernias, obstruction) should be managed according to the International Society of Peritoneal Dialysis guidelines, www.ispd.org (Good practice)

Audit Measure 11: Catheter complications and their resolution

For management of the catheter in the peri-operative period, for catheter related problems including leak (internal and external), poor flow, obstruction and hernias the guidelines developed by the International Society of Peritoneal Dialysis should be used, www.ispd.org (1, 2). Catheter problems due to increased intra-peritoneal pressure, especially leaks, hernias and prolapse are an important medical indication for the use of APD either temporarily or permanently; poor flow or catheter related flow pain should be treated with tidal APD.

1. Flanigan M, Gokal R. Peritoneal catheters and exit-site practices toward optimum peritoneal access: a review of current developments. *Perit Dial Int.* 2005;25(2):132-9.
2. Crabtree JH. Rescue and salvage procedures for mechanical and infectious complications of peritoneal dialysis. *Int J Artif Organs.* 2006;29(1):67-84.

3. Solute Clearance

3.1 Both residual urine and peritoneal dialysis components of small solute clearance should be measured at least six monthly or more frequently if clinically indicated. Both urea and/or creatinine clearances can be used to monitor dialysis adequacy and should be interpreted within the limits of the methods. (Good practice)

Audit Measure 12: Frequency of solute clearance (residual and peritoneal) estimation.

Small solute clearance is one of the measurements of adequate dialysis treatment. Salt and water removal and acid-base balance are considered in sections 4 and 6 respectively. There are two issues in measuring small solute clearance that need to be taken into consideration. First, the relationship to clinical outcomes of residual renal versus peritoneal small solute clearance is quantitatively different. Observational studies have shown that preserved renal clearance, in fact just urine volume, is associated with improved survival, independent of other known factors such as age and comorbidity (1, 2). Randomised controlled trials designed to replace this residual renal function with peritoneal clearance did not show a proportional survival benefit (3, 4). Second, there are two potential surrogate solutes, urea and creatinine, that can be used

to measure solute clearance in PD patients. There is no clear evidence as to which is
the more useful clinically, and both have their problems. Current advice, therefore, is that either or both can be used, but clinicians should be aware of their differing limitations. Urea clearances are limited by the difficulty in PD patients of estimating V accurately, whilst peritoneal creatinine clearances are affected by membrane transport
characteristics (see Appendix).

1. Churchill DN, Taylor DW, Keshaviah PR. Adequacy of dialysis and nutrition in continuous peritoneal dialysis: association with clinical outcome. *J Am Soc Nephrol* 1996;7:198-207.
2. Bargman JM, Thorpe KE, Churchill DN. Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. *J Am Soc Nephrol* 2001;12(10):2158-62.
3. Paniagua R, Amato D, Vonesh E, et al. Effects of Increased Peritoneal Clearances on Mortality Rates in Peritoneal Dialysis: ADEMEX, a Prospective, Randomized, Controlled Trial. *J Am Soc Nephrol* 2002;13(5):1307-20.
4. Lo WK, Ho YW, Li CS, et al. Effect of Kt/V on survival and clinical outcome in CAPD patients in a randomized prospective study. *Kidney Int* 2003;64(2):649-56.

3.2 A combined urinary and peritoneal Kt/Vurea of 1.7/week or a creatinine clearance of 50L/week/1.73m2 should be considered as minimal treatment doses.

The dose should be increased in patients experiencing uraemic symptoms (Evidence)

Audit Measure 13: Cumulative frequency curves for the total solute clearance

Two randomised controlled trials (ADEMEX and Hong Kong) have evaluated the impact of peritoneal solute clearances on clinical endpoints (1, 2). Neither found that an increase of peritoneal Kt/V_{urea} >1.7 was associated with an improvement in survival.

Only one of these studies (ADEMEX) measured creatinine clearance, which was the solute used to make decisions in this case; patients in the control group achieved an average peritoneal creatinine clearance of 46L/1.73m2/week and a total (urine plus renal) of 54L/1.73m2/week. In setting a recommendation for minimal peritoneal clearances, to be achieved in anuric patients, the previous Renal Association guideline
of Kt/V > 1.7 and creatinine clearance >50L/1.73m2/week is supported by both the randomised and observational data. In the Hong Kong study, patients randomised to a
Kt/V <1.7, whilst their mortality was not significantly worse they had a significantly higher drop out rate, more clinical complications and worse anaemia. One observational longitudinal study demonstrated that patients develop malnutrition once
the Kt/V falls below 1.7 with a three-fold increase in the death rate (3). The NECOSAD study found that a creatinine clearance of <40L/wek or a Kt/V urea <1.5 was associated with increased mortality in anuric patients (4).

The vast majority of PD patients will be able to reach these clearance targets, especially if APD is employed (5). These guidelines must however be viewed as recommendations for *minimal* overall clearance. In patients with residual renal function this renal clearance can be subtracted from the peritoneal clearance with confidence that the value of equivalent renal clearances in greater. Equally, in patients
achieving these clearances but experiencing uraemic symptoms, or failing to achieve

adequate acid base balance (see section 6) the dialysis dose should be increased. Drop
out due to uraemia or death associated with hyperkalaemia and acidosis was significantly more common in the control patients in the ADEMEX study (1).
Studies in children include small patient numbers and results are variable, some suggesting a ceiling above which no further improvement in growth and nutritional state occurs because of peritoneal protein losses. It is recommended that the standards for adults should be seen as a minimum for children (6).

1. Paniagua R, Amato D, Vonesh E, et al. Effects of Increased Peritoneal Clearances on Mortality Rates in Peritoneal Dialysis: ADEMEX, a Prospective, Randomized, Controlled Trial. *J Am Soc Nephrol* 2002;13(5):1307-20.
2. Lo WK, Ho YW, Li CS, et al. Effect of Kt/V on survival and clinical outcome in CAPD patients in a randomized prospective study. *Kidney Int* 2003;64(2):649-56.
3. Davies SJ, Phillips L, Russell L, Naish PF, Russell GI. An analysis of the effects of increasing delivered dialysis treatment to malnourished peritoneal dialysis patients. *Kidney Int* 2000;57(4):1743-54.
4. Jansen MA, Termorshuizen F, Korevaar JC, Dekker FW, Boeschoten E, Krediet RT. Predictors of survival in anuric peritoneal dialysis patients. *Kidney Int.* 2005;68(3):1199-205.
5. Brown EA, Davies SJ, Heimburger O, et al. Adequacy targets can be met in anuric patients by automated peritoneal dialysis: baseline data from EAPOS. *Perit Dial Int* 2001;21(Suppl 3):S133-7.
6. Lesley Rees 1, Vanessa Shaw. Nutrition in children with CRF and on dialysis. Pediatr Nephrol, in press

4. Ultrafiltration and fluid management

4.1 Peritoneal membrane function should be monitored regularly (6 weeks after commencing treatment and at least annually or when clinically indicated) using a peritoneal equilibration test (PET) or equivalent. Daily urine and peritoneal ultrafiltration volumes, with appropriate correction for overfill, should
be monitored six-monthly. (Good practice)

Audit Measure 14: Frequency of measurement of membrane function, residual urine and peritoneal ultrafiltration volume

Assessment of membrane function, specifically solute transport rate and ultrafiltration
capacity) is fundamental to PD prescription. (See appendix for methodological description of membrane function tests). This is for the following reasons:
1. There is considerable between-patient variability in both solute transport and ultrafiltration capacity that translates into real differences in achieved solute clearance and ultrafiltration unless they are accounted for in prescription practice (1-5)
2. Membrane function is an independent predictor of patient survival; specifically high solute transport and low ultrafiltration capacity are associated with worse outcomes (6-10)
3. Membrane function changes with time on therapy. There are early changes . usually during the first few weeks of treatment that can be avoided by performing tests 6 weeks after commencing PD. Later changes vary between patients but tend to be increasing solute transport and reduced ultrafiltration capacity; the rate of membrane change is accelerated in patients with earlier loss of residual renal function and greater requirement for hypertonic glucose solutions. (5, 11, 12)
Residual renal function, as discussed above, is one of the most important factors, along
with age, comorbidity, nutritional status, plasma albumin and membrane function that

predict survival in PD patients. Its rate of loss is variable and clinically significant changes can occur within 6 months. Total fluid removal is associated with patient survival, especially once anuric (9, 13, 14), ADEMEX study, data awaiting publication.

1. Twardowski ZJ, Nolph KD, Khanna R, et al. Peritoneal Equilibration Test. *Perit Dial Bull* 1987;7:138-47.
2. Smit W, van Dijk P, Langedijk MJ, et al. Peritoneal function and assessment of reference values using a 3.86% glucose solution. *Perit Dial Int* 2003;23(5):440-9.
3. Smit W, Schouten N, van den Berg N, Langedijk MJ, Struijk DG, Krediet RT. Analysis of the prevalence and causes of ultrafiltration failure during long-term peritoneal dialysis: a cross-sectional study. *Perit Dial Int* 2004;24(6):562-70.
4. Selgas R, Bajo MA, Cirugeda A, et al. Ultrafiltration and small solute transport at initiation of PD: questioning the paradigm of peritoneal function. *Perit Dial Int.* 2005;25(1):68-76.
5. Davies SJ. Longitudinal relationship between solute transport and ultrafiltration capacity in peritoneal dialysis patients. *Kidney Int* 2004;66:2437-45.
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7. Churchill DN, Thorpe KE, Nolph KD, Keshaviah PR, Oreopoulos DG, Page D. Increased peritoneal membrane transport is associated with decreased patient and technique survival for continuous peritoneal dialysis patients. *J Am Soc Nephrol* 1998;9:1285-92.
8. Rumpsfeld M, McDonald SP, Johnson DW. Higher peritoneal transport status is associated with higher mortality and technique failure in the Australian and New Zealand peritoneal dialysis patient populations. *J Am Soc Nephrol.* 2006;17(1):271-8. Epub 2005 Nov 23.
9. Brown EA, Davies SJ, Rutherford P, et al. Survival of Functionally Anuric Patients on Automated Peritoneal Dialysis: The European APD Outcome Study. *J Am Soc Nephrol* 2003;14(11):2948-57.
10. Brimble KS, Walker M, Margetts PJ, Kundhal KK, Rabbat CG. Meta-analysis: peritoneal membrane transport, mortality, and technique failure in peritoneal dialysis. *J Am Soc Nephrol.* 2006;17(9):2591-8. Epub 006 Aug 2.
11. Heimburger O, Wang T, Lindholm B. Alterations in water and solute transport with time on peritoneal dialysis. *Perit Dial Int* 1999;19 Suppl 2:S83-90.
12. del Peso G, Fernandez-Reyes MJ, Hevia C, et al. Factors influencing peritoneal transport parameters during the first year on peritoneal dialysis: peritonitis is the main factor. *Nephrol Dial Transplant.* 2005;20(6):1201-6.
13. Ates K, Nergizoglu G, Keven K, et al. Effect of fluid and sodium removal on mortality in peritoneal dialysis patients. *Kidney Int* 2001;60(2):767-76.
14. Jansen MA, Termorshuizen F, Korevaar JC, Dekker FW, Boeschoten E, Krediet RT. Predictors of survival in anuric peritoneal dialysis patients. *Kidney Int.* 2005;68(3):1199-205.

4.2 Dialysis regimes resulting in fluid reabsorption should be avoided. (Good practice). Patients with high or high average solute transport, at greatest
risk of this problem, should be considered for APD and icodextrin (Evidence)
Audit Measure 15: Identify patients with fluid reabsorption in long dwell

Increased solute transport has been repeatedly shown to be associated with worse survival, especially in CAPD patients (1-4). The explanation for this association is most likely to be because of its effect on ultrafiltration when this is achieved with an osmotic gradient (using glucose or amino-acid dialysis fluids). The reason is twofold: first, due to more rapid absorption of glucose, the osmotic gradient is lost earlier in the
cycle resulting in reduced ultrafiltration capacity. Second, once the osmotic gradient is
dissipated the rate of fluid reabsorption in high transport patients is more rapid. This will result in significant fluid absorption, contributing to a positive fluid balance, during the long exchange.

These problems associated with high transport can be avoided by using APD to shorten dwell length and by using icodextrin for the long exchange to prevent fluid reabsorption. Several randomised controlled trials have shown that icodextrin can

achieve sustained ultrafiltration in the long dwell (5-9) and that this translates into a reduction in extracellular fluid volume (10, 11). Observational studies indicate that high solute transport is not associated with increased mortality or technique failure in APD patients, especially when there is also a high use of icodextrin (3, 12, 13).

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2. Churchill DN, Thorpe KE, Nolph KD, Keshaviah PR, Oreopoulos DG, Page D. Increased peritoneal membrane transport is associated with decreased patient and technique survival for continuous peritoneal dialysis patients. *J Am Soc Nephrol* 1998;9:1285-92.
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7. Wolfson M, Piraino B, Hamburger RJ, Morton AR. A randomized controlled trial to evaluate the efficacy and safety of icodextrin in peritoneal dialysis. *Am J Kidney Dis* 2002;40(5):1055-65.
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for peritoneal ultrafiltration. *J Am Soc Nephrol* 2005;16(2):546-54.
10. Konings CJ, Kooman JP, Schonck M, et al. Effect of icodextrin on volume status, blood pressure and echocardiographic parameters: A randomized study. *Kidney Int* 2003;63(4):1556-63.
11. Davies SJ, Woodrow G, Donovan K, et al. Icodextrin improves the fluid status of peritoneal dialysis patients: results of a double-blind randomized controlled trial. *J Am Soc Nephrol* 2003;14(9):2338-44.
12. Brown EA, Davies SJ, Rutherford P, et al. Survival of Functionally Anuric Patients on Automated Peritoneal Dialysis: The European APD Outcome Study. *J Am Soc Nephrol* 2003;14(11):2948-57.
13. Davies SJ. Mitigating peritoneal membrane characteristics in modern PD therapy. *Kidney Int* 2006;in press.

4.3 Dialysis regimes resulting in routine utilisation of hypertonic (3.86%) glucose exchanges should be avoided (Good practice). Where appropriate this should be achieved by avoiding excess dietary salt intake, using diuretics or icodextrin (Evidence).

There is growing evidence that regular use of hypertonic glucose dialysis fluid (3.86%), and where possible glucose 2.27%, is to be avoided. It is associated with acceleration in the detrimental changes in membrane function that occur with time on treatment (1, 2), as well as several undesirable systemic effects including weight gain
(3, 4), poor diabetic control (5), delayed gastric emptying (6), hyperinsulinaemia and adverse haemodynamic effects (7). In addition to patient education to avoid excessive
salt and fluid intake, where possible the use of hypertonic glucose should be minimised
by enhancing residual diureses with the use of diuretics (e.g. frusemide 250mg daily) (8). Substituting icodextrin for glucose solutions during the long exchange will result in equivalent ultrafiltration whilst avoiding the systemic effects of the glucose load (3, 5, 7, 9). Observational evidence would suggest that icodextrin is associated with less functional deterioration in the membrane in APD patients (2).

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peritoneal dialysis patients. *Kidney Int* 2004;66:2437-45.
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with icodextrin. *Nephrol Dial Transplant* 2005; 20(9):1848-53.
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9. Davies SJ, Woodrow G, Donovan K, et al. Icodextrin improves the fluid status of peritoneal dialysis patients: results of a double-blind randomized controlled trial. *J Am Soc Nephrol* 2003;14(9):2338-44.

4.4 Treatment strategies that favour preservation of renal function should be adopted where possible (Good practice). These include avoidance of episodes
of dehydration, use of diuretics, ACEi and ARBs (Evidence)

This is the single most important parameter in PD patients, and also the one most likely
to change with time. Clinically significant changes can occur within three months. Because secretion of creatinine by the kidney at low levels of function overestimates residual creatinine clearance, it is recommended to express this as the *mean* of the urea
and creatinine clearances. Observational and randomised studies have shown that episodes of volume depletion, whether unintentional or in response to active fluid removal with the intent of changing blood pressure or fluid status, are associated with
increased risk of loss in residual renal function (1-4). Care should be taken not to volume deplete a PD patient too rapidly or excessively. The use of diuretics to maintain urine volume is not associated with a risk to renal clearances (5). ACE inhibitors, (Ramipril 5mg) (6) and ARBs (valsartan) (7) have been shown in randomised studies to maintain residual diuresis.

