This is a report by

Dr Malcolm Coulthard

requested by the *Inquiry into Hyponatraemia-Related Deaths*

on the conduct of the paediatric nephrologists who cared for Adam Strain,

Dr (now Professor) Maurice Savage, and Dr Mary O'Connor

07/11/2011

Format I will respond in order to the questions posed in a document sent to me, dated 04/10/11

(1)   Whether in November 1995 the Royal Belfast Hospital for Sick Children (RBHSC) had the facilities and resources, both in terms of clinical experience and support services, to carry out paediatric renal transplant surgery, including that with the complexities of Adam's surgery

I believe that the RBHSC did have sufficient experience, infrastructure and case-load to be undertaking paediatric renal transplantation in 1995. This view is based on their average annual transplant rate of about 7 children, and their levels of staffing in the departments of paediatric nephrology, transplant surgery and paediatric anaesthesia and PICU. Their primary graft function rate of 48/52 cases indicates a generally successful outcome.

This statement would apply to a child such as Adam. In various places throughout the inquiry discussions, references have been made to Adam's particular surgical complexities. I think this could lead to some inappropriate conclusions in the minds of people who are not familiar with paediatric renal transplantation. As is highlighted in some detail below, although many children that require kidney transplants are less surgically challenging than Adam, his case is in many ways typical of those of many other young children receiving kidneys. The majority of these will be salt-losers, with a relatively high output of weak urine, and many will have had prior surgery upon their ureters and bladders by the time of grafting.

Though some paediatric renal transplant units may consider referring some particularly high-risk cases to a larger centre, this would not apply to children as large as Adam, nor with his spectrum of illness. In my experience, such high-risk children might be very much smaller children (<10 kg), or those with multiple organ disease (eg, with a previous heart transplant, or requiring a combined liver and kidney graft). There would be little point in developing a unit if it could not cope with children such as Adam.

(2)   Please describe and comment on the role of a Consultant Paediatric Nephrologist in relation to a paediatric renal transplant in 1995. In particular, please comment on the role of a Consultant Paediatric Nephrologist in:

(a)   Managing a child in end-stage renal failure

Consultant paediatric nephrologists are the experts in managing children with end-stage renal failure, and generally become the main medical carers for this group of children. They typically coordinate any other aspects of medical care that such children might have, as they and their team usually have such a large input into their lives. They will see them relatively frequently in clinics, and during their almost inevitable hospital admissions, and they may have to advise other doctors (such as GPs or other specialists) about adjusting the dosages of any other medications that may need to be prescribed. In my experience, families whose children have end-stage renal failure seek advice about any and every other medical issue from their paediatric nephrologist before accepting it from any other source.

Because of this holistic role, most paediatric nephrology teams include consultants and junior doctors, but also specialist nurses who frequently have contact with agencies both outside hospital (such as schools and nurseries) as well as inside, dieticians, and also either social workers, or psychologists, or psychiatrists, or play therapists, or a combination of these professionals, to provide broad support. As well as knowing and advising about the renal aspects of their patients, most paediatric nephrologists will also know much about the individual families, their capacities and how they cope with stress.

Specifically, they are also responsible, with other members of the team, for educating the parents and children about their kidney condition, and monitoring their care. This includes making regular observations about general health and development, growth, stability of blood tests, and introducing, explaining the rationale for, and educating about different treatments such as diets, dialysis, and transplantation.
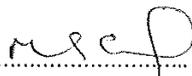
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(b)   Providing information and advice to the child's family including in relation to:

(i)   Child's condition e.g. polyuria and propensity for low sodium

Unlike adult experience, it is common for young children with end-stage kidney failure to produce large volumes of poor quality urine, and to leak sodium into the urine in an unregulated manner. For example, in a study that I undertook of children who were treated for end-stage kidney failure in the UK and Ireland between 1988 and 1997, 111 of 177 (63%) had a diagnosis which would be likely to result in these clinical features (Appendix 1).

These features lead to important clinical impacts. These include the need for the child to take a high salt and/or sodium bicarbonate intake with their diets or drinks in order to keep the plasma sodium (and bicarbonate) levels relatively stable, and thereby to keep them well, and growing. These supplements are sometimes given as tablets, or powders, or solutions, and frequently 2 or 3 times per day.

In addition, there is a tendency for children to void large volumes of urine. This results in them needing to drink far more than other children, otherwise they rapidly become dehydrated. This is especially marked during the night, as they continue to void large volumes during the whole 24 hours, while other children soon pass smaller volumes at night. The practical impacts of this effect are that parents and others need to recognise that children really do need drinks when they ask for them, that they need to carry bottles of water when going out, and that children will often need to wake to void and drink through the night, often several times. In addition, it is vital that families whose children have this problem are aware to bring them to hospital promptly if they develop a vomiting illness which prevents them from keeping fluids down.

The reason for emphasising all of these important effects on the lives of these children and their families is that it is part of routine management of such children for the caregivers to fully understand these issues, as they affect their everyday lives, and are essential in preventing acute illness due to rapid dehydration. Explaining these points to families is therefore a basic part of the job of a consultant paediatric nephrologist.

(ii)   Dialysis and the length of time the child can continue to safely remain on dialysis

As children approach end-stage renal failure, ie when they require renal replacement therapy, the dialysis options would be explained to the parents (and child at an appropriate level). Typically they will have the general principles and options of the 2 types of dialysis explained (peritoneal and haemo), and are likely to be invited to meet other families with children on these. The choice of dialysis modality has a huge impact on the life-style of the child and the family, including on siblings, and often on the parents' work capacity, etc. Thus, it is inevitable that this must be addressed with families as it has such a great impact on them. This is the role of the paediatric nephrologist, usually in close collaboration with the children's kidney specialist nurses.

The length of time that children can remain on dialysis is not a fixed quantity. What is certain is that shorter periods are better than long periods, but that some children have been successfully been managed on dialysis for many years. Dialysis is virtually never seen as an acceptable final form of renal replacement in children (unlike some older adults), but rather it is seen a bridge to transplantation. These are the messages that would be given to families by the paediatric nephrologist and team.

(iii)   Renal transplant options and the transplant centre where such the surgery could/should be carried out e.g. the expertise of the local centre as opposed to any other

I have effectively dealt with this in answer (1) above. If the team (primarily the paediatric nephrologists and transplant surgeons) considered that the particular child's care was within their capability, there would be no reason for them to discuss carrying it out in another centre.

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Note that I believe that the final decision to plan to undertake a transplant should not be made by the paediatric nephrologist alone, but jointly by the paediatric renal team and the transplant surgeons. In practice in our unit, one of the paediatric surgeons always meets the child and family in advance, in a calm outpatient setting, to discuss the particulars of this surgery with them, in the presence of the paediatric nephrologist or specialist renal nurse, or both, before they add the child to the transplant waiting list, or before planning a live-donation from a relative.

During this meeting, the past history of abdominal surgery is always discussed, including with the parents. However, generally this would be in the form of relative reassurance, in the sense that prior surgery is common, and although it makes the procedure more difficult for the surgeons, it is seldom an absolute contra-indication, and there are no realistic alternatives to offer, anyway. Typically parents will learn that prior surgery will make it more difficult, but not unsurpassable.

One important role of having such a meeting and assessment by a transplant surgeon and paediatric nephrologist is to formulate a specific plan for that particular child, and to record it in their case notes. The importance of this is that it may not be that particular surgeon who is available to operate at the time a kidney becomes available, and it allows a calmly considered plan to be used at the time, instead of considering these details under a last-minute time-pressure.

(iv)   Likely complexities of the surgery given any previous surgery

In some rare cases, special considerations will need to be made, such as the risk that the bladder cannot be used, and the urine will have to be drained from a 'bag' on the abdomen. However, in most cases where there has been prior surgery, including Adam's, the situation is as in response (iii). That is, the likely complexities are simply that it may be technically more difficult to perform the transplant, and so may take longer. This would be explained in the way described above, in general terms by the paediatric nephrologist, and in more detail if requested by the surgeon.

(v)   Likely complexities of the anaesthesia given any potential fluid management difficulties

Unless there are very special circumstances, which there were not in this case, such as prior problems with a particular anaesthetic agent, or an abnormal laryngeal anatomy, the information given to the parents of a child about to have an anaesthetic for a paediatric transplant would be the same as for any other child about to undergo a lengthy operation, and this would mainly be of a reassuring nature as paediatric transplant patients would always be expected to be managed by an experienced anaesthetist. The paediatric nephrologist would therefore have a reassuring and supportive role in this regard. I cannot remember a child in whom the anaesthetic posed a specific risk during transplant surgery compared to the overall risk inherent in having renal failure.

The issue of their child's fluid management would not be presented to the parents as a potential difficulty except in that they would be reassured that we as paediatric nephrologists were aware of their child's sodium and water handling problems, and would be liaising with the anaesthetists, and would ensure that it was coped with appropriately. Managed properly, these children are not likely to develop either fluid volume or sodium aberrations. Most children like Adam have had several anaesthetics by the time they reach a transplant, and these issues have therefore frequently been addressed before.

(vi)   The chances of success/risks of failure of the graft following transplantation

These issues would be addressed long in advance of the child ever meeting a transplant surgeon, or being listed for a graft. It is another of the fundamental issues that a paediatric nephrologist would routinely discuss with families. By 1995, the overall success rates for cadaveric grafts were generally good, both in the long and the short term, though not as good as they are in 2011. However, no paediatric nephrologist would allow a parent to contemplate their child having a transplant without

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understanding that nothing is guaranteed, not without understanding that for many reasons, some kidneys do not work and have to be removed.

(vii)   Risks to the child of the anaesthetic and/or surgery

The paediatric nephrologist will have indicated to all parents prior to listing a child for transplant surgery that there is a very small, but real, risk of the child dying under anaesthetic and during surgery. However, this would be emphasised as being extremely small, especially in relation to their child's chances of longer survival without a transplant.

(viii)   Who else should be asked to assist in providing information and advice e.g. Anaesthetist, Surgeon

In our practice, as described above, most of the information about transplantation is provided over a long time, in advance, by the paediatric nephrologists and their teams of nurses, social workers, psychologists, etc. In addition, we would see it as good practice for them to meet the transplant surgeons at least once before listing them, and for them to receive advice in that way. We have also run a 'dry run' transplant day for our children and their families for many years (since before 1995) before listing them, in which we introduce them to the PICU where they will wake up, show them monitors, lines, etc, to try to set the scene about the intensive level of care they will expect to receive then, though I am not sure if this is a wide-spread practice.

It has not been our routine to introduce the families to an anaesthetist in advance, though for every case I can remember, the consultant anaesthetist themselves or their deputy has always met the family soon after admission to take a history of previous anaesthetics, and to explain the procedure from their perspective.

(c)   Managing the process of getting the child on the transplant list and the plans for what should happen when an offer is received, including who else should be involved in the process e.g. anaesthetist, surgeon

In my view, the paediatric nephrologist should liaise with the transplant surgeons as described above before listing the child. At that point, any particular specific decisions about management should be recorded for future reference. Also at that point they should jointly decide the level of urgency for the case. This has major implications for the choice of kidneys that would be accepted. For example, a child who was growing and thriving happily on dialysis without a massive disruption to his parents' ability to cope would be listed to have an especially well matched and in other ways extremely suitable kidney, while a child whose dialysis was precarious and unlikely to last for long might be listed for a far less ideal organ.

In recent years, we have held formal review meetings with the transplant surgeons and laboratory staff involved with tissue-typing, and with transplant coordinators to update each child's degree of urgency in the light of a wide range of factors, and to feed any changes back to parents, but this was only done informally in 1995.

I can only recall involving an anaesthetist into this decision making process at this stage in over 25 years of practice, in a girl with a known laryngeal abnormality who was known to be extremely difficult to intubate.

(d)   Managing the process once the offer is made, including the arrangements to be made and anyone else who should be involved

Making the decision to proceed with the transplant
When a kidney becomes available as a potential offer for a child, this information is first rung to the transplant coordinator for the hospital. They then ring the transplant surgeons and the paediatric

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nephrologists to check that the child is still fit and well (ie, not acutely unwell for any reason) and to decide on the suitability of the organ for that child.

In my experience, the first decision lies with the paediatric nephrologist as they have the most up to date information about the child's progress. The range of issues to consider include the size and age of the donor, their medical condition before retrieval, the time since the organ was harvested, any anatomical issues such as multiple arteries, and the degree of tissue-type mismatch. There are seldom perfect kidneys that score well on every aspect, and few that score badly in every domain, so typically it is a question of judgement. The problem is to balance the almost inevitable 'lack of ideal' aspects of the kidney, against the child's condition, including their medical stability, waiting time so far, social situation, specific surgical problems, and so on.

Involving the transplant surgeons

If the paediatric nephrologist considers the offer to be on-balance an unsuitable one for that child, it will not be accepted, and will be offered to other centres. If s/he considers it a reasonable or a good offer for that child, they will then discuss it with the transplant surgeon, and make a joint decision. If the plan is to proceed, usually the paediatric nephrologist will telephone the family and arrange immediate admission under his/her care.

Part of the discussion between the paediatric nephrologist and transplant surgeon to reach the decision is a review of the specific surgical plan that was already drawn up in advance and documented. This provides an important opportunity to reconsider the particular issues of the child's case in relation to the kidney provided. For example, if surgical access was expected to be particularly restricted in a child, it would influence whether they might only be suitable to receive a small kidney, and so on. It therefore provides a forum for jointly agreeing detailed surgical plans.

Involving the anaesthetists

Paediatric nephrologists are especially aware of the particular sodium and water balance problems of their children with end-stage renal failure. The fluid balance issues for different children going for transplant surgery can be widely different. In some cases, as with Adam, the child has a relatively high and fixed output of urine each day, with sodium lost in parallel, while in other cases the child does not pass any urine, and may never have done so. A major reason for the paediatric anaesthetists personally discussing each case with the consultant anaesthetist (and it always would be a consultant undertaking this role) is to provide an estimate of the child's likely urine output volume and its sodium content. This is important as ongoing losses need to be replaced as intravenous fluid during surgery.

The paediatric nephrologist's estimate of the child's output may be based on a number of facts. In some cases, a 24-hour measurement of urine volume may have been made recently. More often, it is based on a careful assessment of the child's daily intakes. For water, a small amount is lost each day by evaporation, in the breath, stool, etc, and the rest is lost as urine or in the dialysis (again, assuming the child does not have watery diarrhoea, but then a transplant would not be considered anyway). Thus, the estimated output of urine is deduced from the daily fluid intake, minus the estimated evaporative (often called insensible) losses, at about 300 ml/m^2 of body surface area daily, and minus the volume removed by dialysis (the ultrafiltrate). These can be estimated for a 24-hour period and divided by 24 to give an hourly approximation of urine losses.

Virtually all of the sodium ingested each day is passed out into the urine (apart from small amounts lost in sweat and stool, but these are negligible quantities unless the child has diarrhoea), so the daily output is close to the intake. This could be used to estimate the urine sodium losses, but a much more practical and routine way is to base the replacement quantity on the assumption that the urine will have a particular sodium concentration, and use an intravenous fluid with a close concentration.

The ideal way to do this is simply to send a urine sample to the laboratory for sodium estimation at the same time as sending the blood samples on the child's admission for the transplant operation. This is the method that our department has always used. We have had this policy because it is unreasonable to use old measurements of the urine sodium concentration as this is likely to change as the child's kidney condition deteriorates with time. Also, it is such a simple and cheap way of achieving precision.

However, a reasonable and widely used alternative is to assume that the urine output should be replaced with a solution containing half-normal saline (0.45% sodium chloride, with or without glucose as required, which has a sodium concentration of 77 mmol/litre). This is reasonable because this is close to the concentration that most children's kidneys do produce by the time they reach end-stage. An exception would be if the child had an exceptionally high residual urine output, higher than Adam's actually was, in which case a more precise replacement fluid concentration should be tailored by measuring their pre-operative sample.

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In practice, unless the anaesthetist was one that I knew personally had experience at anaesthetising children for kidney transplants, I would also check by discussion with the anaesthetist on the day that they were aware of their particular fluid balance needs. This would include the fact that we would aim to present them with a child who was fluid replete, but not clinically significantly overloaded, and that we would want them to insert a central venous line, and to be generous with their fluid intake such that the central venous pressure (CVP) was increased to a little above normal (say 12 to 17 cm of water, equivalent to 9 to 12 mm Hg) just prior to the surgeon releasing the vascular clamps to the kidney, to ensure that they had enough fluid volume reserve to fill the kidney and provide it with a very adequate blood flow.

Thus, the fluid-management related messages from the paediatric nephrologist to the anaesthetist would include the following two points. First, the approximate estimate of hourly urine output and the closest match of fluid to replace it with, and second the need to deliberately maintain the child with a slight excess of fluid volume to ensure their vascular compartment was well filled or slightly over-filled. It would not occur to me to mention to the anaesthetist that this latter component of his fluid delivery should be with a solution with a sodium concentration that was close to that of plasma because I would assume that any and every anaesthetist (of any grade) would already be fully aware of that fact. Rather, I would leave them to decide the precise details of this, for example if they wanted to use normal saline, or another fluid such as Hartmann's solution. I would not imagine at all that any anaesthetist would consider using a solution with a sodium of just 30 mmol per litre if it was being administered deliberately to be retained within the body, to expand its fluid volume.

Managing the child's pre-operative fluids

It is the role of the paediatric nephrologist to deliver the child to the operating theatre in appropriate condition. One of the ways of doing that is to ensure that they have an adequate quantity of fluid in their body (ideally a slight excess over normal) for the procedure, and that the biochemistry concentrations are all safe and appropriate. The latter would include ensuring that the plasma sodium was in or close to the normal range.