1. Jansen MA, Hart AA, Korevaar JC, Dekker FW, Boeschoten EW, Krediet RT. Predictors of the rate of decline of residual renal function in incident dialysis patients. *Kidney Int* 2002;62(3):1046-53.
2. Gunal AI, Duman S, Ozkahya M, et al. Strict volume control normalizes hypertension in peritoneal dialysis patients. *Am J Kidney Dis* 2001;37(3):588-93.
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4.5 Anuric patients who consistently achieve a daily ultrafiltration of less than 750 should be closely monitored and the benefits of modality switch considered (Good practice)

Audit Measure (adult only): Identify patients with a total fluid removal <750 ml per day. Observational studies have consistently shown that reduced peritoneal ultrafiltration is associated with worse survival rates; whilst this is seen in studies with or without residual urine (1), this effect is most marked in anuric patients (2, 3). In the only prospective study to have preset an ultrafiltration target (750 ml/day), patients who remained below this had higher mortality after correcting for age, time on dialysis,
comorbidity and nutritional status. It is likely this association is multifactorial, but failure to prescribe sufficient glucose or icodextrin and a lower ultrafiltration capacity of the membrane were factors in this study and should be considered (2, 4). The European guidelines have suggested a 1 litre minimal daily ultrafiltration target;(5) there is insufficient evidence to say that such a target must be met at this stage. Blood
pressure, salt (and fluid) intake, nutritional and fluid status should be taken into account. Nevertheless patients with less than 750 ml ultrafiltration once anuric should
be very closely monitored and the potential benefits of modality switch considered.

1. Ates K, Nergizoglu G, Keven K, et al. Effect of fluid and sodium removal on mortality in peritoneal dialysis patients. *Kidney Int* 2001;60(2):767-76.
2. Brown EA, Davies SJ, Rutherford P, et al. Survival of Functionally Anuric Patients on Automated Peritoneal Dialysis: The European APD Outcome Study. *J Am Soc Nephrol* 2003;14(11):2948-57.
3. Jansen MA, Termorshuizen F, Korevaar JC, Dekker FW, Boeschoten E, Krediet RT. Predictors of survival in anuric peritoneal dialysis patients. *Kidney Int.* 2005;68(3):1199-205.
4. Davies SJ, Brown E, Riegel W, et al. What is the link between poor ultrafiltration and increased mortality in anuric APD patients? Analysis of data from EAPOS. *Perit Dial Int* 2006;26(4):458-65.
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5. Infectious complications

5.1 Prevention Strategies

5.1.1 PD units should undertake regular audit of their peritonitis and exit-site infection rates, including causative organism, treatment and outcomes. They should enter into active dialogue with their microbiology department and infection control team to develop optimal local treatment and prevention protocols (Good practice)

5.1.2 Flush-before-fill dialysis delivery systems should be used (Evidence)

5.1.3 Patients should undergo regular (annually or more frequently if indicated) revision of their technique and receive intensified training if this is below standard (Evidence)

5.1.4 Initial catheter insertion should be accompanied by antibiotic prophylaxis (Evidence)

**5.1.5 Invasive procedures should be accompanied by antibiotic prophylaxis and
emptying the abdomen of dialysis fluid for a period commensurate with the procedure (Good practice)**

**5.1.6 Topical antibiotic administration should be used to reduce the frequency of
Staph. aureus and Gram negative exit-site infection and peritonitis (Evidence)**

Audit Measure 16: Routine annual audit of infection prevention strategies

The rationale underpinning the guidelines in this section is laid out in a series of

documents published by the International Society of Peritoneal Dialysis, available on their web-site: www.ispd.org

Prevention strategies: Both the ISPD 2005 guidelines (1) and the NSF Part 1 place increasing emphasis on prevention strategies. Regular audit is essential to this progress

and the following standards should be considered as minimal:

1. Peritonitis rates of less than 1 episode per 18 months in adults and 12 months in children (see NSF part 1)
2. A primary cure rate of 80%
3. A culture negative rate of < 20%

Approaches that have been shown to reduce infection rates in randomised studies include increased intensity of training (2), use of flush before fill systems,(3) antibiotic prophylaxis to cover catheter insertion and prevention of exit-site infections (1). Several studies have addressed the latter issue; following demonstration that the risk of

Staph aureus exit site infection (the organism responsible in 90% of cases) is associated with pre-existing skin carriage, several randomised studies demonstrated that clinical exit-site infection and associated peritonitis could be reduced by either nasal or exit-site application of mupirocin. This has led to the practice of applying mupirocin to all patients;(4, 5) this approach should be discussed with the local microbiology and infection control team. A more recent study, comparing mupirocin with gentamicin cream, found that the latter prevented both *Staph aureus* and *Pseudomonas* exit-site infections and peritonitis episodes (6). This approach should be

strongly considered in patients with a known history of *Pseudomonas* infections; again

the policy should be discussed and agreed with the local microbiology team.

1. Piraino B, Bailie GR, Bernardini J, et al. Peritoneal dialysis-related infections recommendations: 2005 update. *Perit Dial Int.* 2005;25(2):107-31.
2. Hall G, Bogan A, Dreis S, et al. New directions in peritoneal dialysis patient training. *Nephrol Nurs J.* 2004;31(2):149-54, 59-63.
3. MacLeod A, Grant A, Donaldson C, et al. Effectiveness and efficiency of methods of dialysis therapy for end-stage renal disease: systematic reviews. *Health Technol Assess* 1998;2(5):1-166.
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5.2 Treatment

5.2.1 Exit site infection is suggested by pain, swelling, crusting, erythema and serous discharge; purulent discharge always indicates infection. Swabs should be

taken for culture and initial empiric therapy should be with oral antibiotics that will cover *S. aureus and P. aeruginosa* (Good practice)

5.2.2 Methicillin resistant organisms (MRSA) will require systemic treatment (e.g vancomycin) and will need to comply with local infection control policies. (Good practice)

5.2.3 Initial treatment regimes for peritonitis should include cover for bacterial Gram positive and Gram negative organisms until result of culture and

antibiotic sensitivities are obtained. (Good practice)

Audit Measure 17: Routine annual audit of infection outcomes (exit site and peritonitis rates

The ISPD has developed a simple scoring system for exit site signs and symptoms which is easy to use and gives guidance on when to treat immediately rather than waiting for a swab result. Purulent discharge is an absolute indicator for antibiotic treatment (1). The ISPD has become less dogmatic about the initial choice of antibiotic
treatment for peritonitis, provided that gram positive and negative infections are covered. It is recognised that patterns of resistance vary considerably and thus a local
policy must be developed.

1. Piraino B, Bailie GR, Bernardini J, et al. Peritoneal dialysis-related infections recommendations: 2005 update. *Perit Dial Int.* 2005;25(2):107-31.

6. Metabolic Factors

6.1 Standard strategies to optimise diabetic control should be used; these should be complemented by dialysis prescription regimens that minimise glucose,
including glucose free solutions (icodextrin and amino-acids), where possible. (Good practice)

Glycaemic control can be made worse by glucose absorption across the peritoneal membrane. Dialysis regimes that incorporate less glucose and more glucose free (amino acid, icodextrin) solutions have been shown to improve glycaemic control (1), Paniagua (in press).

1. Marshall J, Jennings P, Scott A, Fluck RJ, McIntyre CW. Glycemic control in diabetic CAPD patients assessed by continuous glucose monitoring system (CGMS). *Kidney Int* 2003;64(4):1480-6.

6.2 **Plasma bicarbonate should be maintained within the normal range; this can be achieved in the vast majority of patients by adjusting the dialysis dose and/or dialysate buffer concentration. Occasionally bicarbonate buffered solutions will be required (Good practice).**

Audit measure 18: Cumulative frequency curves of plasma bicarbonate

Two randomised controlled trials have suggested that clinical outcomes, including gaining lean body mass and reduced hospital admissions are achieved if the plasma bicarbonate is kept within the upper half of the normal range.(1, 2) Generally this can be achieved by using dialysis fluids with a 40 mmol buffer capacity (lactate or bicarbonate results in similar plasma bicarbonate levels(3)) and ensuring that the dialysis dose is adequate (see section 3 (b), above) (4). However, for solutions with a
lower buffering capacity, when patients are switched from an all lactate (35 mmol/l) to
a 25 mmol bicarbonate: 10 mmol lactate mix, there is a significant improvement in plasma bicarbonate (24.4 to 26.1 mmol/l), such that a higher proportion of patients will
fall within the normal range (5). Whilst bicarbonate solutions may have a role in biocompatibility (see section 1(e), above), they are generally not required to achieve satisfactory acid-base balance. The main reason for using a 35 mmol buffer capacity solution (25:10 bicarbonate:lactate mix) is to avoid excessive alkalinisation (6). The long-term effects of persistent metabolic alkalosis on the developing skeleton are not known, and an alkaline pH can predispose to soft tissue calcification.

Control of acidosis is especially important in malnourished patients who may benefit from the glucose available in dialysis solutions as a calories source. Amino acid

solutions were developed in an attempt to address protein calorie malnutrition and several randomised studies have been conducted. In using amino acid solutions it is essential to ensure that acidosis does not develop and to use the solution at the same
time as there is a significant intake of carbohydrate (7). Despite demonstration that amino acids delivered in dialysis fluids are incorporated into tissue protein, the randomised trials have failed to show benefit in terms of hard clinical endpoints (8, 9).

1. Stein A, Moorhouse J, Iles-Smith H, et al. Role of an improvement in acid-base status and nutrition in CAPD patients. *Kidney Int* 1997;52(4):1089-95.
2. Szeto CC, Wong TY, Chow KM, Leung CB, Li PK. Oral sodium bicarbonate for the treatment of metabolic acidosis in peritoneal dialysis patients: a randomized placebo-control trial. *J Am Soc Nephrol* 2003;14(8):2119-26.
3. Coles GA, Gokal R, Ogg C, et al. A randomized controlled trial of a bicarbonate- and a bicarbonate/lactate-containing dialysis solution in CAPD. *Perit Dial Int* 1997;17(1):48-51.
4. Mujais S. Acid base profile in patients on PD. *Kidney Int* 2003;Suppl. 83(Deb):in press.
5. Otte K, Gonzalez MT, Bajo MA, et al. Clinical experience with a new bicarbonate (25 mmol/L)/lactate (10 mmol/L) peritoneal dialysis solution. *Perit Dial Int* 2003;23(2):138-45.
6. Dratwa M, Wilkie M, Ryckelynck JP, et al. Clinical experience with two physiologic bicarbonate/lactate peritoneal dialysis solutions in automated peritoneal dialysis. *Kidney Int* 2003;88:S105-13.
7. Kopple JD, Bernard D, Messana J, et al. Treatment of malnourished CAPD patients with an amino acid based dialysate. *Kidney Int* 1995;47(4):1148-57.
8. Li FK, Chan LY, Woo JC, et al. A 3-year, prospective, randomized, controlled study on amino acid dialysate in patients on CAPD. *Am J Kidney Dis* 2003;42(1):173-83.
9. Jones M, Hagen T, Boyle CA, et al. Treatment of malnutrition with 1.1% amino acid peritoneal dialysis solution: results of a multicenter outpatient study. *Am J Kidney Dis* 1998;32(5):761-9.

**6.3 Central obesity can worsen or develop in some PD patients. The risk of this problem, and associated metabolic complications, notably increased atherogenicity of lipid profiles and insulin resistance, can be reduced by avoiding
excessive glucose prescription and using icodextrin. (Good practice)**

Weight gain, or regain, is common after starting peritoneal dialysis and this is associated with a worsening in the lipid profile (1). Randomised studies comparing glucose 2.27% with icodextrin in the long exchange have shown that the latter prevents weight gain, which in body composition studies is at least in part fat weight (2, 3). Recommendations on how to treat dyslipidaemia are published by the ISPD and
include the use of statins (4). There is no currently available trial data on the benefit of
statins in PD patients with a hard clinical endpoint; the 4D study did not include PD patients and there are good reasons for believing that the PD patient population may be
different.

1. Little J, Phillips L, Russell L, Griffiths A, Russell GI, Davies SJ. Longitudinal lipid profiles on CAPD: their relationship to weight gain, comorbidity, and dialysis factors. *J Am Soc Nephrol* 1998;9(10):1931-9.
2. Wolfson M, Piraino B, Hamburger RJ, Morton AR. A randomized controlled trial to evaluate the efficacy and safety of icodextrin in peritoneal dialysis. *Am J Kidney Dis* 2002;40(5):1055-65.
3. Davies SJ, Woodrow G, Donovan K, et al. Icodextrin improves the fluid status of peritoneal dialysis patients: results of a double-blind randomized controlled trial. *J Am Soc Nephrol* 2003;14(9):2338-44.
4. Fried L, Hutchison A, Stegmayr B, Prichard S, Bargman JM. Recommendations for the treatment of lipid disorders in patients on peritoneal dialysis. ISPD guidelines/recommendations. International Society for Peritoneal Dialysis. *Perit Dial Int* 1999;19(1):7-16.

6.4 Awareness of the effects of Icodextrin on assays for estimation of

amylase and glucose (using glucose dehydrogenase) should be disseminated to
patients, relatives, laboratory and clinical staff.

Audit Measure 19: Processes in place to increase awareness of interference of assays by icodextrin metabolites

Use of icodextrin is associated with circulating levels of metabolites that can interfere with laboratory assays for amylase (or actually suppress amylase activity) (1-4) and for glucose when finger-prick tests that utilise glucose dehydrogenase as their substrate are employed (manufactured by Boehringer Mannheim) (5-8). In the case of amylase, the measured level will be reduced by 90%, leading to the potential failure in the diagnosis of pancreatitis. No adverse events have been reported, but clinicians should be aware of this possibility. If clinical concern remains then plasma lipase can be used.

In the case of glucose measurements, the methods using glucose dehydrogenase will *over*-estimate blood glucose levels, leading to a failure to diagnose hypoglycaemia. This has been reported on several occasions in the literature and has contributed to at least one death. Typically these errors occur in places and circumstances in which staff not familiar with peritoneal dialysis work, for example emergency rooms and non-renal wards. A number of solutions to this problem are under active review (e.g. use of alarm bracelets) but it is also the responsibility of health-care professionals to ensure that clinical environments in which their patients using icodextrin may find themselves are notified of this issue on a routine basis.

1. Schoenicke G, Grabensee B, Plum J. Dialysis with icodextrin interferes with measurement of serum alpha-amylase activity. *Nephrol Dial Transplant* 2002;17(11):1988-92.
2. Wang R, Leesch V, Turner P, Moberly JB, Martis L. Kinetic analysis of icodextrin interference with serum amylase assays. *Adv Perit Dial* 2002;18:96-9.
3. Anderstam B, Garcia-Lopez E, Heimburger O, Lindholm B. Determination of alpha-amylase activity in serum and dialysate from patients using icodextrin-based peritoneal dialysis fluid. *Perit Dial Int* 2003;23(2):146-50.
4. Garcia-Lopez E, Anderstam B, Heimburger O, Amici G, Werynski A, Lindholm B. Determination of high and low molecular weight molecules of icodextrin in plasma and dialysate, using gel filtration chromatography, in peritoneal dialysis patients. *Perit Dial Int* 2005;25(2):181-91.
5. Wens R, Taminne M, Devriendt J, et al. A previously undescribed side effect of icodextrin: overestimation of glycemia by glucose analyzer. *Perit Dial Int* 1998;18(6):603-9.
6. Oyibo SO, Pritchard GM, McLay L, et al. Blood glucose overestimation in diabetic patients on continuous ambulatory peritoneal dialysis for end-stage renal disease. *Diabet Med* 2002;19(8):693-6.
7. Mehmet S, Quan G, Thomas S, Goldsmith D. Important causes of hypoglycaemia in patients with diabetes on peritoneal dialysis. *Diabet Med* 2001;18(8):679-82.
8. Janssen W, Harff G, Caers M, Schellekens A. Positive interference of icodextrin metabolites in some enzymatic glucose methods. *Clin Chem* 1998;44(11):2379-80.

7. Laboratory and clinical indices

7.1 Monitoring of biochemical and haematological parameters should be performed monthly or at each clinic visit (Good practice).

Standardised analytical methods of measuring laboratory indices are required if comparative audit against target standards is to be meaningful. Difficulties still arise

since laboratories across the UK use different methods to measure serum albumin and
different correction factors for adjusting serum calcium levels (1).

1. The Renal Association UK Renal Registry, The Seventh Annual Report, December 2004. (www.renalreg.com)

7.2 **Pre-dialysis serum bicarbonate concentrations measured with minimum delay after venepuncture should be between 20 and 26mmol/l. (Good practice)**

The main causal factors of metabolic acidosis are inadequate dialysis delivery, *ongoing*
renal losses, excessive animal protein (sulphur containing amino acid) intake and high
interdialysis weight gains. Whole-body base balance studies in 18 anuric HD patients have highlighted the importance of interdialysis dilution in the aetiology of predialysis acidosis (1). In ill patients metabolic acidosis may also be due to increased protein catabolism, hypotension or hypoxia induced lactate production or bicarbonate losses associated with co-morbid illness. Metabolic acidosis has a range of adverse consequences: an increase in protein catabolism and anti-anabolic effects, negative inotropic effect, loss of bone mineral, insulin resistance, growth retardation in children,
reduced thyroxine levels, altered triglyceride metabolism, hyperkalaemia, lower serum
leptin levels and greater accumulation of beta-2-microglobulin.