How this would be achieved would vary from child to child. In some cases it might mean a haemodialysis session pre-operatively, in some it may involve extra fluids in advance, or prescribing peritoneal dialysis. This decision would be the role of the paediatric nephrologist, and not of the anaesthetist, though the anaesthetist would undoubtedly be informed about how it was planned to achieve this in each case. At delivery of the patient to the care of the theatre team, I would expect the medical hand-over of information to include an assessment by the paediatric nephrologist or a member of their team of how well this goal had been achieved.

Specifically regarding the need of the paediatric nephrologist to repeat a measure the blood biochemistry results immediately pre-operatively, this would depend upon individual circumstances. If the child's admission results were satisfactory, and they were known to normally run stable values, and if no special measures were needed to be taken to adjust them, then I would expect the paediatric nephrologist to explain that to the anaesthetist. This would avoid an extra needle for the child, and the anaesthetist could easily obtain and send a blood sample to the laboratory while inserting a central line – blood is drawn back into a syringe during that process anyway to test the patency of the line, so it would take just a few seconds to do.

On the other hand, if the child's biochemistry was dangerously abnormal, such as having a high potassium concentration, it could require the child to undergo a haemodialysis session pre-operatively, which would alter all of the biochemical parameters. Under these circumstances it would be mandatory for the paediatric nephrologist to measure further values before the child was anaesthetised.

In many cases, as with Adam, an in-between course would occur. A child might go onto their regular peritoneal dialysis overnight programme, but not complete the full number of cycles, and might have some of their usual overnight fluid volume given as milk, some as enteral clear fluid, and some as a drip. Under those circumstances the judgement for the need for a later blood sample would depend upon the exact clinical conditions. For a child who is normally dialysed by PD every night, and who is otherwise his 'normal self' and well, it would be desirable but not mandatory to have a repeat blood test result before anaesthetic induction. If there was a decision made to take such a sample, but if it was difficult to perform and distressing the child, it would be best practice to inform the anaesthetic team at that stage and decide a plan. If that plan was to abandon more attempts pre-operatively, as a paediatric nephrologist I would implicitly interpret the arrangements to be that the blood sample would be taken and sent by the anaesthetist as soon as it was convenient after the child was asleep. I would not expect to have to spell that out to an anaesthetic colleague under such circumstances. This type of arrangement is commonplace in paediatrics in order to avoid unnecessary trauma to children.

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(e)   Obtaining consent, including the requirements of 'A guide to consent for examination or treatment' circulated on 6th October 1995 by the Management Executive Office of the Chief Executive Ref: HSS(GHS)2/95, together with the extent to which anyone else should be involved in the process e.g. Anaesthetist, Surgeon

At present, consent for surgery is always obtained by a surgeon, either the consultant or an experienced junior colleague who is able to explain all of the details of the surgery to the family.

This has not always been the case. In the past, including in 1995, in my experience it was relatively common for the obtaining of the final written consent for a child's kidney transplant to be undertaken by the consultant paediatric nephrologist. In my opinion this was equally as good as the present arrangements. This was for 2 reasons. The first was practical; the consultant paediatric nephrologist would almost inevitably be visiting the parent and child soon after their admission to his/her ward anyway, while the transplant surgeon may be busy elsewhere and unable to visit in person until immediately prior to the surgery. The second concerns the quality of information for the families. A consultant paediatric nephrologist will have a comprehensive understanding of the facts and issues about children's transplant surgery in general, and the details of that child in particular, including levels of risk, so they are likely to be able to provide similar information to the surgeons. In addition, they are already extremely well known to the family, which may prove an advantage for parents taking in information during this stressful period.

It should be remembered that in our local arrangements, the parents will always have met a transplant surgeon in advance of the surgery, and will have covered the relevant issues then. In fact our current arrangements are now for the parents to sign a consent form at that stage, in outpatients with the surgeon, and for that to be filed in the patient's notes. This can then be merely signed as being updated at the time of surgery if the time interval is sufficiently short.

For the anaesthetist, there are different issues. While it could be argued that a consultant paediatric nephrologist may be able to give general information about what parents should expect to happen from an anaesthetic perspective, in my view it is essential that one of the anaesthetic doctors should visit the family anyway, to take a relevant up-to-date detailed history prior to administering the anaesthetic.

(f)   Being in the operating theatre during the transplant surgery

It has always been my personal practice, and that of consultant paediatric nephrology colleagues that I have spoken to on this subject, to visit the operating theatre intermittently during a child's transplant whenever this is practical. This is mainly to be able to provide feed-back to the parents on their child's progress, but sometimes also involves entering into medical discussions with the anaesthetists and surgeons about particular aspects of the child's ongoing care.

This practice is not necessary from a management perspective, however, and does not constitute a formal part of the paediatric nephrologist's role; it is more a 'social' aspect of providing holistic care to these children and their families. What is necessary is for the paediatric nephrologist to be available at all times for telephone discussions with the theatre team should a particular problem arise which they could help with. In many instances it would prove impossible for a paediatric nephrologist to simply visit the theatre during a transplant unless required for a specific reason as they may also be required to be undertaking clinics, etc.

In normal circumstances, making such visits is unlikely to be of great medical importance because the surgical, anaesthetic, and fluid management plans for the operation have already been agreed, and are adhered to.

A particular point to make to avoid potential confusion, having read some of the reports in this case, is that the paediatric nephrologist is not required to be in theatre to administer or oversee the administration of the immunosuppressive (anti-rejection) drugs. It is their role to decide their dosage, and typically at a practical level usually to arrange for them to be prepared or supplied to the theatre staff from the children's ward when the child is taken to theatre. They would then prescribe for them to be given by the anaesthetist at a set point during the surgery, typically at the time of releasing the vascular clamps to start the child's blood perfusing the kidney. They would not be required to action the administration at the time.

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(g)   Transferring the patient from the operating theatre to PICU

Once the operation is completed and the child is considered to have recovered sufficiently from the anaesthetic, their care is transferred from the anaesthetist to that of the ongoing paediatric medical carer(s). Exactly how and where this is done will depend on local arrangements. If the operating suite is close to the PICU, for example, the transfer may be an immediate one directly from anaesthetist to the joint care of the paediatric nephrologist and the paediatric intensivist. This may vary considerably, however. In my own practice, some transfers are as described above, and others are from a distant operating suite to the PICU. In that case, the transfer is from the anaesthetist to the paediatric nephrologist's team in a recovery room adjacent to the theatre for initial monitoring and stabilisation if necessary, followed by a transfer along corridors to the PICU, supervised by the paediatric nephrologist, for ongoing shared paediatric nephrology / PICU staff care.
      Whatever the local arrangements, the paediatric nephrologist will take prime responsibility for the management of the child's kidney care and fluid and biochemical management as soon as the anaesthetist has completed their task. Usually in a PICU setting, the intensivist will take prime responsibility for the child's breathing and pain relief, while the paediatric nephrologist will mainly guide the fluid management. In practice, both teams work cooperatively as one during this period.

(h)   Managing the post-operative phase

The post-operative phase of a paediatric renal transplant is critical – it requires extremely close meticulous management. Usually, most of the issues are ones that are squarely within the realm of the paediatric nephrologist, rather than the transplant surgeons or intensivists, though obviously all operate as a team. The main issues are around maintaining appropriate fluid and electrolyte status, monitoring the functioning of the kidney, nutrition, and pain relief.

(i)   Providing information to the child's family, including where the child has died, and whether or not with others e.g. Anaesthetist, Surgeon

In a straight-forward case, the main doctors that liaise with and inform the family about ongoing events are the paediatric nephrologists. This is for 2 reasons. First, they are the doctors that the family know best, as they have usually built up a relationship over a very long time. Second, as stated in (h), they have the major role to play both pre- and post-operatively.
      These generalisations obviously change with circumstances. For example, if there were unexpected complications of surgery, these would usually be explained to the family jointly by the surgeon involved and by the paediatric nephrologist.
      If a child died, the paediatric nephrologist would definitely be one of the people present when the parents were informed, if not the lead person to introduce the issues, for the reasons stated above, even if the events leading to the death were not directly within their management area (as in Adam, where he went to theatre apparently well, and died there). The other people I would expect to be present would be the doctors that were looking after the child at the time. If there was an obvious surgical cause identified (such as them bleeding to death after an accidental cutting of an artery), I would expect the surgeon to join the nephrologist, but not necessarily the anaesthetist. If it was a non-surgical death (as in Adam's case), I would expect the anaesthetist to join the nephrologist as the patient's general management and support would be his/her primary responsibility at the time, but in most cases I think that the surgeon would usually join the discussion as well as the parents' perceptions would be likely to be that 'the surgery must have gone wrong', and these issues would need addressing.

(j)   Participating in, should the surgery end in the child's death, any process of 'lessons learned' including:

(i)   Morbidity and mortality meeting

I would expect the paediatric nephrologist and their team to participate fully in such meetings, whatever the perceived cause of the death. This is because they take overall charge and responsibility for this group of patients, and may have lessons to learn both about their own practice, but also about those of colleagues in other disciplines which they may be able to influence in future cases.

    I would expect the surgeon to also be involved in all cases of a child who died in theatre, whatever the pre-conceived cause.

    I would expect the anaesthetist to be involved in all cases of children who died in theatre with an unknown cause, or one that is likely to involve their general management, but not necessarily to attend meetings where it is considered obvious in advance that the issues involved strictly paediatric nephrological or surgical issues.

(ii)   Development of departmental recommendations

Paediatric nephrologist are typically, and should be, involved in developing departmental guidelines (in the form of protocols or guidelines) in relation to all areas of children's kidney illnesses, including transplantation. These may sometimes overlap into other disciplines, such as outlining the specific anaesthetic needs for a kidney transplant in terms of requiring the child to be kept 'full' with respect to fluid volume. It is obviously ideal if such areas of overlap are agreed between representatives of all the relevant disciplines.

(iii)   Revisions to clinical protocols/guidelines

The answer is the same as for (ii) above – recommendations have to be updated by occasional revisions. These may be made as a matter of a 'routine' update if they are perceived to have become out of date, or as the result of a particular experience or new innovation.

(iv)   Internal hospital enquiry

The answer is the same as for (i) above.

(3)   The protocols (if any) that were generally available in 1995 (and now) governing or having an impact upon the work or role of a Nephrologist before, during and after a renal transplant procedure

The protocol written in 1990 and available in 1995 is relatively brief. This is almost certainly because at that time Maurice Savage was the lone paediatric nephrologist in Belfast, and it did not need to be expansive – I imagine that its role would have been to act as a guide to his junior staff and a check-list for him. It does not give the impression of being a document which was designed to be read by and to guide members of other related teams, such as the transplant surgeons or the anaesthetists. Given that this was written in the days when such documents were generally available as typed and photocopied papers, rather than circulated on intranets as they typically are today, their sphere of influence and intended influence was likely to have been restricted to the core team in his department.

    In relation to the administration of fluids during surgery, it does allow for the administration of blood (which would probably have been whole blood then, rather than packed red cells as now), or PPF (a solution containing proteins, and sodium at concentrations similar to plasma), or N/2 saline

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(half-normal saline, 0.45%, with a sodium concentration of 77 mmol/l, but commonly rounded to and quoted as 75 mmol/l), and it does refer to the need to 'ensure a good intravascular volume'.

I would interpret this section of the document as a brief statement about the possible range of fluids likely to be required during surgery. It does not specifically mention using normal saline to achieve a 'good intravascular volume', but neither does it mention using N/5 saline (one-fifth normal saline, 0.18%, with a sodium concentration of 30.8 mmol/l, but commonly rounded to and quoted as 30 mmol/l). I would not consider it reasonable for this to be thought of as an instruction to an anaesthetist on which fluids to administer in which quantities for any particular child – such an instruction would need to be a far more complex and comprehensive paragraph.

Given these observations, I consider this document to have been a useful working paper drawn up within a small and closely run department to aid management locally within that team. As such it met its purpose adequately.

The protocol written in 1996 following Adam's death is somewhat different, but as well as the event of his death, things had also evolved within the department since 1990. There were now 2 consultants within the department, the second one bringing with her some different ideas based on her previous experience. It is essential when working in a team, and therefore handing the care of children between consultants as one goes off or comes on duty, to agree a common approach to management.

Once again, it does not appear to be a document that has been written to provide an exhaustive protocol for an anaesthetist to follow, but as with the first one, it gives an outline of the ways in which the paediatric nephrology team expect the child to be managed in theatre in general. To explain this point more clearly, note the wording on page 4 of the Newcastle protocol from 1999 (Appendix 2), which I believe was designed for a similar purpose to the Belfast one:

> **Contact the anaesthetic staff on call.** They should be reminded that the standard paediatric transplant protocol is to be followed. This entails the peri-operative administration of methyl prednisolone and a radial arterial and central venous line being sited. The CVP is to be maintained between 7 and 15 cm of water during the operative procedure using colloid boluses (see p.5).

Indeed, it would be cause for immense concern if such a general guidance document was considered to be a comprehensive guide on how to maintain fluid balance during a general anaesthetic.

Not surprisingly, after the lesson of Adam's death the Belfast 1996 document suggests that the fluids likely to be used to bring the CVP up to appropriate levels now only include blood, plasma or normal saline. This was an appropriate change.

My only additional comment in relation to fluid balance advice is that it would make more logical sense to suggest measuring the pre- and post-operative urine sodium concentrations and to use these as a guide to the replacement solutions needed, rather than to assume that 0.45% saline would remain an ideal solution.

NOTE ABOUT CVP MEASUREMENTS

It was drawn to my attention whilst reading the Belfast and Newcastle guidelines side-by-side that there is a potential for confusion to be introduced about the range of CVP measurements being aimed at in different centres. This is because CVP may be expressed either as cm of water, or as mm of mercury (mm Hg), and these values are fairly similar. The reason for the 2 different units is that originally the pressures were read directly from a manometer consisting of a column of water, and this was gradually replaced by measurements using electronic pressure gauges calibrated in mm Hg, to match the way in which arterial pressure is traditionally recorded.

1 cm of water is equivalent to 1.4 mm Hg. Thus, in our guideline in 1999, when we suggested aiming at about 7 to 15 cm water, this is equivalent to a maximum of 10.7 mm Hg. In the Belfast 1996 guideline, the figures of 8 to 10 mm Hg are suggested. Since the most significant number is the top of the range, this boils down to Newcastle suggesting about 11 and Belfast suggesting 10 mm Hg, that is very close agreement on what the target upper pressure limit is.

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(4)   Please state and explain the factors that Dr. Savage as a Consultant Paediatric Nephrologist should have considered in:

      (a)   Accepting the donor kidney in principle over the phone

These are outlined in the first 2 paragraphs of my reply to question 2(d) above.

      (b)   Accepting the donor kidney after cross-matching was complete

This is not an appropriate question. The decision is made in principle to proceed or not to proceed on the assumption that the cross-match is going to be negative (ie, acceptable). Generally the theatre time is booked for shortly after the cross-match result is expected. If it turns out to be unacceptable, then the transplant cannot proceed, and the kidney will be offered to another potential recipient. If it turns out to be acceptable, which it does in the vast majority of cases, then this is the green light to proceed.

      (c)   In particular, state if, in your opinion, Dr. Savage should have considered the particular risks and disadvantages of the transplant surgery whether by himself or with others, including the implications (if any) of:

          (i)   Adam's age and size
          (ii)   Adam's multiple previous operations
          (iii)   Extent of the cold ischaemic time
          (iv)   The *"widely separated arteries on 1 patch"* (as compared to a single artery or 2 that were not widely separated)
          (v)   Half match of the donor kidney
          (vi)   Size of the kidney from the 16 year old donor
          (vii)   Possibility of not proceeding with the transplant surgery

I will answer all of these sub-questions together, and refer you again back to the first 2 paragraphs of my reply to question 2(d) above. Each and every aspect listed from (i) to (vii), plus others such as how easy their dialysis management was proceeding, and if there are any potential live-donors available, are considered by the paediatric nephrologist making the decision of whether to accept a kidney and to proceed with a transplant. There are few absolute contraindications to proceeding, but there are fine judgements to be made. In practice this is done on the basis of experience and simultaneous assessment of all of the above factors. I am quite certain that Dr Savage will have made just such a judgement at the time, and that as his primary medical carer for years will have made the best decision possible at the time.

(5)   Please state, given Adam's history and his regular need for dialysis, how long you believe Adam could have continued on dialysis if the donor kidney that was offered on 26th November 1995 had not been accepted for any reason

For reasons I have dealt with already, this is an impossible question to answer in any precise way. There are so many individual future variables – nobody can see into the future with precision!

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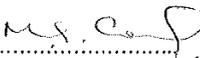
(6)   Please describe and comment on the discussions that a Consultant Paediatric Nephrologist should have with the family of a paediatric patient who required renal transplant surgery. In particular, please comment on what Dr. Savage should have discussed with Adam's mother at each of the following stages:

Again, I refer you back to the answers I have already provided when asked what the role of a paediatric nephrologist is in managing families undergoing transplantation.

The points I have added below are additional observations only, and need to be read in the context of my previous answers.

(a)   When the need for a renal transplant for Adam was first apparent

As well as the detailed steps to be undergone, it is emphasised at this point that there is no real alternative to transplantation. Even if it were sustainable for a lifetime, longterm dialysis does not provide a sufficiently good quality of life to be acceptable as a final therapy in children.

(b)   When Adam was placed on the renal transplant list

In addition to the other points, the possibility of live-donor transplantation, with its advantages and disadvantages, would be discussed. In some units this is considered best to be a 'passive' process in which the family are left to raise it as an issue first (to avoid implied moral pressures being applied).

(c)   When a donor kidney became available

As already explained, parents will have heard all of the information in general terms before this point. However, in the stress of actually being confronted with it happening, the same ground needs to be covered briefly again, with the specific details sometimes being referred to. In practice, many families are happier to be given summary information such as an overall assessment of it being a 'satisfactory' or a 'very good' kidney than to try to take in lots of details at this point.

(d)   Upon arriving at the hospital, and pre-surgery

This is essentially the same time as (c).