Pre-dialysis venous bicarbonate levels between 17.5 and 20 mmol/l were associated with the lowest risk of death in a large cohort study of 13535 hemodialysis patients whilst the relative risk of death was increased threefold if the pre-dialysis venous bicarbonate was < 15 mmol/l (2). In a DOPPS study of more than 7000 unselected HD
patients the corrected mid-week serum bicarbonate concentration averaged 21.9 mmol/l and correlated inversely with the nPCR and serum albumin (3). The adjusted risk of death, hospitalization or malnutrition was higher in patients with serum bicarbonate levels less than 16 or above 24 when compared with patients in the reference group with moderate pre-dialysis acidosis (3). Short-term benefits of correcting pre-dialysis acidosis from below 19mmol/l to 24mmol/l, by either increasing
the dialysate bicarbonate concentration (4-7) or the addition of oral bicarbonate supplements (8), have been shown in several small crossover studies. Correction of acidosis reduced whole body protein degradation in a study of 6 patients (4), increased
the sensitivity of the parathyroid glands to serum calcium in studies of 21 and 8 patients (5,6), improved triceps skin thickness as an index of nutritional status in 46 patients (7) and increased serum albumin after 3 months in 12 patients without any change in body weight, Kt/V, and nPCR (8). Other studies have shown no increase in
serum albumin after correction of acidosis.

1. *Mioni R, Gropuzzo M, Messa M et al. Acid production and base balance in patients in chronic hemodialysis. Cli Sci 201;101:329-37*
2. Lowrie EG, Lew NL. Death risk in hemodialysis patients: The predictive value of commonly measured variables and an evaluation of death rate differences between facilities. Am J Kidney Dis 1990; 15: 458-482
3. Bommer J, Locatelli F, Satayathum S et al. Association of predialysis serum bicarbonate levels with risk of mortality and hospitalisation in the Dialysis Outcomes and Practice

Patterns Study (DOPPS). Am J Kidney Dis 2004;44:661-71
4. Graham KA, Reaich D, Channon SM et al. Correction of acidosis in hemodialysis decreases whole-body protein degradation. J Am Soc Nephrol 1997;8: 632-7
5 Lefebvre A, de Verneioul MC, Gueris J et al. Optimal correction of acidosis changes progression of dialysis osteodystrophy. Kidney Int 1989;36:1112-8
6. Graham KA, Hoenich NA, Tarbit M et al. Correction of acidosis in hemodialysis patients increases the sensitivity of the parathyroid glands to calcium. J Am Soc Nephrol;1997;8:627-31
7. Williams AJ, Dittmer ID, McArley A, Clarke J. High bicarbonate dialysate in hemodialysis patients: effects on acidosis and nutritional status. Nephrol Dial Transplant 1997;12:2633-7
8. Movilli E, Zani R, Carli O et al. Correction of metabolic acidosis increases serum albumin concentrations and decreases kinetically evaluated protein intake in hemodialysis patients: a prospective study. Nephrol Dial Transplant 1998;13:1719-22

7.3 Serum potassium should be between 3.5 and 6.5 mmol/l (Good practice)
The risk of developing hyperkalaemia is inversely related to renal function. 3-5% of deaths in dialysis patients have been attributed to hyperkalaemia (1). Non-compliance
with the PD prescription and/or diet is the main cause of hyperkalaemia in dialysis patients but drug therapy, such as ACE inhibitors, angiotensin receptor blockers, nonsteroidal
anti-inflammatory drugs, beta-blockers and potassium supplements, may be implicated.
A Cochrane meta-analysis of non-dialytic emergency interventions for hyperkalaemia concluded that intravenous glucose with insulin and nebulised or inhaled salbutamol were effective in reducing serum potassium levels but the studies were limited by the absence of data on cardiac arrhythmia or mortality rates (2). Whilst the combination of
salbutamol and intravenous glucose with insulin was probably more effective than either therapy alone the evidence for efficacy of intravenous bicarbonate or potassium
exchange resins in this Cochrane review of randomized or quasi-randomised trials was
equivocal and neither should be used as monotherapy for severe hyperkalaemia .

1. Morduchowicz G, Winkler J, Drazne E et al. Causes of death in patients with end-stage renal disease treated by dialysis in a centre in Israel. Isr J Med Sci 1992;28:776-9
2. Mahoney BA, Smith WAD, Lo DS, Tsoi K, Tonelli M, Clase CM. Emergency interventions for hyperkalaemia (Cochrane Review). In: The Renal health Library, 2005. Oxford: Update Software Ltd (www.update-software.com)

7.4 Serum phosphate should be within, and preferably nearer to the 50th centile for age. (Good practice) (The normal range for phosphate declines from birth to adult levels by the age of 3 years)
7.5 Serum calcium, adjusted for serum albumin, should be within the age appropriate normal range. (Good practice)
7.6 Serum albumin corrected calcium x phosphate product should be less than <4.5 mmol$_2$/L$_2$ (K/DOQI guidelines) or <5 mmol$_2$/L$_2$ (European PD working group advice).
7.7 The optimal range for PTH is controversial. There is emerging evidence that levels should be maintained at less than twice the upper limit of normal for the intact PTH assay used. (Good practice)
Audit measure 21 - Cumulative frequency curves of serum calcium, phosphate calcium x phosphate product and PTH concentrations
7.8 Haemoglobin concentration should be greater than the lower limit of the age appropriate normal range. (Evidence) The target haemoglobin concentration should be 1g/dl higher, to allow for the normal distribution around the mean haemoglobin

value of the patient population and intra individual variation of laboratory measurements and hydration status.

Audit measure 22 - Cumulative frequency curves of haemoglobin concentration

7.9 Ferritin levels should be between 100 and 800 mcg/l. *However, given the increased*

risk of thrombotic events with higher ferritin levels that have been shown in recent trials, the revised K/DOQI guidelines for the management of anaemia recommend that the serum ferritin levels should be maintained between 100 . 500mcg/L in adults. In the absence of paediatric studies, in patients at risk of thrombosis (e.g. those with low serum albumin, arteriovenous fistulae or synthetic grafts), the serum ferritin levels above 500mcg/L should be avoided.

Haemoglobin levels should be maintained in the age appropriate normal range, aiming for Hb between 11-12gm/dL in children above 2 years of age.

7.8 Growth, wellbeing and school attendance are very important indicators of dialysis adequacy and should be assessed at least monthly in those under two years of age (length, weight and head circumference) and at least 3 monthly in older children (height, weight and pubertal stage, school attendance). Assessment of dry weight may

be difficult in the growing child and also needs checking with at least the same frequency, with close collaboration with a paediatric renal dietician.

Audit measure 22 Height, weight, head circumference and pubertal progression

7.9 An assessment of school progress, both in hospital and locally, can be used as an

assessment of well-being, and should be made annually

Audit measure 23 . School attendance

7.10 Blood pressure should be maintained within the age appropriate normal range

Audit measure 24 - Cumulative frequency curves of BP pre-dialysis

8. Access to and withdrawal from dialysis

RATIONALE

8.1 All children with CKD should be considered for renal replacement therapy by

stage 4 (Good practice)

CKD should be suspected in children with: bilateral renal anomalies on antenatal scans (many children with CKD are now diagnosed antenatally); a creatinine above the normal age appropriate range; bilateral renal defects on scans e.g. for UTI; a family history of CKD; persistent proteinuria; or after an episode of acute renal failure. All such children should be referred to a paediatric nephrologist. Early referral provides the opportunity for delaying the progression of CKD by treating hypertension and proteinuria, for optimising growth and preventing renal bone disease. Importantly, it also allows for timely forward planning for renal replacement therapy.

In adults, avoiding late referral provides the opportunity for intervention to prevent or reduce the complications of renal failure and time to plan for renal replacement therapy. Patients who have been under nephrology care for more than 1 month are more likely to start HD using an AVF (1). A retrospective analysis of 109,321 incident HD patients in the USA found that the relative risk of death of patients with no predialysis

nephrology care was 1.51 and the relative risk of death of patients with one or two months pre-dialysis nephrology care was 1.23 when compared with patients with at least 3 months nephrology pre-dialysis care (2).

1. Rayner HC, Besarab A, Brown WW et al. Vascular access results from the Dialysis Outomes and Practice Patterns Study (DOPPS): performance against Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines. Am J Kidney Dis 2004; 44 (Suppl 3): 22-26
2. Khan SS, Xue JL, Kazmi WH et al. Does pre-dialysis nephrology care influence patient survival after initiation of dialysis? Kidney Int 2005; 67:1038-1046

8.2 **If there is no medical contraindication the choice of initial dialysis modality should be based on patient choice. (Good practice)**

The provision of patient choice and equity of access to dialysis and transplantation have been reinforced by the National Service Framework Part 1 Dialysis and Transplantation (1). There has been only one small prospective randomized trial comparing HD and peritoneal dialysis in incident patients and this showed no differences in short-term patient outcomes in the small numbers of patients that could
be enrolled into the study but the study data were not powered adequately to reach any
other conclusion (2). In the absence of evidence that either HD or peritoneal dialysis provide superior patient outcomes the selection of initial dialysis modality should be based on the patient.s choice after full education about the different forms of renal replacement therapy that are available, including home HD and live donor and cadaveric transplantation (3).

*However, although patient choice is paramount, guidance from unit staff is necessary: venous access can be difficult to achieve and maintain in those less than 5
years of age, and needling of a fistula can be particularly difficult in an uncooperative patient. For these reasons, as well as social ones already discussed, PD is recommended in young children.*

1. The National Service Framework for Renal Services Part 1: Dialysis and Transplantation, Department of Health, London, UK, January 2004. (www.doh.gov.uk/nsf/renal/index.htm)
2. Korevaar JC, Feith GW, Dekker FW et al. Effects of starting with hemodialysis compared with peritoneal dialysis in patients new on dialysis treatment: A randomised controlled trial. Kidney Int 2003; 64 :2222-2228
3. National Institute of Clinical Excellence. Full guidance on home compared with hospital haemodialysis for patients with end-stage renal failure October 2002 (www.nice.org.uk)

8.3 **After full education and counselling a small proportion of families may opt for active non-dialytic management of advanced chronic kidney disease, including nutritional, medical and psychological support rather than plan to initiate dialysis. The numbers of patients not taken on to dialysis and the reasons
for this decision should be subject to audit. (Good Practice)**

The decision whether to start or not to start RRT may be difficult (1). It is impossible to set quantitative standards in this difficult area of care, but principles of action can be
enunciated and agreed. All patients who are found to have advanced renal failure should be considered for dialysis, and the patient.s age, social circumstances or required level of community support should not be a factor leading to exclusion. Nor should lack of facilities for dialysis be acceptable on its own as grounds for exclusion,
or fear of litigation a basis for a decision in either direction. Careful medical assessment

of any co-morbid conditions from which the patient may suffer is needed, together with whatever medical measures (short of dialysis) are required to correct them or minimise their effects (2). Similarly, patients who have deteriorated will need careful medical and psychological assessment. If it appears that only a brief period of survival
of unacceptable quality is likely on dialysis (e.g. less than three months), then the possibility of not starting or stopping dialysis needs to be considered. The interest of the individual patient must remain paramount, and although the opinions of relatives should be consulted, they should not be binding. The responsible consultant nephrologist should solicit views of the patient.s family doctor, next of kin, and all carers within the multidisciplinary caring team. The decision to start or not to start RRT must be taken by both the consultant), and the family. The family will need to be
fully informed throughout, and to be aware of the options. The most realistic and accurate description of starting or not starting, continuing or not continuing dialysis should be given. The substance of these discussions must be recorded in the patient.s
notes. If the decision is taken not to initiate, or to stop dialysis, then a management plan of supportive care must be put in place. This must then be carried through in a way that ensures continued support, achieves what seems best from the patient.s and
family.s point of view, and finally enables the patient to die with dignity, when the time
comes. Achieving this will often require co-ordinated work with the palliative care team, who should be involved early in the management plan (3). Certain patients who
are severely ill, often with conditions affecting several organs, may have a concurrent
acute deterioration of their chronic renal failure. The nephrologist, may feel, after discussion, that dialysis is inappropriate given the very poor prognosis from the underlying conditions. Under these circumstances the referring physician would discuss
matters with the patient, if possible, and with the family. Guidelines on shared decision-making in the initiation or withdrawal of dialysis have been developed (4). Two approaches may be taken when a patient presents in uraemia whose ability to cope with, and to enjoy and benefit from dialysis treatment is doubtful. The first approach attempts to make a .clean. decision on whether or not to start dialysis after a
process of consultation and discussion; the second, often called .trial of dialysis., involves starting a proportion of such patients on dialysis, but with a pre-discussed plan to review whether this should continue beyond a specified point in the near future
. usually a few weeks or months. Clearly the expectation is that the outcome in this case will be withdrawal of some patients from dialysis.

1. Tobe SW, Senn JS (for the End-Stage Renal Disease Group). Foregoing renal dialysis: case study and review of ethical issues. Am J Kidney Dis 1996; 28:147.153
2. Campbell ML. Terminal care of ESRD patients forgoing dialysis. ANNA J 1991; 18:202.204
3. Cohen LM, Germian M, Poppel DM et al. Dialysis discontinuation and palliative care. Am J Kidney Dis 2000; 36:140.144
4. Galla JH. Clinical practice guideline on shared decision-making in the appropriate initiation of and withdrawal from dialysis. J Am Soc Nephrol 2000; 11:1340-1342

8.4 Renal replacement therapy should commence when a patient with an eGFR < 15ml/min/1.73m2 has symptoms or signs of uraemia, fluid overload or malnutrition in spite of medical therapy or before an asymptomatic patient has an eGFR < 6ml/min/1.73m2. (Good practice)

There are no criteria based on definitive evidence to advise when to start dialysis. In the absence of severe hyperkalaemia or pericarditis there is no definitive evidence to indicate when an asymptomatic patient with advanced renal failure should initiate dialysis. There is consensus that patients should start dialysis when they develop symptoms or signs of fluid overload, hypertension, poor nutrition or uraemia which cannot be controlled by medical therapy such as high dose diuretics, even if their estimated residual renal function is relatively high. Nutritional status and dietary protein intake decrease progressively as renal function declines (1). The medical treatment of the complications of renal failure such as anaemia has improved in the past 10 years and this may explain recent reports of a lack of any relationship between
the presence or absence of traditional symptoms of uraemia and residual renal function
in patients with stage 5 chronic kidney disease (2). The patients with a higher haemoglobin concentration had fewer symptoms (2) and so relying on the onset of symptoms may result in patients starting dialysis too late. Conversely studies in the Netherlands and Scotland comparing patients who started dialysis at two different levels of residual renal function have shown no advantage to patient survival if adjustments are made for lead time bias in the group of patients starting dialysis with higher residual renal function (3-6). In the multicentre prospective Netherlands study 94 of the 253 incident patients began dialysis later than recommended in the US NKF
KDOQI guideline and the adjusted benefit in survival after 3 years on dialysis was 2.5
months in the timely starter group (4). However this benefit may be attributed to leadtime
bias since the average delay in initiation of dialysis in the late starter group was 4.1 months. A randomized prospective study to compare 3 year morbidity and mortality after initiating dialysis when patients have a Cockcroft and Gault creatinine clearance of 10-14ml/min/1.73m2 or 5-7ml/min/1.73m2 is underway (IDEAL study) (7).

With the evidence that nutritional status deteriorates progressively as renal function declines (1) and symptoms of advanced renal failure are not closely related to the degree of residual renal function in the modern era (2) it is appropriate that international guidelines have attempted to identify the level of residual renal function at
which an asymptomatic patient should initiate dialysis. The above considerations fit well with the European Best Practice Guidelines which recommended that renal replacement therapy should commence when a patient with an eGFR < 15ml/min/1.73m2 has symptoms or signs of uraemia, fluid overload or malnutrition in spite of medical therapy or before an asymptomatic patient has an eGFR < 6ml/min/1.73m2 (8).

**Audit measure 17 . Record of the serum creatinine, the estimated GFR and comorbidity
at initiation of chronic renal replacement therapy (dialysis or transplantation)**

1. Ikizler TA, Greene JH, Wingarde RL et al. Spontaneous dietary protein intake during progression of chronic renal failure. J Am Soc Nephrol 1995; 6: 1386-1391
2. Curtis BM, Barrett BJ, Jindal K et al. Canadian survey of clinical status at dialysis initiation 1998-1999: a multicentre prospective study. Clin Nephrol 2002; 58:282-288
3. Traynor JP, Simpson K, Geddes CC et al. Early initiation of dialysis fails to prolong survival in patients in end-stage renal failure. J Am Soc Nephrol 2002; 13:2125-2132
4. Korevaar JC, Jansen MA, Dekker FW et al. When to initiate dialysis: effect of proposed US guidelines on survival. Lancet 2001; 358:1046-1050
5. Korevaar JC, Dekker FW, Krediet RT. Initiation of dialysis: is the problem solved by NECOSAD? Nephrol Dial Transplant 2003; 18: 1228-1229
6. Termorshuizen F, Korevaar JC, Dekker FW et al. Time trends in initiation and dose of dialysis in end-stage renal disease patients in The Netherlands. Nephrol Dial Transplant 2003; 18: 552-558
7. Cooper BA, Branley P, Bulfone L et al. The Initiating Dialysis Early and Late (IDEAL) study: study rationale and design. Perit Dial Int 2004; 24: 176-181
8. European Best Practice Guidelines for haemodialysis Part 1. Nephrol Dial Transplant 2002; 17: Supplement 7 S1-S111 (http://ndt.oupjournals.org/content/vol17/suppl_7/index.shtml).