(7)   In addition, please state whether you would have expected Dr. Savage to have discussed the following with Adam's mother, and if so, what he should have discussed, and at what stage he should have discussed it:

(a)   The risks and disadvantages of the transplant surgery with this donor kidney

(b)   Significance (if any) of Adam's age and size

(c)   Implications of Adam's multiple previous operations

(d)   Extent of the cold ischaemic time

(e)   The *"widely separated arteries on 1 patch"* (as compared to a single artery)

(f)   Half match of the donor kidney

(g)   Size of the kidney from the 16 year old donor

(h)   Possibility of not proceeding with the transplant surgery

I have already answered points (a) to (h) in my last answer. Once an actual kidney is available to discuss with parents, as opposed to considering a possible future offer, the paediatric nephrologist will consider each aspect of the organ and of the child's current condition, and make a judgement of the wisdom to proceed, balancing potential hazards against potential benefits. They will then convey their view of how that balance looks to the family.

The amount of information that individual parents want varies widely. Some make it explicit that they simply trust you, and do not want to be bothered with all of the technical details, while others are curious about those details and want to be told about them all; I am certain that Dr Savage will have offered as many of the details as Adam's mother requested.

If the situation is clearly a good one, with a near-perfect kidney, even a parent with the most interest in details would probably not want more than a summary of each point. If the situation was much more closely balanced between proceeding or not proceeding, most parent would wish to be informed about and often involved in help reach the right decision. For example, if a child had had a previous graft clot, and the subsequent kidney was especially small, or had 3 arteries supplying it (both of which increase the risk of clotting), but was a perfect match (which is rare), I have no doubt that these aspects would be shared fully. I am certain that this is how Dr Savage would have handled it in every case, that is adapted as closely as possible to the families needs and wishes.

(i)   Composition of the Anaesthetic and Surgical teams, including the inclusion of Mr. Stephen Brown (if she had previously made clear her objection to his further involvement in Adam's care – for which see Debra Slavin's PSNI Statements and her Inquiry Witness Statements)

I would of course be happy to answer these questions if parents were to ever ask them, but I have never known that specifically to happen.

Surgeon It may well happen that some parents and nephrologists will talk about who is going to do the operation in passing, for example if the parent were to ask if the operation was going to be done by the surgeon they met in clinic or not. However, if they did not ask, or if it was a surgeon they had not met before, I would not consider this to be an issue. The assumption that parents always make (correctly) is that the nephrologist would not be allowing the operation to proceed if the surgeon was not fully trained and competent.

Of course, if the surgeon themselves obtains consent the family meet them at that stage, but they are unlikely to meet the rest of the surgical team.

With particular reference to Mr Brown's involvement, I am not even sure if Dr Savage knew about any prior dispute between him and Adam's mother, nor if he knew that Mr Brown was going to assist. Even if the answer to both of these questions was yes, I do not think that Mr Brown's involvement in Adam's transplant was one that would be especially important for Adam's mother to know about since he was merely playing a surgical assistant's role. He was not there specifically in his capacity as a consultant paediatric surgeon (which she may have objected to previously), but merely as a useful 'pair of hands' to assist the main player.

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Under those particular circumstances, I personally would not have mentioned his being an assistant to Adam's mother. I cannot see how this information would have helped her, but I can see that it may have inappropriately unsettled her without rational justification, at an already stressful time. My opinion could be considered to be patronising, but I would not have mentioned it for that reason.

(8)   Please comment on whether you would have expected Dr. Savage to have discussed any of the following with Dr. Taylor, as the anaesthetist for Adam's transplant surgery, and if so, what he should have discussed, and at what stage he should have discussed it:

(a)   Diagnosis of obstructive uropathy and a degree of renal dysplasia, together with polyuric failure, including the implications of that diagnosis for the formulation of a fluid management plan for Adam's transplant surgery

I would have expected Dr Savage to have discussed these features with Dr Taylor once Adam was admitted for the transplant surgery, and had been assessed initially. At that point it would be reasonable to expect the operation to proceed, and appropriate to give the anaesthetists time to plan their management strategy.

(b)   Multiple previous anaesthetics and operations, including previous CVP lines

I would expect him to mention these points at the same time as (a). This would indicate to him that he would be able to review a number of anaesthetic record sheets for detailed information about Adam's previous responses, and also that his central venous line may be particularly difficult.

(c)   Previous urological history

This might be useful to mention at the same time, merely because it could point to an increased chance that the operation might take a longer rather than a shorter time.

(d)   Daily urine output and the rate of his urine output, and generally the capacity of his bladder

His estimated daily urine would be a key piece of information to discuss during the telephone call. This is because this is highly individual among such patients, and can vary widely. Many children reaching end-stage renal failure produce no urine, so do not require to have any fluid replaced to compensate for this during surgery, while others pass relatively large volumes of urine that should be replaced. In this case, given that Dr Savage's estimate of Adam's urine output was about 1.5 litres daily, this would approximate to a requirement of just over 60 ml per hour, assuming that this did not fall during surgery (which frequently happens, as the blood pressure may fall in an anaesthetised compared to an awake child).
        I do not think that the capacity of the bladder would be particularly important information to discuss with the anaesthetist during this phone call. What matters is how much fluid loss has to be replaced. In any case, in my experience, it has been routine for children like Adam to have their bladder catheterised at the beginning of a transplant operation, which effectively removes the reservoir capacity of the bladder, and results in the urine being drained into a calibrated bag or clear plastic measuring box where its volume can be readily appreciated, instead of being guessed.
        If the urine output really had been 200 ml per hour, as Dr Taylor appears to have deduced from the information given to him, and if he had not been catheterised at the start of surgery, as was the case, then during the course of a potential 3 to 5 hour operation he would have been expected to produce from 600 ml to 1 litre of urine. This would either cause his bladder to distend grossly, where it

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would carry a risk of impeding access for the surgeons as they were dissecting in the lower abdominal retro-peritoneal space to expose his blood vessels for anastamosis, or it would result in him voiding some or most of it onto the operating table. Neither would have been a good alternative to catheterising him, which is a standard procedure in many centres.

More important in children who do have a relatively high residual urine output would be to give an estimate of its sodium concentration, to aid in choosing the right replacement fluid. Ideally this would be based on a current or recent measurement, or it could be guessed to be a typical end-stage level of about 75 mmol/l. A child's pre-dialysis urine sodium concentrations would be irrelevant, and basing the sodium replacement upon such values would be inappropriate.

(e)   Daily intake, including the information that he was on a high calorie Nutrison feed of 2.1 litres daily given through a gastrostomy bag, that rate of delivery of that feed, the feed supplements also administered due to his propensity for low sodium

The daily enteral intake is part of the background information leading to Dr Savage's estimate of Adam's urine output, and would not be particularly pertinent to pass on during the phone call. The fact that it was delivered via a gastrostomy could, however be relevant so that the anaesthetist was aware of the presence of this tube. His propensity for a low sodium could also be mentioned, though losing sodium through the kidneys is virtually always part of being a child with polyuric renal failure, and adds little of clinical importance to the anaesthetist over and above the estimated volume of urine and its estimated sodium concentration.

(f)   Peritoneal dialysis, the prescription (volume, and number of cycles etc) together with his weight before and after his dialysis

I would expect to inform the anaesthetist that the child was on PD, and that we would be performing that until he went to theatre, but I would not expect to inform them about the prescription being used. This is because the anaesthetist would not be using that information, as the PD would be discontinued prior to transfer to theatre.

The key reason why I would want and expect to inform the anaesthetist about the fact that he was on PD would be to let them know that we (the paediatric nephrology team) would be delivering the child with either normal, or possibly slightly abnormal but safe, concentrations of important chemicals in the blood, including the electrolytes sodium and potassium, as well as calcium, and how we were planning to do that. The 'assumed deal' between the paediatric nephrologist and the anaesthetist when discussing these arrangements in my experience, is that the nephrologist is proposing to deliver the child to theatre with an appropriate fluid volume and with satisfactory blood chemistry, and that the anaesthetist can take over management at that point by assuming that this is the case.

After delivering a child to theatre in this situation, I would not expect an anaesthetist to make calculations about how I might or might not have achieved this, basing his assumptions on information such as the time that the child was given fluids until, or how many cycles of PD they had had, and over what period. Rather, if they were concerned that the child may have arrived dehydrated or overloaded with fluid, I would expect them to talk to me about that in person either at the point of medical handover, or at their convenience by telephone at any point in time in the proceedings. The fact that Adam had neither a drip nor dialysis from 5 am would not concern me as a paediatric nephrologist; this has been dealt with elsewhere, including below.

The reason for me taking this view is not a question of personal or professional pride; the paediatric nephrologist should always be happy to be questioned and to enter into debate about the best way to manage a child, or to be challenged about whether they had achieved their goal of sending the child to theatre in appropriate condition. Rather, it is because such interpretation and calculations require specialist knowledge and experience which is within the remit and realm of the paediatric nephrologist and not within the expertise of most anaesthetists. In the same way, a paediatric nephrologist would reasonably expect an anaesthetist to put the child to sleep competently without themselves expecting to contribute or interfere with those matters or details.

In my opinion, the assumptions that Dr Taylor presents that he made when he concluded that Adam was likely to be dehydrated at the start of surgery are simply wrong. The result of this is that his

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assumption that Adam required a bolus of fluid to correct a fluid deficiency was wrong. Had he been correct that there was a volume shortfall, the nature of the fluid that he assumed would be needed to compensate for it was also wrong.

Let me explain why:

- The fact that Adam happened to receive most of his daily fluids and calories overnight at an infusion rate close to about 200 ml/hour was likely to be one of practical convenience, and is a technique widely used in children on overnight PD. It is done this way so that the child does not have the inconvenience of the pump feeding to be carried out during his waking day, and so that as the bulk of the daily fluid is delivered overnight the timing coincides with the time that excess fluid is being removed by the PD, so it prevents it from accumulating (as the kidneys alone cannot remove it at this rate), and clears the volume from the body while it is being given.

  Dr Taylor appears to have made the assumption that Adam must be passing urine at about 200 ml per hour to cope with the feed, and hence that he needed 200 ml of intravenous fluid to make up for it intra-operatively each hour (that is at a rate of about 4.8 litres per day). He appears to have drawn this conclusion in spite of also apparently being given the information (which was also in several places in the notes) that Adam's daily total urine output was of the order of 1.5 litres. An hourly fluid requirement of 200 ml was therefore a completely wrong assumption; for most of the 24-hours Adam was not being fed and had a much lower rate of fluid intake.

- The fact that Adam's urinary sodium was likely to be lower than that in plasma, and the previous incorrect assumption that he was excreting around 200 ml of urine each hour, led Dr Taylor to assume that Adam's 'calculated' losses and consequent presumed deficit should be replaced by a fluid of similar sodium concentration to that in his urine. This is the reason he gives for administering a solution containing about 30 mmol/l of sodium, compared to a normal plasma concentration of between 135 and 145 mmol/l, as some urine samples from Adam measured before he had reached end-stage kidney failure were that low.
  This whole argument is entirely wrong for 2 reasons. First, a large quantity of Adam's fluid losses were as peritoneal ultrafiltrate, which has a sodium concentration similar to plasma, so most of his overnight losses were the equivalent of losing more like normal rather than one-fifth-normal saline. Second, Adam was being dialysed with PD as well as being ultrafiltered. This means that if his plasma sodium concentration were to either rise or fall overnight, and therefore to start to change from the sodium concentration of the dialysis fluid being used (which is very close to normal plasma levels), then the sodium would move across the peritoneal membrane in whichever direction was necessary to correct the perturbation. This is what dialysis is. The mechanism for this is increasingly powerful if the perturbation is high (because the concentration gradient that drives the diffusion of the sodium ions increases as the plasma sodium becomes more different from the PD sodium level). PD is also particularly powerful in small children. This is because dialysis occurs across the surface of the peritoneal membrane, and (like body surface area) the peritoneal membrane surface area increases greatly in proportion to body weight in smaller bodies.
  For all of these reasons, it is rare to ever see a markedly abnormal plasma sodium concentration in a child at the end of a PD session, even after a shorter than routine treatment period. Had he known this, or had he asked Dr Savage about it instead of making his own guesses and assumptions about childhood dialysis, Dr Taylor would have realised that Adam was very unlikely to have started his anaesthetic with a normal or close-to-normal plasma sodium concentration, and thus with no need for a fluid bolus at all.

(g)   General state of health and the results of the Renal Protocol investigations, including his weight

I would expect the paediatric nephrologist to inform the anaesthetist about the child's general state of health and their approximate weight when making the phone call referred to in paragraph (a). They would also inform the anaesthetist that they would be measuring the child's renal protocol investigations. Thereafter, they would assume that the anaesthetist was going to fill in subsequent details themselves when visiting the child a little later, pre-operatively.

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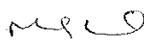
(h)   Examination of Adam, explaining the anaesthetic and risks and assisting in the process of taking consent from Adam's mother

I would expect Dr Savage or a member of his team to examine Adam, and Dr Taylor or his deputy to do so as well, with their own emphasis of points of importance, and for that anaesthetist to explain the anaesthetic and its risks to his mother.

I have discussed extensively elsewhere what I would expect to be the process of obtaining informed signed consent for surgery from Adam's mother.

(9)   Please state whether you would have expected Dr. Taylor and Dr. Savage to have discussed and agreed Adam's pre-operative and/or intra-operative fluid management regime

I would have expected Dr Savage to have provided Dr Taylor with an estimate of Adam's daily urine output, and ideally with a measurement or a reasonable estimate of his likely urinary sodium concentration. I would also have expected Dr Savage to ensure that Dr Taylor was familiar with the concept of the anaesthetist ensuring that the child's blood volume was adequately high to perfuse the newly connected kidney, relying largely upon a CVP measurement. This is in line with the recommendations that we make in our own transplant protocol in Newcastle.

However, I would not expect Dr Savage to offer any more detailed advice unless asked to do so by Dr Taylor because a consultant anaesthetist would be expected to be able to correctly manage Adam's fluids with that information alone. It should be obvious to such a person that any significant volumes of urine losses should be replaced with an equal volume of appropriate fluid, such as ½-normal saline, and that any extra fluids that need to be administered should be given with fluids with a sodium concentration close to that in plasma, such as normal saline, or Hartmann's solution, or a plasma product. Having provided that information, Dr Savage should expect a competent anaesthetist to do this without further unsolicited advice.

It should be noted that the general principles of fluid management when looked at in this way are essentially simple, even if the exact choice of the volume and type of fluid to be given at any particular point in time during the operation may require experience, judgement and skill. The idea of having to make complex calculations throughout, which Dr Taylor has emphasised in his reports, does not fit easily with my expectations or experience of other anaesthetic colleagues. What is needed is to measure the losses (including the urine) throughout, and replace it accordingly. And to measure the plasma sodium concentration to monitor results, especially if a screening measurement produces an unexpected value.

(10)   If Dr. Savage should have been involved in the formulation of either of those regimes, then please comment on:

(a)   What Dr. Savage could and should have been able to contribute to their formulation

As stated above, Dr Savage provided sufficient information to allow a competent anaesthetist to be able to plan and deliver a safe fluid management programme for Adam's transplant. I do not recognise the need for the complex calculations that Dr Taylor repeatedly refers to in his testimony; what is required is the meticulous application of relatively simple principles. I am sure that if Dr Taylor had expressed a desire for help from Dr Savage with formulating a plan, he would have readily provided it.

(b)   Whether you would have expected Dr. Taylor to alert Dr. Savage to any changes that he was proposing to make to either Adam's pre-operative or his intra-operative fluid management regime and, if so, those changes, together with the reasons for them, to have been discussed and agreed between them

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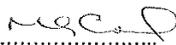
I do not think that Dr Taylor was, nor should he have been, in charge of Adam's pre-operative fluid management. I am confident that if Dr Taylor had wanted to discuss his intra-operative fluid management with Dr Savage, he would have been happy and willing to advise.

(c)   Whether you would have expected Dr. Taylor to have alerted Dr. Savage to the fact that he had not sent bloods off for electrolyte testing as soon as he gained IV access if, as Dr. Savage claims he had made it clear to Dr. Taylor such testing was important and that they had agreed it would be done (Ref: WS-002-03, pgs. 9, 13, 14, 29, 33, 34, 34 and 42 – Dr. Savage's 3rd Inquiry Witness Statement)

It is common practice in paediatrics to consider with great care ways of minimising trauma to children. The importance and positive value to the child of each and every blood test taken from them is always weighed against the immediate and longterm negative impacts of inflicting painful procedure upon them, especially for young children who cannot rationalise or understand the significance of what is happening to them. For that reason, the decision of whether to continue to attempt to take blood, or whether to delay it, is a common dilemma for children's doctors, and compromises have to be made in the children's interests.

For that reason, if a child is due to have an anaesthetic, it is very common for anaesthetists to be asked to undertake blood tests once the child is asleep, even if the tests themselves are of no particular relevance to the conduct of the anaesthetic. The reason to emphasise this is to point out that it is a very common arrangement. Once such a test has been requested by the paediatrician to the anaesthetist, that is therefore regarded as the end of the paediatrician's responsibility in relation to making those arrangements. As a paediatrician, one would not expect to have to then remind the anaesthetist about it, or to check up on him or her to make sure they had remembered to do it.

In Adam's case, the result of the test was of most importance to Dr Taylor himself, rather than any of the other doctors, because its relevance was to make any adjustments, if necessary, to Adam's management during the operation, when Dr Taylor was himself taking primary responsibility for his medical care. Therefore, he had a double reason to take responsibility himself for taking and sending off the blood sample; he had been asked and had agreed to do so, and he was the person who would act upon the results.

Also, in Adam's case, the decision to delay the blood test and for it to be taken by the anaesthetic team was not a casual or lightly-taken one. Rather, the decision was made during overnight telephone calls between doctors from the paediatric nephrology and anaesthetic teams, including Dr Taylor himself.