8.5 Any decision to discontinue haemodialysis should be made jointly by the patient (when age appropriate) and their carers and the responsible consultant nephrologist and the renal team and the family practitioner. The decision and reasons for it should be recorded in the patient.s notes. Renal units should develop guidelines for palliative care of such patients, including liaison with community services. (Good practice)

In addition to patients who clearly present greater than average problems from the outset, there are individuals who have had a period of worthwhile life on dialysis, but whose quality of life worsens because of medical or psychological deterioration, or both simultaneously. Additional difficulty arises when dementia, often fluctuating, or irrecoverable neurological deficit after a cerebrovascular event makes it difficult or impossible to ascertain what the patient.s own feelings and wishes might be (1). In practice, the decision to withdraw dialysis has much in common with decision not to start a patient on dialysis. This is because caring staff, patients and relatives all face similar difficult judgements and decisions about the likely quality and quantity of life on
dialysis. A similar process to that outlined in deciding whether or not to plan to start dialysis (see above) should be followed when assessing if withdrawal of dialysis is appropriate. There is one study from the UK that suggests that withdrawal from dialysis plays a major role (17%) in overall death rates on dialysis (2), as it does in the
USA and Canada (3,4). Recent data from the Dialysis Outcomes and Practice Patterns
Study have shown that the rate for withdrawal from HD is 3.5 per 100 patient-years and that not surprisingly .do not resuscitate. orders are associated with older age and
nursing home residence (5). In a recent UK study withdrawal of dialysis was the commonest cause of death (38%) in the group of patients commencing dialysis when more than 75 years old (6). Withdrawal of dialysis is an increasing cause of death in dialysis patients and the date of the decision and the reasons for it should be recorded
in the patient.s casenotes (7). Renal units should develop guidelines for withdrawal of
dialysis that include liaison with palliative care and community services.

1. Singer J, Thiel EC, Naylor D et al. Life-sustaining treatment preferences of hemodialysis patients: implications for advance directives. J Am Soc Nephrol 1995; 6:1410.1417
2. Catalano C, Goodship THJ, Graham KA et al. Withdrawal of renal replacement therapy in

Newcastle upon Tyne: 1964-1993. Nephrol Dial Transplant 1996; 11:133.139
3. Cohen LM, McCue JD, Germain M, Kjellstrand CJ. Dialysis discontinued: a good death? Arch Intern Med 1995; 155:42.47
4. Friedman EA. The best and worst times for dialysis are now. ASAIO J 1994; 40:107.108
5. Fissell RB, Bragg-Gresham JL, Lopez AA et al. Factors associated with "do not resuscitate" orders and rates of withdrawal from hemodialysis in the international DOPPS. Kidney Int; 2005 68: 1282-1288
6. Munshi SK, Vijayakumar N, Taub NA et al. Outcome of renal replacement therapy in the very elderly. Nephrol Dial Transplant 2001; 16:1721-1722
7. McLean AM. Dialysis treatment withdrawal . Legal aspects (UK). Nephrol Dial Transplant 1998; 13:1152-1153

APPENDIX

Assessment of Membrane Function

(a) A number of methods to assess peritoneal membrane have been developed, the most commonly used, supported by clinical observation being the Peritoneal Equilibration Test (PET). This test measures two aspects of membrane function, low molecular weight solute transport (expressed as the dialysate:plasma ratio of creatinine
at four hours), and the ultrafiltration capacity of the membrane. In the PET as originally described, ultrafiltration capacity is the net volume of ultrafiltration achieved at four hours using a 2.27% glucose exchange (1, 2). In the simplified Standard Permeability Analysis (SPA) test, it is the net volume of ultrafiltration using a 3.86% exchange (3, 4)

(b) Using a standard PET, an ultrafiltration capacity of < 200 mls (includes overfill) is associated with a 50% risk of achieving < 1000 mls ultrafiltration in anuric patients. Using a SPA test, an ultrafiltration capacity of < 400 mls indicates ultrafiltration failure.

(c) The methods of performing PET and SPA tests are well described in the literature,

The following points should be remembered in the interpretation of results:

□ High concentrations of glucose interfere with many assays for creatinine. It is important to work with the local biochemists to ensure that the appropriate correction for measurement of creatinine in dialysate has been taken into account.

□ Remember that dialysis bags are overfilled, mainly due to the additional fluid volume required to perform the .flush before fill. procedure. Dialysis manufacturers are being encouraged to publish overfill volumes which differ significantly. The typical volume is 100-200ml. The value of 200 ml UF capacity defining ultrafiltration failure quoted above *includes* the flush volume as this is easier for patients to perform (the alternative is weighing before and after flush which is time consuming and difficult).

□ The patient should follow their usual dialysate regime, draining out as completely as possible before the test dwell. Large residual volume of dialysate will affect the results.

□ Intra-patient variability of the ultrafiltration capacity (~ 20%) is greater than for the solute transport (<10%). Results of the PET/SPA, in particular the ultrafiltration capacity, should always be interpreted in the light of additional exchanges performed during the same 24-48 hour period (usually collected to assess solute clearance . see below).

□ The PET/SPA are not surrogates for measuring solute clearance.

Measurement of Solute Clearance

In measuring solute clearance and planning changes to the dialysis regime, three clinical parameters are essential: Estimates of (1) *patient size*, (2) peritoneal *solute transport* and (3) *RRF*. In each case, the choice of surrogate .toxin., urea or creatinine, interacts with each of these parameters in different ways. At present, there
is no clear evidence from the literature that one surrogate is superior to another. Where possible, clinicians should measure both, attempt to reach at least one of the targets, and understand why there appears to be a discrepancy. A number of commercial computer programs exist that are designed to aid dialysis prescription. Whilst some have been validated, good practice dictates that a change in dialysis prescription is checked for efficacy by repeating clearance studies.

(1) Patient Size

In calculating urea clearances, patient size is expressed as an estimate of the total body
water (volume of distribution of urea). It is recommended that the Watson formula is used for this (5):

Males: V = 2.447 . 0.09156 * age (years) + 0.1074 * height (cm) + 0.3362 * weight kg)

Females: V = -2.097 + 0.1069 * age (years) + 0.2466 * weight (kg)

Alternatively 58% of body weight (kg) may be used; this is less precise, and will give lower values for Kt/V, especially in obese patients. Creatinine clearances should be corrected for body surface area, normalising to 1.73 m_2.

(2) Peritoneal Solute Transport

Solute transport rates have an important influence on peritoneal creatinine clearance,
but not on urea clearance. This means that it is easier to achieve creatinine clearance
targets in high transport patients. It should be remembered, however, that these patients might have less satisfactory ultrafiltration. In designing optimum dialysis regimes, patients with low solute transport will require equally spaced medium length dwells, such as are achieved with CAPD and single extra night exchanges (e.g. 5 x 2.5
litre exchanges). Those with high transport are more like to achieve targets with short
dwells (APD) plus polyglucose solutions (e.g. 4 x 2.5 litre exchanges overnight, 1 x 2.5 litre evening exchange and 1 x 2.5 litre daytime icodextrin).

(3) Residual Renal Function (RRF)

This is the single most important parameter in PD patients, and also the one most likely
to change with time. Clinically significant changes can occur within three months. Because secretion of creatinine by the kidney at low levels of function overestimates residual creatinine clearance, it is recommended to express this as the *mean* of the urea
and creatinine clearances.

Estimating Total Ultrafiltration

The total achieved ultrafiltration is best measured from the 24-hour dialysate collections used to calculate solute clearance. For APD patients this is simple as machines now calculate the ultrafiltration volumes precisely. Furthemore, many models

store this information over several weeks so that an average value can be obtained. In
CAPD patients it is important to remember that each bag is overfilled to achieve flush before fill; the total dialysate drain volume must be measured and sampled from to calculate solute clearance accurately, but the overfill must then be subtracted to calculate the net ultrafiltration. If this is not done then over a 24-hour period the overestimate of ultrafiltration may be anything from 200 to 800 ml depending on manufacturer.(6, 7)

Peritoneal sodium losses are largely determined by convection and are thus proportional to the ultrafiltration volume. Typically 1 litre of ultrafiltration results in 100 mmol of sodium loss in CAPD patients and 70-80 mmol in APD patients.

1. Twardowski ZJ, Nolph KD, Khanna R, et al. Peritoneal Equilibration Test. *Perit Dial Bull* 1987;7:138-47.
2. Davies SJ, Brown B, Bryan J, Russell GI. Clinical evaluation of the peritoneal equilibration test: a population-based study. *Nephrol Dial Transplant* 1993;8(1):64-70.
3. Ho-dac-Pannekeet MM, Atasever B, Struijk DG, Krediet RT. Analysis of ultrafiltration failure in peritoneal dialysis patients by means of standard peritoneal permeability analysis. *Peritoneal Dialysis International* 1997;17(2):144-50.
4. Smit W, van Dijk P, Langedijk MJ, et al. Peritoneal function and assessment of reference values using a 3.86% glucose solution. *Perit Dial Int* 2003;23(5):440-9.
5. Watson PE, Watson ID, Batt RD. Total body water volume for adult males and females estimated from simple anthropometric measurements. *Am J Clin Nutr* 1980;33:27-39.
6. McCafferty K, Fan S. Are we underestimating the problem of ultrafiltration in peritoneal dialysis patients? *Perit Dial Int* 2006;26(3):349-52
7. La Milia V, Pozzoni P, Crepaldi C, Locatelli F. The overfill of bags for peritoneal dialysis as a cause of underestimation of ultrafiltration failure. *Perit Dial Int* 2006;26(4):503-5.

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Directorate of Legal Services
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Your Ref:

Our Ref:
HYP B04/1

Date:
9th September 2011

Ms Bernie Conlon
Inquiry Secretary
Arthur House
41 Arthur Street
Belfast
BT1 4GB

Dear Madam

RE: INQUIRY INTO HYPONATRAEMIA RELATED DEATHS – ADAM STRAIN

I refer to Professor Savage's witness statement forwarded on the 13th of April 2011 and in particular question 18 a-d.

Professor Savage's statement indicated that he could not recall how he discovered that there had been 9 other deaths from an apparently similar cause. I am instructed that Professor Savage has now located correspondence which he sent to Dr. Postlethwaite on 5th July 1996 in which he refers to Dr. Verrier- Jones as being the source of the information that 9 children had died from either hyponatraemia or fluid overload. I now enclose the following for your attention:

1. Professor Savage's revised answer to question 18.
2. Letter dated 5th July 1996 from Professor Savage to Dr Postlethwaite.
3. 2002 Audit authored by Dr Postlethwaite and others.
4. 2009 Case Report by Cansick and others

Yours faithfully

pp Nicola Doolor

Wendy Beggs
Assistant Chief Legal Adviser

Direct Line: [redacted]
Email: [redacted]

Providing Support to Health and Social Care

(18) *"The majority of children with renal failure have similar problems concerning electrolyte levels. Since Adam's death these would be measured more frequently. I have discovered that in the UK there have been 9 other deaths from an apparently similar cause though these have not been published ...The information about the 9 other deaths was told to me verbally later - it was not published. "*(Ref: 011-015-113)

(a) State when and in what circumstances you *"discovered that in the UK there have been 9 other deaths from an apparently similar cause though these have not been published "* and identify the person(s) who verbally told you of them

The death of Adam Strain was devastating to all of us in the renal team who had looked after him. As a result of this I discussed his case with many colleagues in the UK and indeed possibly further afield at Nephrology meetings. On one of these occasions, a colleague told me that they believed there had been nine or ten other deaths from a similar cause.

After these many years I was initially unable to recall the identity of the individual who alerted me to the other deaths from similar causes. Recently however, I have located a letter which I wrote in 1996 to Dr R J Postlethwaite, the Paediatric representative on the UK Transplant Audit Group (copy provided). Following my letter an audit of all deaths of children following renal transplantation was performed and the results published (Postlethwaite R J et al, Pediatric Transplantation 2002: 6:367-377).

In this letter I mention a presentation made at a meeting of the British Paediatric Association by Dr Kate Verrier-Jones where it was indicated there were 9 children who died from either hyponatraemia or fluid overload following a kidney transplant. This presentation is the source of my statements. Both Dr Postlethwaite and Dr Verrier-Jones were Senior Paediatric Nephrologists in Manchester and Cardiff respectively, who have since retired from clinical practice.

Subsequently, although there have been publications related to death from hyponatraemia related to renal transplantation, and most recently one from the Hospital for Sick Children in Great Ormond Street (Cansick et al, Pediatric Nephrology (2009) 24:1231-34), I have been unable to find any publication that specifically identifies the number of deaths from dilutional hyponatraemia in the UK.

(b) State in detail what you discovered in relation to the *"9 other deaths from an apparently similar cause"* including the date of each death

I was unable to obtain details of "9 other deaths from an apparently similar cause" or substantiate the actual number. However, a paper was published in 2002 entitled "The outcome of paediatric cadaver renal transplantation in the UK and Eire" (Postlethwaite R J et al, Pediatric Transplantation 2002: 6:367-377). This audit of 1252 paediatric renal transplants between 1st January 1986 and 31st December 1995 reports a total of 113 deaths. The cause of death is identified in 6 as due to fluid overload and in 9 as cardiac failure (Table 1, page 371). Fluid overload may be associated with both cardiac failure and hyponatraemia. The paper does not specifically identify the number of children with hyponatraemia.

(c) Describe and explain any actions you took in relation to this "discovery"

Following the discovery of information in relation to deaths from an apparently similar cause, I wrote to the Paediatric Nephrologist on the UK Transplant Audit Group (see paragraph 18a) giving brief details of the death of Adam Strain. I suggested an audit of transplant related deaths be carried out by the British Paediatric Nephrology Association and sought details of the other possible deaths if they could be made available.

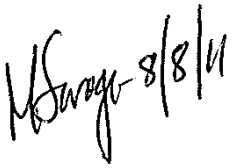
8/8/11

This audit was subsequently carried out by a Paediatric Task Force of United Kingdom Transplant and was published as previously mentioned (Pediatric Transplantation 2002: 6: 367-377).

(d) Document reference 060-018-036 states *"...a number of renal transplants complicated by hyponatraemia leading to death in 10 (reported in May 1996)..."*

- State whether you provided the information relating to *"a number of renal transplants complicated by hyponatraemia leading to death in 10 (reported in May 1996)"*
- If so, state to whom did you provide that information
- State when you provided that information
- State the reasons why you provided that information
- Describe fully the circumstances and details of the *"number of renal transplants complicated by hyponatraemia leading to death in 10 (reported in May 1996)"* including the date of each death

With reference to the document 060-018-036, I presume this refers to the handwritten addition to the statement in my deposition to the Coroner mentioned under 18 b) above and I can only say that this was anecdotal evidence at that time. The bullet points above are addressed in my response above (18 a-c).



The Nuffield Department of Child Health

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Our ref. Your ref.

5 July 1996

Dr R J Postlethwaite,
Royal Manchester Children's Hospital,
Pendlebury,
Manchester.
M27 1HA.

Dear Bob,

I understand you are now going to represent the paediatricians on the UK Transplant Audit Group and there is an area in which you may be able to help me.

Before Christmas, we had an unfortunate experience in Belfast in which a child died while undergoing transplant surgery. This was a boy who had polyuric renal failure, having been born with cystic dysplastic kidneys and vesico-ureteric reflux. He had been managed conservatively for 2 years and then was on CAPD for 2 years awaiting transplant. Before going to theatre, he was a well active boy with a normal electrolyte block, and in particular a sodium of 139. There were no signs of fluid overload and his chest x-ray was clear. During the course of surgery he had his CVP monitored, along with the usual parameters but did not have any electrolyte assessments. He was in theatre for 4 hours due to technical difficulties with the operation mainly associated with the fact that he had 5 previous urological operations. He did not breath spontaneously on withdrawal of the anaesthetic and on admission to Intensive Care when I saw him he had fixed dilated pupils with bilateral papilloedema and chest x-ray revealed pulmonary oedema. His sodium at that time was 119. We immediately commenced dialysis to remove fluid and treat him with intravenous Mannitol, but a CAT scan shortly afterwards revealed that he had coned. He was ultimately pronounced brain dead.

At Kate Verrier-Jones' presentation at the BPA she indicated that there were 9 children who had died either from hyponatraemia or fluid overload. This information was discussed within our hospital and came to be subsequently mentioned at the child's inquest. As a result of this the Coroner requested that I should attempt to find out if there was any similarity between these deaths and whether any procedure could be introduced to avoid a recurrence of the problem.

I would be grateful therefore, if you could tell me if it is possible to access information about these 9 deaths, either from UK Transplant or by identifying the units from which the children came so that I could write directly to the nephrologists involved with their care. I have talked to Kate about this and it may well be that an audit of all deaths of paediatric dialysis and transplant patients is something that the BAPN should consider. If you think this is a better course of action I would be happy to become involved and would be willing to undertake at least part of the work involved.

Yours sincerely,

Maurice Savage

Maurice Savage
Consultant Paediatric Nephrologist

cc Dr Susan Rigden, Department of Paediatrics, Guy's Hospital,. St Thomas's Street, London. SE1 9RT.

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The outcome of pediatric cadaveric renal transplantation in the UK and Eire

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Abstract: An analysis of all pediatric cadaveric renal transplant recipients in the UK and Eire was undertaken to review the outcomes of pediatric cadaveric renal transplantation and to consider the implications for organ allocation procedures for pediatric recipients. Factors influencing the outcome of 1,252 pediatric cadaveric renal transplants in the UK and Eire in the 10-yr period from 1 January 1986 to 31 December 1995 were analyzed by Cox proportional hazards regression, including analysis of four distinct post-transplant epochs (0–3 months, 3–12 months, 12–36 months, and beyond 36 months). At the time of analysis (December 2000), 113 (11%) recipients had died and 47% of grafts had failed. In the multi-factorial modelling, the factors significantly affecting transplant outcome were cold ischaemia time, donor and recipient age and human leucocyte antigen (HLA) matching. Epoch analysis demonstrated that these factors operated at different times post-transplant. Cold ischaemia time had a strong influence on outcome at 3 months. A highly significant increased risk of graft failure was associated with donors under 5 yr of age. Young recipients had an increased risk of failure in the short term, but beyond 1 yr post-transplant there were few failures in young recipients while a steady rate of graft loss persisted in the older children. In terms of HLA matching, the worst outcome was observed for two HLA-DR mismatched grafts, while 000 and favorably matched kidneys (100, 010, 110 HLA-A, -B, -DR mismatches) survived longest. Hence, a policy of exchanging organs on the basis of HLA matching is justified for 000 mismatched and favorably matched kidneys. The poor outcome associated with very young donors should discourage pediatric units from transplanting kidneys from such young donors. The reasons for late losses in older recipients need investigation.

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Key words: pediatric cadaveric renal transplantation – renal transplantation outcome – graft failure – causes of death – center effect – HLA matching – donor age – recipient age

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An analysis of the outcome of primary cadaveric renal transplantation in adults in the UK resulted in a revision of the allocation procedures for adult recipients to maximize the transplantation of HLA-matched kidneys, as well as to take account of factors such as waiting time and matchability of the recipient (1). A later report from the USA has similarly concluded that 'a superior graft outcome with little increase in the duration of cold ischaemia time justifies national sharing of HLA-matched kidneys' (2).

The annual reports of the European Dialysis and Transplant Association included outcomes of pediatric renal transplantation and by 1989 had information on 2,113 pediatric renal transplants (3). The most recent systematic data on outcomes in pediatric transplantation comes

Abbreviations: CD, cadaveric donor; CI, confidence interval; CMV, cytomegalovirus; HLA, human leucocyte antigen; LRD, living-related donor; NAPRTCS, North American Pediatric Renal Transplant Cooperative Study; RR, relative risk; UKT, UK Transplant; UNOS, United Network for Organ Sharing.

from North America, particularly from the NAPRTCS registry (4–6) and the UNOS registry (7, 8).

Pediatric recipients were specifically excluded from the UK adult study and therefore the Kidney Advisory Group of United Kingdom Transplant Support Service Authority (now reconstituted as UKT) established a task force to review the outcomes of pediatric cadaveric renal transplantation.

Methods

Study cohort

The study cohort comprised all pediatric cadaveric renal transplants performed in the United Kingdom and Republic of Ireland in the 10-yr period from 1 January 1986 to 31 December 1995. A pediatric recipient or donor was defined as under 18 yr of age at the time of transplantation.

During the study period a total of 1,252 kidney-only pediatric CD transplants were performed in 1,070 recipients. Of these transplants, 1,010 (81%) were first grafts and 242 (19%) were re-grafts. For 30 transplants the HLA-DR typing was incomplete and a further two transplant recipients had no follow-up data reported to the UKT by the time of the analysis. Thus, a total of 1,220 transplants are included in the outcome analysis, of which 989 were first grafts and 231 (19%) were re-grafts; 99.6% had 1-yr follow-up data and 98.0% had 5-yr follow-up data.

Factors analyzed

Factors influencing transplant survival times were analyzed on a multi-factorial basis using the proportional hazards regression model introduced by Cox. Donor factors analyzed were age, gender, blood group, cause of death, and CMV status. Recipient factors analyzed were age, gender, ethnic origin, blood group, primary renal disease, CMV status, waiting time, and graft number (primary vs. re-transplant). Other factors analyzed were year of graft, center status (pediatric or non-pediatric), number of transplants per center, cold ischaemia time, kidney exchange (i.e. whether the kidney was used locally or moved to another center), and HLA matching.

HLA matching was based on the broad and split antigens of HLA-A, HLA-B, and HLA-DR, as detailed in the report on adults (1). HLA typing was performed using a standard microcytotoxicity test or DNA typing methods.

In the UK, on the basis of the adult HLA Task Force analysis, HLA matching is considered in three groups: a 000 mismatched kidney has no mismatches at the HLA-A, HLA-B, or HLA-DR loci; a favorably matched kidney has one mismatch at either the HLA-A and/or the HLA-B loci but no mismatch at the HLA-DR locus (100, 010, 110 mismatches); and all other HLA mismatches are grouped together and termed non-favorable (1). Investigation of HLA matching effects for pediatric recipients was not restricted to these groups, but they were used as a framework for analysis.

Data for cold ischaemia time were available for only 706 grafts. Data for CMV status of graft and recipient was available for only 383 grafts, as this information was not routinely collected by UKT for the whole study period and was not available from all centres. Finally, ethnic origin of the recipient was only known for 71% of grafts. Analyses of these factors were carried out on reduced data sets to test for significance in the Cox model. Primary disease was modelled with a missing data category (9%) and data for all other factors were complete.

Centres meeting the British Association for Paediatric Nephrology criteria for comprehensive pediatric renal centres (9) are referred to in this report as 'pediatric centres' and other centres in which pediatric transplantation was performed are referred to as 'non-pediatric centres'. Centres were further designated as low volume (< 50 pediatric cadaveric transplants in the study period), medium volume (51–100) or high volume (> 100).

Detailed information about immunosuppressive regimens was not available but retrospective information about the use of cyclosporin and anti-T-cell antibody induction regimens was collected.

Statistical analysis

For this analysis, transplant survival time was determined by time from transplant to transplant failure, this being the earlier of return to regular dialysis or patient death. Where no failure was reported the survival time was censored at the date of the last follow-up. Follow-up data to December 2000 were included in the analysis. Cox's proportional hazards regression models were used to analyze the combined effect on survival of many factors. All models were stratified by center to allow for inherent center differences. In addition to overall survival, because the influences of different factors on transplant survival varied depending on the time post-transplant, the modelling investigated the influences on survival in different epochs post-transplant: the first 3 months post-transplant, 3–12 months post-transplant, 12–36 months post-transplant, and the time beyond 3 yr post-transplant. Log cumulative hazard plots did not show any deviation from the proportional hazards assumption within each period, and Cox's proportional hazards models were fitted to the data for each of the four epochs.

The results are presented in terms of estimated relative risks of failure for different groups of individuals compared with the risk for a baseline (reference) group. A relative risk of greater or less than 1.0 indicates, respectively, a higher or lower risk than that associated with the baseline group. A 95% CI was calculated for each relative risk. Kaplan-Meier survival curves were used to illustrate the effects of significant factors identified in the multi-factorial analysis. Any associated p-values were derived from a univariate log-rank test; we used a 5% level of significance. All statistical analyses were performed using the SAS software package (version 6.12).

Results

Characteristics of the study cohort and changes over the study period

Primary disease was reported for 974 of the 1,070 patients transplanted. Congenital renal dysplasia (25%), obstructive uropathy (14%), and reflux nephropathy (12%) were the most commonly reported renal diseases.

There was negligible change in recipient age distribution over the 10-yr period. The median recipient age varied by only 2.5 yr, with the minimum median age being 9.5 yr in 1991 and maximum median age being 12 yr in 1986, 1987 and 1990.

Pediatric CD transplants were carried out in 13 pediatric centres and 21 non-pediatric centres. Four pediatric centres were high volume, one was low volume, and the remaining eight medium volume. One-hundred and twenty five CD transplants were performed in 21 non-pediatric centres, with individual centres performing between one and 18 CD transplants over the period of analysis. The median recipient age of those transplanted at pediatric units was significantly lower than those treated in non-pediatric units (11 yr, inter-quartile range 6–14 vs. 16 yr, inter-quartile range 14–17 yr; Wilcoxon test, $p = 0.001$).

In the whole study period only 32 kidneys from donors under 2 yr of age were used, 31 of these occurring in the first 4 yr but with only a single donor in this age range in the 6 yr between 1990 and 1995 (Fig. 1). There was also a progressive reduction in the use of kidneys from donors between the ages of 2 and 5 yr, from 23% ($n = 30$) of donors in 1986 to 6% ($n = 9$) in 1995. The decreasing use of younger donors is clear when comparing median donor ages over the duration of the study. Median donor age has been steadily increasing from 9 yr (inter-quartile range 4–21) in 1986 to 13.5 yr (inter-quartile range 10–20) in 1995 (Wilcoxon test, $p < 0.0001$). This corresponds to a decreasing use of donors younger than 5 yr of age and an increase in the use of donors aged 10–17 yr, from 17% in 1986 to 48% in 1995, although there has been a reduction in the use of donors 18–35 yr of age.

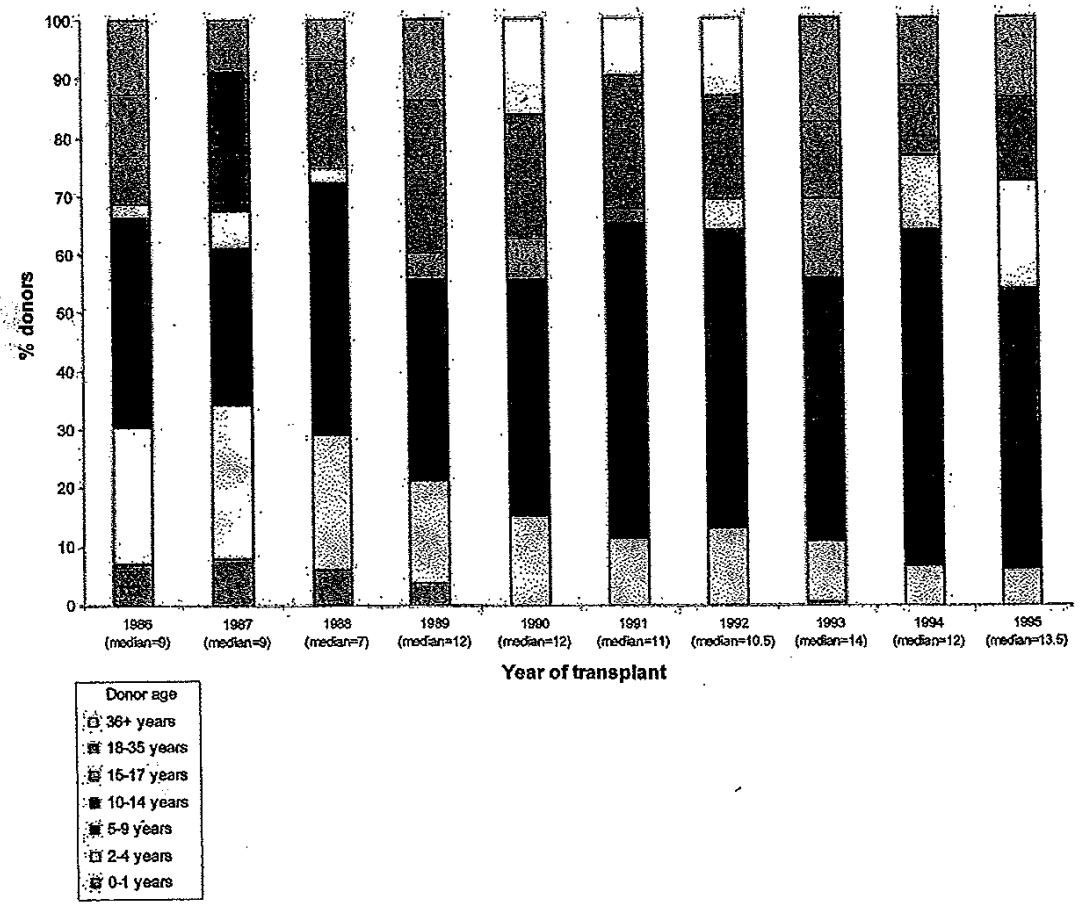

Fig. 1. Donor age by year of transplant.

The degree of HLA-A, -B, and -DR matching has improved substantially during the analysis period (Fig. 2). The proportion of five or six HLA-A + B + DR mismatched grafts has fallen from 18% in 1986 to 1% in 1995. The proportion of all grafts with two DR mismatches has also fallen. In 1986, 27 (23%) transplants were two DR mismatched, of which 15 had a total of five or six HLA-A + B + DR mismatches. In contrast, in 1995, only three transplants were two DR mismatched, of which two had a total of three mismatches and one a total of four mismatches.

One of the 13 pediatric centres did not introduce cyclosporin until 1989, while in all the others cyclosporin was used throughout the study period. Of the 13 pediatric centres, six centres had never used induction anti-lymphocyte antibody regimens. One center used it for second grafts and the other six centres reported occasional use for 'rare cases, such as those with previous aggressive rejection' or 'the occasional "high risk" patient (previous severe rejection/ high cytotoxic antibodies)'. Thus, in the period of analysis, induction regimens with anti-lymphocyte antibodies were rarely used.

Causes of patient death

Of the 1,070 pediatric patients receiving a cadaveric kidney transplant in the study period, 113 (11%) were reported to have died at the time of the analysis. Nine (8%) deaths occurred within 1 month of transplant, 19 (17%) between 1 month and 1 yr of transplant, and 85 deaths (75%) occurred more than 1 yr after transplantation. Thirty-eight (34%) deaths occurred in patients with a functioning transplant. The causes of death are set out in Table 1.

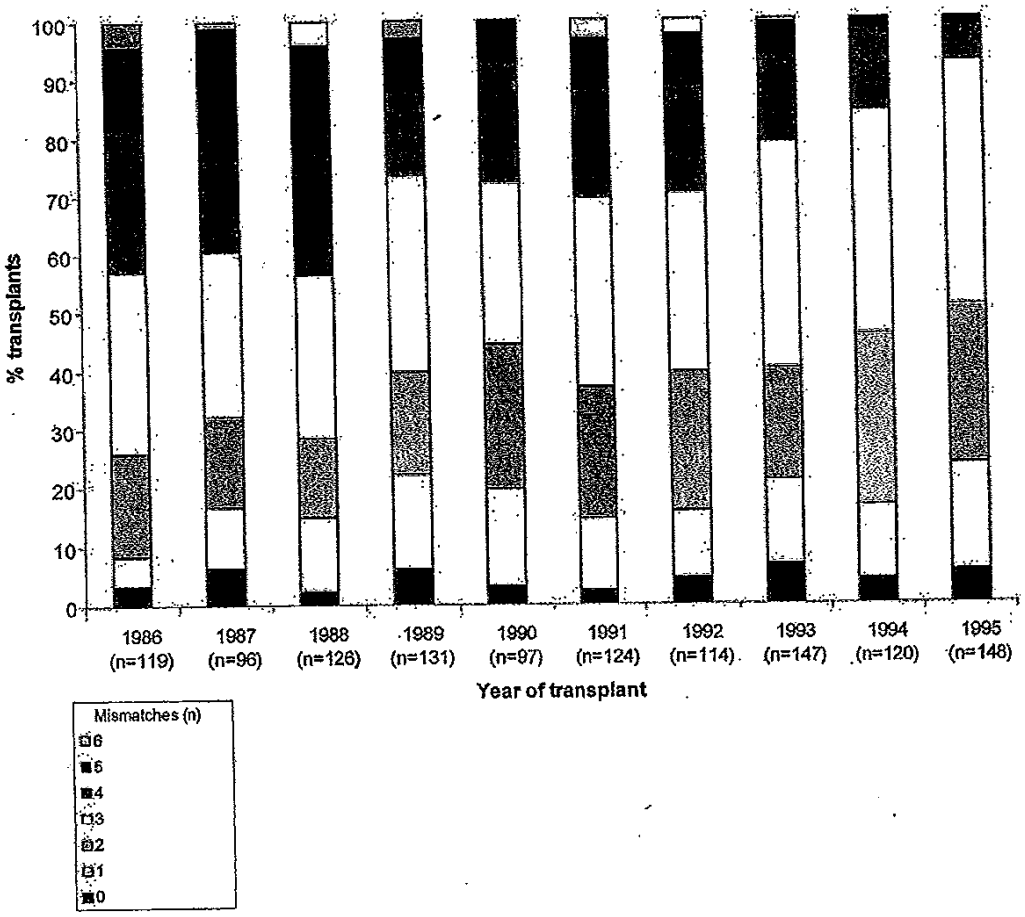

Fig. 2. Number of transplants and human leucocyte antigen (HLA) mismatching by year.