(d)   What you would have expected Dr. Savage to do had he learned that the electrolyte test had not been, and was not being, carried out

This is a hypothetical question. I cannot understand its relevance. The planned immediate intra-operative blood test was planned to aid Dr Taylor in his management. Dr Taylor makes it clear in his testimony that he did not rate its importance as high as the need to proceed promptly to undertake the transplant as it already had a long cold-ischaemia time.

Since the process of inserting a central venous line includes withdrawing blood into a syringe to test the patency of the line, to sample blood at that stage would take less than an extra minute. Given the fact that the kidney cold ischaemia time was approximately 30 hours at that stage, Dr Taylor had clearly downgraded the importance of measuring Adam's blood test considerably at that stage, as delaying the start of surgery would have only added another approximately 0.05% to the waiting time.

This was a decision for Dr Taylor, not Dr Savage.

(11)   Please comment on whether you would have expected Dr. Savage to have discussed any of the following with Mr. Keane, as the Surgeon for Adam's transplant surgery, and if so, what he should have discussed, and at what stage he should have discussed it:

(a)   Diagnosis of obstructive uropathy and a degree of renal dysplasia

(b)   Multiple previous anaesthetics, CVP lines and operations, the result of previous surgery being that one of his ureters was cross-connected to the other rather than to his bladder

(c)   Retention of his native kidneys

(d)   Previous urological history, including that his native kidneys were polyuric

(e)   Daily urine output and his rate of urine output, and generally the capacity of his bladder

(f)   General state of health and the results of the Renal Protocol investigations

(g)   Examination of Adam, explaining the surgery and risks and assisting in the process of taking consent from Adam's mother

I would have expected Dr Savage to discuss all of the above points with Mr Keane either at the time that the kidney was offered and accepted, or between that time and the start of the operation. It appears that he did so.

(12)   Dr. Savage makes a pre-transplant 'checklist' for Adam's surgery at Ref: 059-006-011. Please comment generally as to the adequacy of this 'checklist' including:

(a)   Whether in your opinion there were any elements missing from the checklist

The notes made by Dr Savage listed key issues and medications that his team would need to ensure were available to be administered in theatre and directly after. It was a thorough and organised easily readable list, and entirely appropriate. There were no key issues missing. The purpose of writing such notes is to highlight points of particular relevance to that patient, not to reproduce a list of all possible options.

(b)   The comment that "no mannitol" was required in view of Adam's "natural polyuric state"

This was relevant because mannitol is frequently used around the time that the kidney transplant vessels are unclamped, but would not be indicated in Adam's case (though its administration would not have been harmful).

(c)   Whether the checklist was in line with the renal transplantation guidelines operating at RBHSC at the time ("Renal transplantation in small children" – Dr. Maurice Savage, September 1990 – WS-002-03, Appendix 3)

Yes

(13)   Dr. Savage took the consent from Debra Slavin (Ref: 058-039-185 - Consent Form dated 27th November 1995). Please comment upon the issues that either he should have discussed with her and the extent to which he should have arranged for others to discuss with her (e.g. Anaesthetist, Surgeon)

I have answered this fully above (Q2, (e)).

Report by Dr Coulthard for Adam Strain death inquiry.   Signed ....

20.

(14)   You state at p.32 of your first Report for the Inquiry (4th August 2010) that *"my interpretation of the pressure traces provided in the case notes assumes that the horizontal dotted line half way between the zero mark and the 60 mm Hg line represents a value of 30 mmHg."*

If the maximum CVP on the graph is instead 40mmHg (which appears on the graph at the beginning of the CVP monitoring line just before 07.30), and the horizontal dotted line half way between the zero mark and the top of the graph therefore represents a value of 20 mmHg, how does this affect your comments in your statements regarding the management of Adam's CVP?

If the scale was a linear one from 0 to 40, rather than from 0 to 60, then I would have interpreted the pressures to be to have risen "from a starting value of over 13 [instead of 20] at about 7:50 am ... [and] ... to [have reached] about 20 [instead of 30] by about 8:30 am, and to stay at or above that level for most of the rest of the operation."
 Since the target upper pressure limit in the Belfast transplant protocol was 10 mm Hg (and by comparison, the Newcastle one is similar at 10.7), I would still have concluded that I could not understand why this was not regarded as a danger signal to indicate fluid overload.

(15)   Please comment on the presence of Drs. Savage and O'Connor in the operating theatre on the morning of 27th November. In particular, please comment on:

(a)   The purpose for which they were there and what they should have been doing in theatre

(b)   Whether they should have commented to the anaesthetic or surgical staff about:

(i)   initial rate of fluid administration
(ii)   departure from the prior fluid management plan (on the basis of which Dr. Savage had prescribed *"no mannitol as natural polyuric state"*)
(iii)   initial CVP reading of 17mmHg
(iv)   relative changes in the CVP readings

I have already given detailed comments about this in Question 2 (f).
 All of the routine communications between the Drs Savage and O'Connor and the anaesthetic team should have taken place when they discussed Adam's details before commencing the anaesthetic, to allow for proper and efficient planning. This would include the advance plan to not administer mannitol in his case.
 When present in theatre, it would not have been their role to check on issues such as the fluid administration rate, nor the CVP readings being taken. If either of these issues had been drawn to their attention, for example if the anaesthetist had chosen to discuss them, then of course they would have given them appropriate consideration.

(16)   Please comment on what you would estimate was the maximum capacity of Adam's bladder, given his age and previous clinical history

This is (a) impossible for me to guess since it could vary widely between children with the same diagnosis, and I was unable to find any relevant information in the notes.

Report by Dr Coulthard for Adam Strain death inquiry. Signed ....   21.
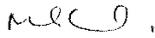
(17)   Please comment on whether you would have expected Adam's normal urine output to increase in response to his increased fluid intake. If so, please state to what extent you would have expected it to increase. If not, explain why this would have been the case

I would not have expected Adam's urine output to increase at all in response to an increase in the fluid intake.

I have explained in detail elsewhere that by the time a child's kidneys have reached end-stage, that is when they are unable to maintain the child's condition safely without support from either dialysis or transplantation, they have always lost their ability to respond to variations in physiological requirements. Thus, they are simply unable to respond to the body's signals to alter factors such as the sodium or water excretion rates.

In effect end-stage kidneys are always working 'flat out'. They never meet their physiological targets, and the body's signalling systems are continuously switched fully on, but the kidneys cannot function any quicker. This means that any extra signals, such as the need to excrete yet more water in response to being given some extra, makes no difference to the amount of urine they make.

Since writing my previous reports it has been drawn to my attention that in Adam's immediate post-operative period, he was administered 30 grams of mannitol (a total of 150 ml of 20% solution). Mannitol is a sugar that is not metabolised by the body, other than by being excreted by the kidneys. If it is given to a child in end-stage kidney failure it will remain in their blood for many days, unless it was dialysed out. It acts to maximise the rate of urine excretion in patients whose kidneys are capable of responding to forces that drive up their urine production rate. When it was given to Adam, he passed a total of 1460 ml of urine over the ensuing 24 hours, the same rate of urine production he was estimated by Dr Savage to have on a normal day. This provides powerful confirmatory evidence of the limited capacity to increase the urine volume in his case.

(18)   Please comment on your impression of the CVP values during Adam's surgery, including:

(a)   Whether either nephrologist should have asked about the fluid regime as a precaution given the CVP levels

(b)   What volume of fluid might precipitate an initial CVP value of 17mmHg

(c)   Whether the relative changes in the CVP from 17mmHg, including the brief rise to 30mmHg, would have been a cause for alarm

I have addressed all of these points before. As far as I am aware, Adam's CVP measurements were not discussed with either nephrologist, and it was not their role or duty to inquire about them. In the absence of any discussion about them, they would be entitled to assume that they were being maintained within the normally prescribed limits.

It is not possible to determine the precise volume of fluid overload that would correspond to any particular raised CVP reading. There are many other variables that may contribute to the compliance of the child's venous system which make such a simple correlation impossible.

Given the fact that the CVP normally runs much lower than these values, and the fact that a pressure of about 10 mm Hg is considered to be an indication that the vascular compartment is fully expanded or 'full', any consistent value above that, be it 17 or 30, would be cause for concern, if not alarm.

(19)   Please state whether you would have expected a Nephrologist to have been trained and able to use a blood gas analyser machine in November 1995

This would not be expected to be a task that most paediatric nephrologists would have carried out either in 1995 or in 2011, though some may have chosen to be trained in this skill.

Report by Dr Coulthard for Adam Strain death inquiry.   Signed ....,   22.