Causes of graft failure

Of the 1,250 transplants with some follow-up information reported, 582 (47%) were reported to have failed by the time of the analysis. A cause of graft failure was given for 500 (86%) of these failures (Table 2). Thirty-two per cent of the graft failures occurred in the first month post-transplant, 10% between 1 month and 3 months, 11% between 3 months and 1 yr, and 47% after 1 yr. Rejection was the commonest cause of graft failure reported (55%). In the first month, however, it only accounted for 38% of losses, with vascular problems accounting for 39%. Recurrent primary disease accounted for only 3% of graft failures, but these losses occurred at all times post-transplant.

Table 1. Cause of death

Cause of death	Number	Percentage of deaths
Infection		
Viral, generalized	1	1
Viral, pulmonary	3	3
Bacterial, pulmonary	2	2
Bacterial, septicaemia	9	8
Other (not viral hepatitis)	1	1
Cardiac failure	9	8
Fluid overload	6	5
Cardiac arrest, cause unknown	9	8
Haemorrhage		
Cerebro-vascular accident	4	4
Gastrointestinal	2	2
From surgery	1	1
From graft site	1	1
Other	2	2
Uraemia due to graft failure	5	4
Patient declined further treatment	1	1
Therapy ceased for other reason	2	2
Cachexia	1	1
Lymphoid malignant disease	4	4
Respiratory failure	4	4
Other identified cause of death	9	8
Intra-operative death	0	0
Accident	3	3
No cause of death reported	34	30
Total	113	

Outcome analysis

Non-significant factors

Graft number was non-significant in relation to transplant outcome, although there were very few third and fourth grafts to analyze.

The CMV status of both donor and recipient (pregraft) and any interaction thereof were found to be non-significant.

Waiting time was also non-significant with relation to transplant survival, but those patients not registered on the national waiting list prior to transplant tended to have poorer outcome in the first 3 months post-transplant.

No center effects could be demonstrated either between individual pediatric centres or comparing pediatric centres with non-pediatric centres or by analysis of center volume.

Other factors found not to significantly relate to graft outcome were recipient; gender, blood group, ethnic origin (based on data with known ethnic origin – 71% of grafts), and primary disease; donor; gender, blood group, and cause of death; and whether the organ was local or imported.

As illustrated by the Kaplan-Meier plot (Fig. 3), graft outcome was significantly better in 1991–95 compared with 1986–90 (Log-rank

Table 2. Cause of graft failure

	Time to failure									
	< 1 month		1 month to < 3 months		3 months to < 1 yr		1 yr +		Total	
Cause of failure	No.	%	No.	%	No.	%	No.	%	No.	%
Hyperacute rejection	8	4	0	0	0	0	2	1	10	2
Rejection while taking immunosuppressive drug(s)	63	34	42	71	39	60	156	57	300	52
Rejection after stopping all immunosuppressive drugs	0	0	1	2	1	2	5	2	7	1
Recurrent primary renal disease	4	2	0	0	4	6	7	3	15	3
Vascular or ureteric operative problems	22	12	1	2	3	5	2	1	28	5
Vascular (arterial or venous) thrombosis	50	27	0	0	0	0	1	0	51	9
Infection of graft	5	3	2	3	1	2	0	0	8	1
Removal of functioning graft	0	0	0	0	1	2	1	0	2	0
'Non-viable' kidney	9	5	4	7	1	2	0	0	14	2
Recipient died, graft was functioning at time of death	4	2	4	7	7	11	23	8	38	7
Other	4	2	2	3	2	3	19	7	27	5
Unknown	16	9	3	5	6	9	57	21	82	14
Total	185		59	100	65	100	273	100	582	

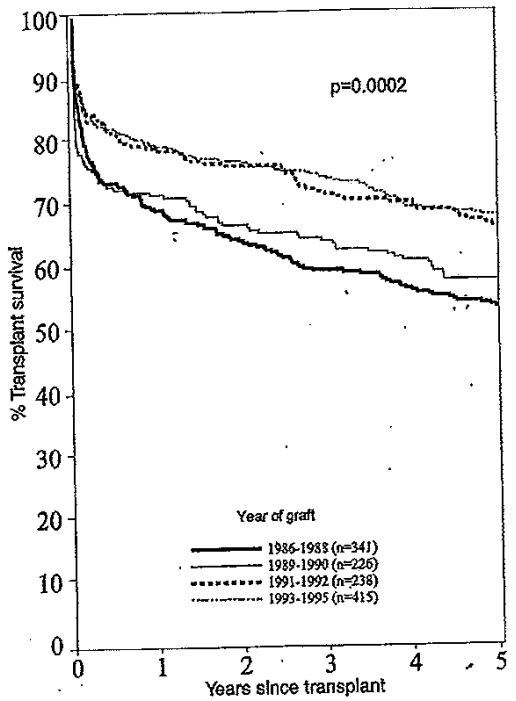

Fig. 3. Transplant survival by year of transplant.

test, p = 0.0002). However, when the effects of increasing donor age and improved HLA matching are taken into account, these fully explain the improvement seen in later years.

Significant factors

In the multi-factorial modelling, the factors significantly related to post-transplant survival were cold ischaemia time, donor and recipient age, and HLA matching. The epoch analysis for 0–3 months, 3–12 months, 12–36 months and after 36 months showed that some factors had differing effects over post-transplant epochs. Table 3 shows results of analysis of overall transplant survival and of the epoch analysis carried out.

There was a trend towards improved transplant survival for grafts with shorter cold ischaemia times (Fig. 4). In the epoch analysis of a reduced data set with known cold ischaemia times (n = 706), cold ischaemia time was shown to have a strong influence in the first 3 months post-transplant, the risk of failure increasing by 4% with each additional hour of cold ischaemia (p = 0.004).

Table 3. Relative risks of transplant failure

			Overall survival			0–3 months			3–12 months			12–36 months			36+ months		
Factor	Level (baseline)	No.	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p
Recipient age (years)	0–1	29	0.80	(0.44–1.47)	0.5	1.77	(0.85–3.66)	0.1	0.97	(0.20–4.71)	1.0	0.28	(0.03–2.37)	0.2	–	(–)	–
	2–4	160	0.88	(0.65–1.19)	0.4	1.77	(1.18–2.68)	0.006	0.47	(0.15–1.52)	0.2	0.25	(0.09–0.78)	0.02	0.43	(0.22–0.85)	0.01
	5–9	286	1.05	(0.84–1.32)	0.7	1.77	(1.24–2.51)	0.002	0.98	(0.49–1.94)	0.9	0.38	(0.18–0.78)	0.008	0.77	(0.51–1.16)	0.2
	(10–14)	430	1.00			1.00			1.00			1.00			1.00		
	15–17	315	1.25	(0.99–1.57)	0.06	1.47	(0.99–2.18)	0.05	1.44	(0.77–2.72)	0.3	1.68	(0.89–2.85)	0.05	0.81	(0.54–1.24)	0.3
Donor age (years)	0–1	30	2.77	(1.68–4.58)	<0.0001	3.56	(1.76–7.19)	0.0004	1.34	(0.27–6.58)	0.7	4.16	(0.83–20.88)	0.08	2.58	(0.90–7.40)	0.08
	2–4	179	1.72	(1.25–2.35)	0.0008	2.50	(1.51–4.12)	0.0004	1.22	(0.53–2.83)	0.6	2.24	(0.97–5.17)	0.06	0.87	(0.47–1.60)	0.6
	5–9	290	1.23	(0.91–1.67)	0.2	1.55	(0.94–2.53)	0.08	0.67	(0.29–1.54)	0.3	2.40	(1.17–4.95)	0.02	0.82	(0.48–1.41)	0.5
	10–14	248	1.15	(0.85–1.56)	0.4	1.39	(0.85–2.28)	0.2	0.50	(0.20–1.22)	0.1	1.14	(0.51–2.54)	0.7	1.28	(0.76–2.14)	0.4
	15–17	96	0.91	(0.61–1.37)	0.7	0.73	(0.35–1.53)	0.4	0.14	(0.02–1.08)	0.06	1.58	(0.67–3.71)	0.3	1.30	(0.68–2.50)	0.4
	(18–35)	223	1.00			1.00			1.00			1.00			1.00		
	36+	154	1.48	(1.09–2.02)	0.01	1.31	(0.74–2.29)	0.4	1.40	(0.66–3.00)	0.4	1.13	(0.53–2.42)	0.8	1.98	(1.18–3.35)	0.01
HLA match	Favorable	287	0.65	(0.48–0.88)		0.74	(0.46–1.19)	0.2	0.40	(0.18–0.85)	0.02	1.35	(0.60–3.03)	0.5	0.45	(0.25–0.82)	0.009
	Other 0 DR/1 DR mismatch	777	0.74	(0.58–0.94)	0.01	0.97	(0.68–1.38)	0.9	0.39	(0.21–0.73)	0.003	0.88	(0.43–1.83)	0.7	0.58	(0.35–0.95)	0.03
	(2 DR mismatches)	156	1.00			1.00			1.00			1.00			1.00		

HLA, human leucocyte antigen.

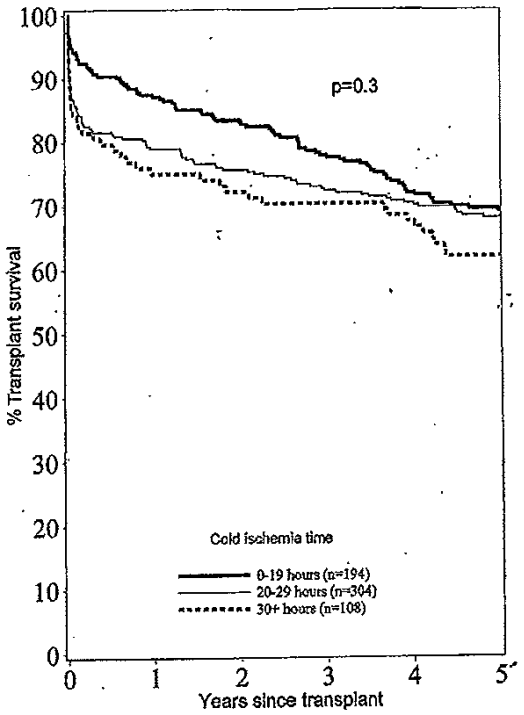

Fig. 4. Transplant survival by cold ischaemia time.

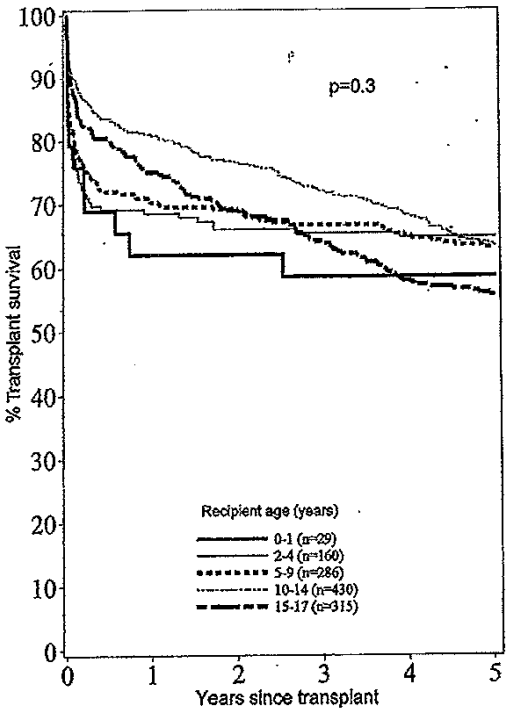

Fig. 5. Transplant survival by recipient age.

In the Cox modelling of distinct post-transplant epochs, the age of both recipient and donor were found to significantly affect post-transplant survival. Owing to differing effects of recipient age on outcome in these epochs, the Kaplan-Meier analysis shows a non-significant effect (log-rank test) on the 5-yr outcome (Fig. 5). The effect of donor age is more consistent across epochs and the Kaplan-Meier analysis shows a highly significant difference between age groups (Fig. 6). Table 3 shows that in the first 3 months after transplantation, recipients aged 10–14 yr of age were least likely to suffer graft failure and for this analysis represent the reference group (see the Methods). Both younger and older recipients had a greater risk of graft loss in the 0–3 months epoch. Between 3 and 12 months this increased risk in young recipients compared with those aged 10–14 yr was lost and young recipients fared better than the reference group in the 12–36 months and 36+ months epochs. In these last two epochs, those aged 10–14 yr or 15–17 yr at transplant were most likely to experience failure of their transplants (Table 3). The effects are illustrated in Fig. 5: for recipients under 10 yr of age at transplant, the survival curves suggest few failures beyond 12 months post-transplant, while the curves for recipients ≥10 yr of age show a continuing decline in transplant survival over the 5-yr study period.

The effects of donor age are illustrated in Fig. 6. Donors under 5 yr of age were associated with poor transplant outcome, while the best outcome was associated with transplants from donors 15–17 yr of age. Table 3 shows that the most significant effect of young donor age is in the first 3 months post-transplant. During this time the risk of transplant failure is approximately three times as great when the donor is under 5 yr of age compared with when the donor is 18–35 yr of age (baseline group). Beyond 36 months after receiving a graft, older donors were also associated with increased risk of graft failure compared with the baseline group (RR = 1.98, p = 0.01). We found no significant interaction effect of donor and recipient age.

Figure 7 illustrates transplant survival of the three HLA matching groups found to be most significant in the multi-factorial analysis. The worst outcome was observed for two DR mismatched kidneys, while 000 and favorably matched kidneys were associated with the best transplant outcome. No significant additional benefit for the small number of 000 mismatched

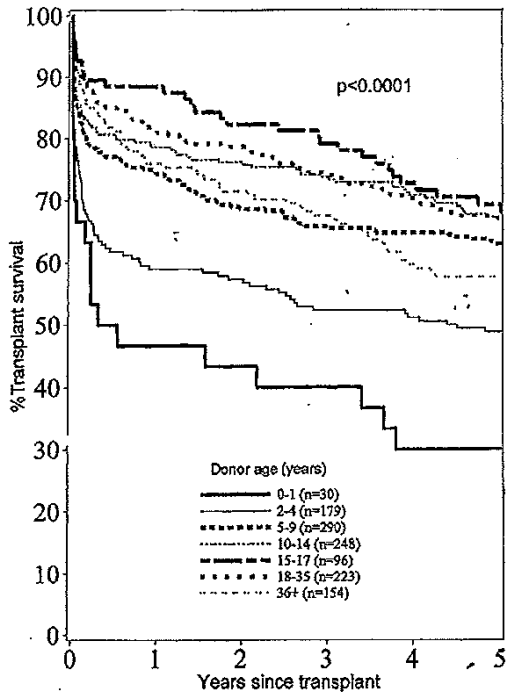

Fig. 6. Transplant survival by donor age.

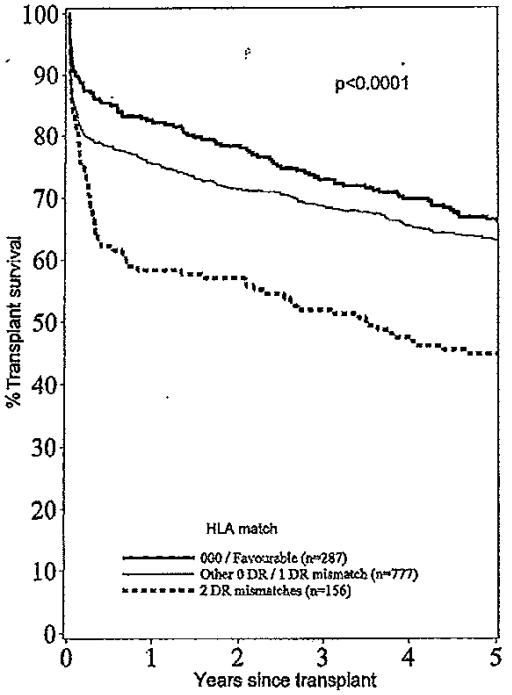

Fig. 7. Transplant survival by human leucocyte antigen (HLA) match grade.

kidneys over favorably matched kidneys could be demonstrated. The multi-factorial analysis showed a weak influence of HLA match in the first 3 months but a stronger effect thereafter. Beyond 36 months, grafts with two HLA-DR mismatches were approximately twice as likely to fail as those with fewer than two mismatches ($p < 0.03$). Even if grafts with causes of failure coded as 'vascular or ureteric operative problems' or 'vascular (arterial or venous) thrombosis' were excluded from the analysis, the effect of HLA matching remained non-significant in the 0–3 months epoch.

Discussion

The influence of donor age on transplant outcome is consistent with a number of reports from registries (4, 5, 10–12) and individual centres (13, 14). Indeed, there seems to be only one report (15) that does not agree with the general finding that outcome worsens progressively with younger donor age. Given the reports of good outcomes in adults with young donor kidneys transplanted en bloc (16–18) this is probably a more appropriate way to utilize the kidneys from young donors. If successful, there is no reason that this could not be extended to pediatric recipients in the future.

The effect of young recipient age is also in agreement with most reports from registries and single centres (4, 5, 10–12). As with donor age, any minimum age criterion for transplantation is, to some extent, arbitrary and the analysis is supportive of the general adoption of 2 yr of age as the minimum age criterion for cadaveric transplantation. However, it is noteworthy that at 5 yr, the outcome for young recipients is as good as that of older recipients, the early poor outcome being offset by better outcome than that seen for older pediatric recipients beyond 1 yr. Therefore, the avoidance of transplantation in patients < 2 yr of age must be viewed as a relative contraindication to cadaveric donation, and transplantation should be considered if there are problems with dialysis. Additionally, it has been reported that outcomes are better with LRD than CD in children under the age of 2 yr (19). The optimal approach to management of those under 2 yr of age with renal failure requires further assessment.

It is possible that the combination of small recipients and small donors has more than an additive effect but we were unable to show this in

our data, probably owing to the small number of such grafts.

The results confirm the impact of HLA matching on transplant outcome in cadaveric donation in children (4, 5, 10). In contrast to the adult study (1), we were unable to show any added advantage of 000 HLA-A, -B, -DR mismatched transplants over favorably matched kidneys, although there were very few of these (n = 55). In addition to inferior transplant survival, another consequence of using poorly matched kidneys in children is increased sensitization to HLA antigens, which makes subsequent transplantation difficult. Data on HLA sensitization for this cohort will be communicated in another report.

The epoch analysis revealed some important effects. The only comparable analysis is that of UNOS where five out of 26 factors accounted for 81% of the variability in long-term graft survival, namely: transplant center, recipient age and race, transplant year, and panel-reactive antibody (8). Most of these issues have already been discussed. There was insufficient information about panel reactivity to use in the multi-factorial analysis but we could show no effect of graft number. The most important finding was the strong effect of recipient age on 5-yr graft survival, with increased risk of loss at 5 yr in patients < 11 yr of age compared with those who were 11–20 yr of age. We confirmed this important finding with recipients ≤ 10 yr of age at transplant doing significantly better than young people 10–18 yr of age. The reason for this is not clear, but the suggestion that non-compliance is probably a factor (8) is plausible. Another possible factor in this inferior outcome is transfer to adult units. Watson has recently reported worryingly high rates of transplant at this time (20). Increased awareness and expertise in recognizing non-compliance and more detailed study of models of transitional care for this vulnerable age group might improve the outcome for these patients.

With longer follow up (> 3 yr), the increased graft loss associated with donors > 35 yr of age is noteworthy. Increased use of much older donors to maximize HLA matching would probably be inadvisable. As with donor age, any cut-off point is to some extent arbitrary; the current national rules for allocation limit donor age for pediatric recipients to 50 yr.

A further finding on epoch analysis was the secondary worsening of outcome for the very youngest donors with > 3 yr of follow-up. There are number of pieces of evidence that suggest antigen-independent mechanisms play a major role in the progression of chronic renal allograft 'rejection' (21) and in some models nephron supply is a major determinant of long-term graft outcome (22). Clearly there are other possible explanations of this late functional decline but, whatever the cause, this is a further argument against the use of very young donors in pediatric cadaveric renal transplantation.

Cold ischaemia time, whilst not affecting overall outcome, did have a significant effect on outcome at 3 months. This is in agreement with the findings in the NAPRTCS study where a cold ischaemia time of > 24 h was one of the variables predictive of the requirement for dialysis for 7 days post-transplant which in itself had a deleterious effect on long-term graft outcome (4, 23). Thus, increased cold ischaemia time does adversely affect graft outcome, but any cut-off such as 24 h is arbitrary, i.e. the shorter the cold ischaemia time the better the outcome.

The overall outcome of transplantation for this group of children has improved significantly over the study period, but the multi-factorial analysis shows that this is entirely explained by reduction in the use of small donors and the improved HLA matching. The adult study showed an improvement in transplant survival additional to that caused by better HLA matching. This was attributed to changes in immunosuppressive therapy (1). The NAPRTCS have shown a similar improvement in pediatric CD outcome, which they attribute to changes in practice, such as judicious use of CD, increased use of prophylactic anti-lymphocyte antibody, and better maintenance immunosuppression (4, 6, 12, 24). Such conclusions need to be supported by multifactorial analysis to uncover the effects of any confounding variables.

We were unable to show any effect of graft number on outcome. This confirms the NAPRTCS findings where the apparent inferior outcome of re-transplants (4) was shown to be entirely caused by the confounding effect of the use of small donors (25).

Similarly, in keeping with the adult study (1), and in contrast to the findings of the NAPRTCS (4, 6) and UNOS (8), we could find no influence of ethnic origin on outcome. The racial mix may explain this. In our data, 88.6% of those with known ethnic origin were White, 9.5% were Asian, 1.7% were Black, and 0.2% were of another ethnic minority group. In American reports, African–American racial origin, but not Hispanic origin, adversely affects outcome (4, 6, 8).

Center effects have long been recognized in adult renal transplantation (26) but this is a result of many factors, with center volume being only one of many possible factors and probably

not the most important (27–31). The results in the adult UK study mirrored these previous studies with variation in survival between centres but with no clear relationship between the number of transplants performed and transplant survival (1). UNOS compared results from 'professional' pediatric centres with those of other centres that transplanted 'only a few children'. Transplant survival was similar in older children in the two types of center but 'survival results of transplants in infants and young children differed, however, and suggested that the more experienced pediatric centres had an advantage with this special group' (7). This difference, however, 'was explained by the more aggressive pursuit of LRD transplants at the "professional" pediatric centers'. In a subsequent UNOS report, center variation was the chief pretransplant factor influencing graft survival at 1 and 5 yr in pediatric renal transplantation (8). However, UNOS was unable to show that center volume or degree of dedicated resources explained this center effect. The NAPRTCS reported that graft survival for both CD and LRD was better at 3 months and 5 yr in the moderate- and high-volume centres compared with the low-volume centres (high volume > 100 transplants, moderate volume 51–100 transplants, and low volume ≤ 50 transplants over an 8-yr period). These differences were not, however, significant and only achieved significance if the use of anti-lymphocyte antibody induction was excluded from the analysis: 'the significance of differences between the low volume and other groups depends upon the inclusion or exclusion of anti-lymphocyte antibody induction as a covariate in the proportional hazards model' (5). We were unable to show any center effects on transplant outcomes.

This report was not primarily concerned with the causes of graft loss and there was no attempt to standardize or verify the reported causes of graft loss. This accounts for obvious inaccuracies such as hyperacute rejection being reported as a cause of late graft loss. Despite these reservations, the overall pattern of causes of graft loss is clear. Not unexpectedly, the pattern of causes of loss varied with time post-transplant. Technical problems (including thrombosis) accounted for 39% of early losses but only 1% of late losses. In the first month, all types of rejection accounted for 38% of losses whereas this rose to 60% of losses after 1 yr. This is consistent with data from the NAPRTCS which show that renal vascular problems, particularly renal vein thrombosis, are major determinants of early graft loss (4–6). A further report from the NAPRTCS showed that recipient age, donor age, CD (vs. LRD), and cold ischaemia time of > 24 h were all associated with vascular thrombosis post-transplant (32). In one report from a single center there were no episodes of vascular thrombosis in 108 consecutive pediatric renal transplants (72% LRD). The authors attribute their excellent results to 'strict adherence to surgical detail, aggressive fluid management in the small child and careful integration of urologic and transplant surgery' (33). Thus, avoiding young donors and recipients, limiting cold ischaemia time and attention to surgical technique and peri-operative care should reduce early graft losses.

The overall mortality rate, not adjusted for duration of follow-up, is significantly higher (10.6%) than that reported by the NAPRTCS (6.5%) (4), but different categorizations and the large number of deaths with no cause of death reported make meaningful comparisons difficult.

In summary, donor and recipient age and HLA matching were the most important determinants of outcome of pediatric cadaveric renal transplantation. Although cold ischaemia time does have an impact on outcome, this is restricted to the first 3 months after transplant and was not significant in long-term outcome. Thus, as with the UK adult analysis, a policy of exchanging organs on the basis of HLA matching is fully justified for 000 mismatched and favorably matched kidneys. In the past children have, in general, received poorer HLA mismatched kidneys than adults. This analysis suggests that HLA matching is equally important for transplants in children and allocation schemes need to consider how HLA matching in children can be improved. In addition, the poor outcome associated with very young donors should discourage pediatric units from transplanting such young kidneys. The effects of recipient age are less clear cut. Age below 2 yr is a relative contraindication to cadaveric transplantation. Five-year follow-up data for patients 10–18 yr of age raises questions about transplantation in this age group and about non-compliance and transfer to adult services. The effects of these factors operate at different times post-transplant and can be obscured unless the analysis takes account of this.

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TRANSPLANTATION/BRIEF REPORT

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Seizures following renal transplantation in childhood

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Abstract Few studies have investigated the incidence of seizures following renal transplantation in childhood. The aim of this study was to determine this incidence and to identify risk factors. Retrospective casenote analysis was carried out on 119 transplants performed in 109 children over 10 years. Twenty-one transplants (in 20 children) were complicated by seizures, the majority of which occurred in the first 55 days after transplantation. Seizures were more common in the 5- to 10-year-old age group (P=0.03), but were no more common in those with a prior history of seizure (P=0.69). Their aetiology was predominantly multifactorial; hypertension (n=15), fever/infection (n=4) and acute allograft rejection (n=6) were commonly identified risk factors; 2 were secondary to intracerebral pathology. Most seizures were short lived, required minimal therapy and had a good long-term neurological outcome. In conclusion, seizures are relatively common following paediatric renal transplantation. Parents are now routinely counselled of this risk.

Key words Transplantation · Seizures · Therapy · Cyclosporine A

Introduction

Many of the pathophysiological events and therapies associated with renal transplantation place the paediatric recipient at increased risk of seizures, although there have been few comprehensive studies documenting their incidence [1]. The aetiology of seizures following transplantation appears to be multifactorial; severe hypertension is a common feature and may be secondary to fluid overload, corticosteroid or cyclosporine A (CsA) therapy, or acute allograft rejection [1–6]. Children with marked polyuria in the post-transplant period are at increased risk of biochemical disturbance, including hypocalcaemia and hypomagnesaemia, the latter being compounded by the enhanced magnesiuria associated with CsA therapy [7]. Immunosuppression places the child at increased risk of infections, including those of the central nervous system. The aims of this study were to determine the incidence of seizures in children following renal transplantation, to identify possible aetiological factors and to propose guidelines for their prevention and management.

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Patients and methods

Between January 1986 and June 1996, 126 renal transplants (123 cadaveric, 3 living-related donor) were performed at this institution in a total of 112 children (72 male, 40 female). The spectrum of primary diseases resulting in end-stage renal failure was typical for a United Kingdom tertiary referral paediatric nephrology centre. The anaesthetic, surgical and fluid/electrolyte management of these children remained unchanged throughout this 10-year period, and only one alteration was made to the maintenance immunosuppression protocol; children transplanted before May 1993 received CsA and prednisolone, whereas those transplanted after this date (n=47) received triple therapy with CsA, prednisolone and azathioprine. CsA was administered intravenously in the immediate post-operative period, with oral therapy being commenced once enteral feeding had been commenced. Target trough CsA levels were 200–400 ng/ml for children treated with dual immunosuppressive therapy and 50–150 ng/ml during the later triple-therapy period. Episodes of acute allograft rejection were treated with intravenous methylprednisolone (15 mg/kg daily for 5 days), ATG or OKT3 being reserved for those with steroid-resistant rejection. Where a donor/recipient cytomegalovirus (CMV) mismatch was present, intravenous hyperimmune CMV immunoglobulin was given, although no other prophylactic antibiotic, antiviral or other drug therapy was routinely administered.

The hospital casenotes were retrospectively analysed to determine whether seizures had occurred in either the pre- or post-transplant period. Where seizures occurred, data were recorded regarded the seizure type, duration, therapy administered, clinical observations and subsequent investigations in an attempt to determine their aetiology. Laboratory investigations were performed in all children, including blood count, plasma biochemistry and trough CsA levels. Cerebral imaging studies [magnetic resonance imaging (MRI) n=8, computed tomography (CT) n=2] were performed where neurological abnormalities were detected following seizures, and electroencephalograms (EEGs, n=5) were performed where seizures were prolonged or atypical. Cerebrospinal fluid was also examined in 2 children.

Results

Full clinical information was available for all 126 transplants. Seven grafts failed within the first 48 h because of technical problems [venous thrombosis (2), arterial thrombosis (2), intimal dissection, rotation on vascular pedicle and cold injury] and were excluded from the analysis; no seizures occurred in this group. In the remaining group of 119 transplants performed in 109 patients (72 male, 37 female), the mean age (range) at the time of transplantation was 9.1 years (0.9–17.3 years). Twenty-one transplants (17.6%) in 20 children (14 male, 6 female) were complicated by seizures, 13 (61.9%) of which occurred in the first 8 weeks post transplantation, with 18 of 21 (85.7%) occurring by 6 months (Fig. 1). There was no difference between boys and girls in the incidence of seizures. Seizures were, however, significantly more common in the 5- to 10-year-old age group (32.4%) compared with the 0- to 5-(11.1%), 10- to 15-(12.8%) and 15- to 18-(0%) year-old age groups (P=0.031, χ^2). The incidence of seizures in children immunosuppressed using dual therapy was no different from that in the children administered triple therapy (14.9% vs. 19.4%, P=NS). Of the seizures that occurred following 21 transplant procedures, 11 were single, 9 multiple and 1 child developed status epilepticus. Sixteen seizures lasted less than 10 min, 4 lasted 10–30 min and 1 more than 60 min. Seizures were predominantly generalised tonic clonic (n=18), although simple partial seizures (n=2) and absence attacks (n=1) also occurred. The majority of seizures terminated spontaneously, although 7 required acute administration of anticonvulsants; all received intravenous diazepam in the first instance, with 4 receiving additional rectal paraldehyde and/or intravenous phenytoin.

Twenty-one children had a history of seizures prior to transplantation, although only 2 were receiving regular anticonvulsant therapy at the time of engraftment. Five (23.8%) of these patients had further seizures following transplantation. Of the 88 children where there was no such prior history, 15 (17.0%) developed seizures in the post-transplant period. This difference is not significant (P=0.69, χ^2).

The aetiology of the observed seizures was in most instances multifactorial, although in 15 of the 21 (71.4%) transplants complicated by seizure, blood pressure readings in excess of the 95th percentile for age corrected for height [8] had been recorded in the immediate pre-seizure period. The overall prevalence of hypertension in the seizure and non-seizure groups was not significantly different; 72 of 92 (78.2%) children in the non-seizure group where full clinical data were available were receiving antihypertensive therapy at the time of discharge from hospital after transplantation (P=0.57, χ^2). The degree of hypertension did, however, appear to be somewhat greater in the seizure group 15 of 21 (78.2%) having a greatly elevated systolic blood pressure (mean of 163 mmHg at a mean age of 8.7 years) compared with 35 of 92 (38.9%) in the non-seizure group who were receiving greater than one antihypertensive agent at the time of discharge from hospital (P=0.01, χ^2)). Additionally, 4 children were febrile (all associated with proven urinary tract infections), 6 had acute allograft rejection, 1 had significant hypomagnesaemia and 1 significantly elevated CsA levels (1,600 ng/ml), the only child in this series with levels in excess of two times the upper limit of the target therapeutic range. In 2 children, no obvious cause for their seizure was identified (Table 1). No child was receiving intravenous CsA although 3 children were receiving a course of intravenous methylprednisolone at the time of or in the 48 h prior to the seizure. No association was detected between the aetiology of renal failure or the degree of HLA matching and the subsequent development of seizures.

Of the eight MRI scans performed, three showed significant abnormalities; two of these scans were in children with previous normal neurodevelopment, and showed intracerebral haemorrhage in one and generalised cerebral oedema in the other. The third child was known to have global developmental delay prior to transplantation, and was shown to have demyelination and cortical atrophy. Both CT scans were normal, one of these being in the aforementioned patient subsequently shown to have demyelination on MRI. Three of the five EEGs showed abnormalities. Two of these children have significant long-term residual neurological morbidity (global developmental delay and behavioural problems following intracerebral haemorrhage, and hemiparesis and global developmental delay associated with cortical atrophy and demyelination). These and a further 3 children developed ongoing seizures requiring long-term anticonvulsant therapy with sodium valproate (n=4) or carbamazepine (n=1).

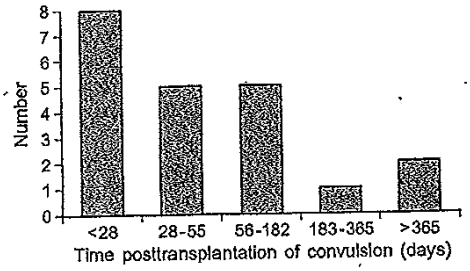

Fig. 1 Time of convulsion post transplantation

Table 1 Risk factors association with seizures following 21 renal transplants in 20 children

Risk factor	Number
Hypertension alone	9
Hypertension associated with rejection	4
Hypertension associated with rejection and fever	1
Hypertension associated with cyclosporine A toxicity	1
Fever alone	2
Fever associated with rejection	1
Hypomagnesaemia	1
No cause identified	2

Discussion

We report a relatively high incidence of seizures complicating renal transplantation in childhood, confirming the earlier data of McEnergy et al. [1] who detected a post-transplant seizure rate of 20.1% in a cohort of North American children, a number of whom were transplanted in the pre-CsA era. A similar incidence of seizures has also been reported following the transplantation of other solid organs [9, 10]. In keeping with the findings of previous studies, it was not possible to clearly identify a single aetiological factor as being the cause of the seizure in the large majority of cases, although children who developed seizures were commonly noted to be hypertensive in the period immediately prior to their seizure. Overall, the usage of antihypertensive agents was not higher in the group of children who developed seizures compared with those who did not, although the degree of hypertension did appear to be more severe in the seizure group. It may, however, be the rate of change in blood pressure that is of more importance than the absolute value at any one timepoint. That rapid resolution and no further recurrences of seizures occurred following satisfactory control of hypertension provides further evidence that it is indeed an important risk factor. Fever and acute allograft rejection, either in isolation, together or in association with hypertension, were recorded in 8 cases where seizures occurred. Only 1 child was found to have significant hypomagnesaemia and another high trough CsA levels; all children underwent regular assessment of these biochemical parameters in the post-transplant period.

The majority of seizures were short lived and non-recurrent and the long-term neurological outcome in the majority of children was excellent. Only 5 children required long-term anticonvulsant therapy, including 2 who developed convulsions secondary to significant intracerebral pathology, with resultant long-term neurological handicap. In 1 of these cases, the intracerebral lesion (cortical atrophy and demyelination) almost certainly antedated the transplant and was not a consequence of it, whereas the other (intracerebral haemorrhage) was secondary to intraoperative haemodynamic changes at the time of engraftment.

We have clearly shown that children with a history of seizures prior to transplantation are not at increased risk of seizures post engraftment, and in those not receiving maintenance anticonvulsant therapy we cannot recommend the use of prophylactic therapy at the time of transplantation. Many anticonvulsants will increase CsA metabolism secondary to cytochrome P-450 hepatic enzyme induction, with resultant sub-therapeutic drug levels.

Factors precipitating hypertension clearly need to be avoided where possible; significant degrees of fluid overload should be avoided by meticulous attention to fluid balance, intravenous methylprednisolone should be infused slowly, and care should be taken to avoid CsA levels rising above the target range. Children on corticosteroids should receive a "no-added-salt" diet. Where hypertension unavoidably occurs, stringent blood pressure control should be effected by the prompt use of antihypertensive agents. The regular monitoring of plasma biochemistry should allow anticipation and appropriate treatment of electrolyte imbalance, and suspected infections should be treated empirically.

The parents of children undergoing renal transplantation at our institution are now routinely counselled of the risks of seizures, in addition to the other recognised complications of renal transplantation, as part of the pre-transplant work-up.

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BRIEF REPORT

A fatal case of cerebral oedema with hyponatraemia and massive polyuria after renal transplantation

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Abstract We report the case of a child who died from severe cerebral oedema in the context of hyponatraemia and extreme polyuria immediately after renal transplantation. The patient was treated according to a standard post-transplantation protocol, receiving 0.45% saline solution for urine output replacement. The case highlights the dangers of massive fluid therapy in the context of polyuria and, therefore, the need for intensive monitoring.

Keywords Hyponatraemia · Seizure · Cerebral oedema · Kidney transplant · Hypotonic fluid · Polyuria · Salt wasting

Introduction

We report the case of an 11-year-old boy, who had extreme polyuria shortly after live-related renal transplantation. He developed seizures associated with a serum sodium concentration of 126 mmol/l and his condition rapidly progressed to tonsillar herniation and death. We detail the sequence of events, discuss potential causes of this tragic occurrence and describe how we changed our post-transplantation care protocol to enable earlier detection of such abnormalities.

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Case report

An 11-year-old boy weighing 30.3 kg was admitted for a pre-emptive live-related transplant. He had suffered meningococcal septicaemia at the age of 34 months, complicated at that time by severe neurological dysfunction, with coma, seizures and peripheral vascular involvement with skin and bone loss. He had been undergoing short-term dialysis for nearly 4 weeks, but his renal function [glomerular filtration rate (GFR) by the chromium-51–ethylene diamine tetra-acetic acid (Cr^{51}-EDTA) method was 37 ml/min per 1.73 m^2 body surface area at 3 years] had recovered sufficiently to be managed conservatively. He was left with a minor seizure disorder treated with sodium valproate at the time of transplantation. Electroencephalography (EEG) showed discharges over the right temporoparietal area, and a cerebral magnetic resonance imaging (MRI) scan when he was aged 4.5 years showed mild cerebellar atrophy, with normal ventricular size. He attended mainstream school and had learning support.

His renal function deteriorated from the age of 10 years, with his serum creatinine rising from 1.6 mg/dl to 3.8 mg/dl (145–330 μmol/l), so work-up was commenced for renal transplantation. He was polyuric, with a daily urine output of 3–4 l.

He underwent a live-related renal transplantation, with 0,1,1 mismatch, from his mother. He was given 0.25 mg/kg tacrolimus and prednisolone 600 mg/m^2 before theatre and had a urethral catheter placed after being anaesthetised. The operation was uneventful; the patient had normal vessel

anatomy. There was good blood flow and immediate urine output. The cold-ischaemia time was 30 min, and anastomosis time was 25 min. Intraoperatively, his systolic blood pressure (SBP) was 100-130 mmHg and central venous pressure (CVP) was 10-15 cmH_2O. He was given a total of 2,200 ml of fluid during the procedure [1,000 ml Hartmann's solution (near isotonic sodium lactate) and 1,200 ml 4.5% albumin] and 60 mg furosemide. A dopamine infusion (3 μg/kg per minute) and a patient-controlled morphine infusion were commenced. He received routine immunosuppression with tacrolimus, azathioprine and prednisolone.

Immediately postoperatively, he was warm and well perfused, with a core–toe temperature gap of 2.4°C. He had a normal heart rate (HR; 90-105 beats/min) but was hypertensive (SBP 130-140 mmHg). His CVP was 8-11 cmH_2O. He regained consciousness fully and was extubated, with saturations of 98–100% in room air, respiratory rate 25/min. He had mixed metabolic and respiratory acidosis, pH 7.25, with a carbon dioxide partial pressure (pCO_2) of 42 mmHg (5.6 kPa) (venous gas). His initial postoperative serum sodium level was 141 mmol/l (see Table). A bedside fluid balance sheet was established, which included the volume of urine in the catheter bag (1,180 ml) but not the fluids given in theatre (2,200 ml) or the undocumented losses (urine lost during anastomosis of the ureter to the bladder, and blood losses). These losses were retrospectively estimated by the surgeon to be 300–500 ml.

The patient developed massive polyuria almost immediately after anastomosis, passing urine up to 58 ml/kg per hour. He was treated according to the unit's protocol, with replacement of insensible losses of 400 ml/m^2 per day and of the previous hour's urine volume with the same volume of 0.45% saline solution, alternating with 0.45% saline solution/2.5% dextrose. Two hours postoperatively he developed signs of poor peripheral perfusion, with a core–toe temperature gap of 6°C; HR was 90–105 beats/min, and SBP was 130–150 mmHg. It was concluded that he had a fluid deficit, and he was given an extra 1,449 ml 0.9% saline solution over 2 h. At 4 h he had a generalised tonic–clonic seizure, which was terminated immediately following administration of 0.1 mg/kg lorazepam. Blood glucose measured with a stix was 8.6 mmol/l, and central venous gas showed uncompensated metabolic acidosis, with a pH of 7.1. He was hyponatraemic (126 mmol/l), initially thought to be an artefact but confirmed on a repeat sample (121 mmol/l). At 5 h he had a further generalised tonic–clonic seizure, which again responded to lorazepam, but at that time his pupils were fixed and dilated. He was

Table 1 Results of blood and urine tests and fluid balance

Parameter	Time after anastomosis								
	Preoperative	Postoperative	1 h	2 h	3 h	4 h Seizure	5 h Seizure	Normal range	Unit
Sodium	140	141				126	121	133–146	mmol/l
Total CO_2	22	18				15	17	20–30	mmol/l
Urea	97 (34.5)	76 (27.2)				38 (13.7)	33 (11.7)	7–17 (2.5–6.0)	mg/dl (mmol per litre)
Creatinine	6.0 (528)	4.3 (379)				2.0 (178)	1.6 (143)	0.4–0.9 (35–80)	mg/dl (μmol/l)
Total calcium	11.3 (2.81)	9.7 (2.42)				6.8 (1.7)	6.5 (1.61)	8.8–10.7 (2.19–2.66)	mg/dl (mmol/l)
Magnesium	1.9 (0.8)	2.0 (0.83)				0.9 (0.36)	0.7 (0.28)	1.7–2.3 (0.7–0.95)	mg/dl (mmol/l)
Albumin	42	51				41	37	37–56	g/l
Glucose		202 (11.2)				175 (9.7)		63–99 (3.5–5.5)	mg/dl (mmol/l)
Osmolality								270–285	mosmol/kg
Haemoglobin	11.6	9.3				8.6		11.5–15.5	g/dl
Urine									
Sodium	112								mmol/l
Osmolality									mosmol/kg
Fluids									
In		2,200[a]	1,303	1,485	2,383	2,591	1,898		ml
Out[b]		1,240[c]	1,170	1,760	1,740	1,620	1,150		ml
Cumulative Balance		+960	+1,093	+818	+1,461	+2,432	+3,180		ml

[a] Total amount of fluid given intra-operatively
[b] Except for 200 ml from the wound drain, all output was urine
[c] Immediate postoperative output did not include intra-operative losses, which were not documented (see text)

intubated and ventilated; a computed tomography scan revealed severe cerebral oedema, with uncal and tonsillar herniation; he was diagnosed as being brainstem dead the following morning. Using hypertonic (3%) saline solution, we achieved normonatraemia after 8 h to allow organ donation.

Discussion

Our case highlights the dangers of massive fluid therapy and biochemical disturbances in the face of extreme polyuria. There are obvious questions regarding the actiology of the patient's seizures, hyponatraemia and polyuria. Moreover, considering that the patient was treated according to a standard protocol, used for over 15 years in more than 200 paediatric renal transplantations, we describe how the protocol was changed in order to prevent a similar tragedy from occurring.

What caused the patient's seizures and subsequent tonsillar herniation?

Seizures are a recognised complication after renal transplantation, with a frequency of up to 24%, with potential causes including fluid overload, and corticosteroid and calcineurin-inhibitor therapy [–]. Our patient was known to have had seizures previously, indicating that he had a lowered seizure threshold which was reduced further by the hypocalcaemia and hypomagnesaemia after transplantation (Table). The first seizure in our patient occurred when the serum sodium level was 126 mmol/l, a level not usually associated with seizure activity. However, hypo-osmolality was likely to have been the key aetiological factor, as the drop in serum sodium level was compounded by the rapid fall in urea after transplantation. His calculated serum osmolality dropped by approximately 80 mosmol/kg between transplantation and first seizure.

Why was the patient polyuric?

The massive diuresis after anastomosis (58 ml/kg per hour) was extremely unusual. There is one report of an adult with diuresis of 25–50 ml/kg per hour after having received a live-unrelated renal transplant, who was also given fluid replacement with 0.45% saline solution and who developed hyponatraemia [lowest serum sodium (Na) concentration 113 mmol/l] and multiple generalised tonic–clonic seizures [ ].

Our patient had 3–4 l/day (4–5 ml/kg per hour) native urine output, and the massive fluid losses after transplantation would have included a proportion from the native kidneys. However, excretion of ~1,800 ml/h requires a GFR of at least 30 ml/min, whilst the estimated GFR in our patient was 6 ml/min, uncorrected for surface area. Therefore, the majority of urine must have derived from the graft. Glucose given in the replacement fluid caused mild hyperglycaemia, with levels of 10–11 mmol/l, leading to osmotic diuresis. However, this leads to free water losses and hypernatraemia and is, thus, probably less relevant here.

Why did the patient become hyponatraemic?

The patient's venous sodium level had dropped from 141 mmol/l post-operatively to 121 mmol/l 5 h later. Hyponatraemia is due to either a deficiency in salt or an excess of water.

A separate quantitative analysis of water and salt balance, also called tonicity balance, can help identify the pathophysiology of hyponatraemia [ ]. From the beginning of surgery till his death, the patient was given 11.8 l and lost 8.6 l (see Table), a net positive balance for water of 3.2 l. An expansion of his total body water (estimated at 20 l or 65% of body weight) by this amount is consistent with the observed dilution of his serum sodium from 141 mmol/l to 121 mmol/l ($141 \times 20/23.2 = 121.6$). Based on this first part of the tonicity balance, excess fluid accounted for the hyponatraemia. This fits also with the observed decrease of albumin and haemoglobin in the blood (see Table). However, in order to retain the extra 3.2 l as free water, he must have been in equal sodium balance, i.e. the amount of sodium lost in the urine must have been equal to the sodium received. Whilst the urinary sodium was not measured, the amount received can be calculated from the fluids administered, and it totalled 1,140 mmol. An excretion of 1,140 mmol sodium in 8.6 l of urine equates to 133 mmol/l and represents 20% of sodium filtered during that time (assuming a GFR of 100 ml/min), indicating sodium wasting. This compares to reports of fractional sodium excretion (FE_{Na}) as high as 46% in deceased-donor renal allografts on the day of transplantation [ ].

Why did the patient have sodium wasting?

Sodium wasting is likely to have been due to hypoxic–ischaemic injury to the graft. The high FE_{Na} reported in deceased-donor allografts was associated with ischaemic changes on biopsy [ ]. In another study, hyponatraemia was seen in 88 of 125 adult recipients, also associated with an increased FE_{Na} [ ]. The dramatic postoperative decrease of serum calcium and magnesium concentrations (Table), which clearly exceeded the 16% dilution explained by the fluid balance, also suggests tubular dysfunction.

Sodium wasting can also be an appropriate physiological response of the kidney to volume overload, but it should not lead to hyponatraemia, as water can be excreted

alongside. However, other factors could have led to water retention, such as stress and morphine, recognised non-osmotic stimuli for antidiuretic hormone [ ], or furosemide, which impairs urinary dilution.

How should a polyuric patient be treated?

For a patient with gross polyuria (> 10 ml/kg per hour) we suggest giving a fixed intake of 10 ml/kg per hour, with frequent (two-hourly) clinical and biochemical assessments that include blood pressure, peripheral perfusion, CVP, and serum and urine sodium and osmolality, to guide further replacement. We use 0.45% saline solution, based on our subsequent experience with typical post-transplantation urinary sodium concentrations of approximately 80 mmol/l. Any extra fluid for perceived volume depletion must be given in isotonic form. We use a glucose-containing solution at a steady rate for replacement of insensible losses, but fluids given for urine output replacement and boluses are glucose-free.

Conclusion

Our patient developed seizures and tonsillar herniation due to hypo-osmolality associated with the administration of large volumes of hypotonic intravenous fluids in the context of extreme polyuria. Other factors, such as his previous brain injury, might have contributed to the fatal outcome. Regardless, the case highlights the importance of close clinical and biochemical monitoring after transplantation, especially in the context of polyuria. Although, in this case, the rapidity of events suggests that these measures might not have prevented death, we hope that lessons from this case will help to modify practice and prevent future tragedies.

References

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