(20)   Dr. Webb records in Adam's clinical notes that Adam's cerebral oedema *"may have occurred on the basis of unexplained fluid shifts – 'osmotic disequilibrium syndrome'"* (Ref: 058-035-140). This view is repeated further by Dr. Webb in a letter to Dr. George Murnaghan, Director of Medical Administration dated 12th December 1995 (Ref: 059-061-147) and in his Inquiry Witness Statements (WS-107-1, p.3-4, Answers 3(a)-(d) and WS-107-2, p.2-3, Answers 1(c) and 3(a)). It is also mentioned on Adam's autopsy request form (copy attached). The author of this document is currently unknown

(a)   Please explain what you believe is meant by *'osmotic disequilibrium syndrome'*

(b)   Please comment on Dr. Webb's view that Adam's cerebral oedema *"may have occurred on the basis of unexplained fluid shifts – 'osmotic disequilibrium syndrome'"*

To my knowledge, I have not been supplied with Dr Webb's witness statements WS-107. However, I have read his letter to Dr Murnaghan in file 059, and I believe I can answer the question. I have previously given a detailed description of how a rapidly falling plasma sodium concentration can lead to cerebral oedema (pages 15 and 16 of my first report). This can be summarised by saying that sodium and other ions exert an osmotic effect in solution, and this causes important forces to apply across cell membranes, which in turn causes fluid shifts. The term 'osmotic disequilibrium syndrome' refers to this process whereby factors normally held stable by a steady osmotic level become disturbed when the osmolality changes. His use of the term 'fluid shifts' immediately before that is referring to the same process. I presume that his use of the term 'unexplained' in this context refers to the fact that Dr Webb did not have a full explanation for the fall in plasma sodium concentration available to him at the time of writing the letter.

(21)   You noted in your second Report for the Inquiry (dated 4th December 2010) that because of the maintenance of fluid intake at a high level in renal transplants to prevent hypovolaemia:

> *"[c]hildren often have a mild and controlled degree of deliberate fluid overload. Occasionally, this is extensive enough to result in pulmonary oedema, but this is rare, and because it is anticipated it is typically dealt with promptly and does not cause clinical problems. I personally have seen 2 children with overt pulmonary oedema following renal transplantation in my career of over 25 years, both of whom were treated easily and did not suffer any consequences of this, and both had successful longterm kidney transplants."*

(a)   Please find attached an article titled *"Anesthesia for pediatric renal transplantation with and without epidural analgesia – a review of 7 years experience"* (Coupe et al, Pediatric Anesthesia 2005, 15: 220-228). In a study of 53 paediatric patients at Westmead Children's Hospital undergoing renal transplantation, 8 had pulmonary oedema as a postoperative complication. Of those who were given analgesia (18 of the 53), 5 had pulmonary oedema as a postoperative complication

(b)   Please comment on whether, in your experience, the results found regarding postoperative pulmonary oedema at Westmead Children's Hospital were expected or unusual, and explain why

(c)   Please comment on whether this study has any effect on your assertion that pulmonary oedema is 'rare' in paediatric renal transplantation

Coupe et al define pulmonary oedema in 2 ways in their retrospective analysis of 53 paediatric transplant patients, radiological and clinical, and this accounts for the apparent difference in the diagnosis rates from my own experience.
    Radiological   There is always some interstitial fluid (water between the lung cells) within normal lungs, as in all other tissues. Because of the air within the lungs, radiological (x-ray) studies of lungs reveal lighter areas due to the presence of these tissues contrasted against the black

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background of the air. The whiteness of the lung-fields on a chest x-ray depends on a number of factors, including the density of the overlying tissues (chest wall), the depth of the inhaled breath at the time of taking the picture, and the amount of water within the tissues and the lungs' air sacs (alveoli). Among the reasons why the lungs may reveal a pattern of increased whiteness is an increase in the quantity of interstitial and alveolar fluid due to pulmonary oedema. Chest x-rays can therefore be used to contribute towards making a diagnosis of this condition, though used alone they may produce false-positive and false-negative diagnoses, compared to a confirmed clinical diagnosis. In this series they categorised 8 children as having pulmonary oedema in that way.

Clinical A clinical diagnosis of 'overt pulmonary oedema', the term I used in my report, consists of shortness of breath with fine crackles heard with a stethoscope in the lung bases, an increased inspired oxygen requirement, and consistent radiological changes. This is a condition that is important because it needs to be treated. Coupe et al describe 1 such case in their series of 53, a rate entirely consistent with our own. It is of note that that particular child received proportionately much more fluid than any of the other children.

Conclusion Coupe's paper should be criticised for using the term 'pulmonary oedema' somewhat loosely, and in a way that suggests to the unwary that they are describing children with a clinical condition rather than children whose only evidence of pulmonary oedema was a compatible radiograph. It therefore does not alter my assertions about the risks of over clinical pulmonary oedema in paediatric renal transplantation in any way.

(22)   You also stated that Adam was *"at risk of suffering from both of these types [cerebral and pulmonary] oedemas."* Please identify any evidence that Adam was actually suffering from pulmonary oedema at any time during his care and treatment

I did not claim that Adam did suffer from pulmonary oedema. Instead, I pointed out that, by virtue of being a child having a renal transplant and being given a deliberately high fluid load, he was at a theoretical slightly increased risk of suffering from pulmonary oedema. In his case, as the fluid overload was so excessive, this risk was higher than the usual slightly increased risk.

(23)   Please find attached a blank table regarding Adam's fluid balance. We would be grateful if you could fill in the table as follows:

(a)   What you believe to have been Adam's daily fluid intake prior to his admission to RBHSC on 26th November 1995

(b)   What you believe to have been Adam's daily fluid output prior to his admission to RBHSC on 26th November 1995

(c)   What you believe to have been Adam's fluid losses at each of the indicated stages on 26th and 27th November 1995, including your calculations and losses due to:

(i)   Insensible losses
(ii)   Urine output
(iii)   Blood loss
(iv)   Dialysis loss

(d)   What fluid was actually received by Adam at each of the indicated stages on 26th and 27th November 1995

(e)   Given what you believe the fluid losses to have been and what fluid was actually received by Adam, what you believe his fluid excess/deficit was at each of the indicated stages on 26th and 27th November 1995

(f)   Any comments and relevant information regarding the sodium content of the input fluids and losses

(g)   Any reasons why planned fluid infusion (content or infusion rate) should change due to changes in estimated loss

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This completed form is attached as Appendix 3

Notes on the form:

A) I have assumed that the urine output was 62 ml hourly, as explained in my First Report, page 21. I have also assumed that its sodium concentration was likely to be about 75 mmol/l (typical values for children with high output renal failure at the time of transplantation), rather than closer to Adam's measured values, as these were taken under different pathophysiological conditions, before his kidneys had progressed to being end-stage. I have also assumed that this would normally have been fixed, but that it may have fallen during the period under anaesthetic. This is because end-stage kidneys have little reserve, and if the body's equilibrium is upset in any way (ie, during physiological stresses) the remaining kidney function frequently falls, and sometimes ceases until the equilibrium is re-established.

B) I have explained elsewhere that peritoneal dialysis does not usually remove as much fluid from children when they are not fluid replete (First report, page 27). I also speculated in that report that in Adam's case it was likely that his typical ultrafiltrate (UF) volume would have been approximately 300 ml, but that it would vary fairly widely around that figure as it would be less if he had less fluid to remove, and higher if he had more to remove, effectively resulting in a buffering effect. I have since seen Adam's mother's diaries which record his actual UF values, and can confirm that during the 3 months before his transplant his mean UF was 292 ml, and that it varied from 82 to 642 ml. I have written a further report on this. Therefore, where I have estimated his fluid loss from dialysis between 22:00 and 05:00 hours, I have indicated the uncertainty of the UF volume and have given a 300 ml range. (Note that I have also assumed that the UF loss will have had a sodium concentration of 130 mmol/l for reasons that will be clear from my first report).

C) For convenience, I have grouped all of Adam's intra-operative IV crystalloid (clear fluid) inputs during the hours of 08:00 and 10:00 hours. This is for simplicity, and is not intended to represent the actual rates during each hour of the surgery. In fact, most of the hypotonic crystalloid *was* administered during this early phase of surgery. This means that if I had divided it up more precisely (which would have involved some speculation), the effect on the calculated speed of the sodium dilution (by effectively adding free water) would have been much more dramatic during this initial period than is shown when the whole intra-operative period is presented (in the row of boxes below).

D) Strictly speaking one should calculate separately the red cells and the plasma in blood in respect to their sodium concentrations because the intra-cellular concentration is much lower than that in plasma. Instead, I have presented the figures as if the red cell sodium was also about 130. However, I have made the same deliberate calculation error for the red cells that he was transfused with, so these should approximately cancel out.

My conclusion is that by presenting these data in this way, with all of the roundings and assumptions that are needed and explained above and in my first report, it confirms that the overall salt and water exchange that occurred resulted in ...

- him arriving in theatre in approximately normal salt and water balance, and ...

- him receiving the equivalent of just over 1 litre of normal saline, plus the equivalent of nearly 900 ml of salt-free water, which would therefore have diluted his plasma sodium concentration.

(24) Please explain what you regard, from a Nephrologist's perspective, as the lessons to be learned from Adam's death and state whether you consider the changes made by Drs. Savage and O'Connor to the 1990 RBHSC Renal Protocol to be an adequate response (Ref: WS-002-03, Appendix 2)

In my opinion, there is 1 key lesson to be learned from Adam's death, and this does not apply only to paediatric nephrologists, but to all paediatricians and physicians that may work in any way with children, including anaesthetists. That is that there are some doctors who have responsibility for

Report by Dr Coulthard for Adam Strain death inquiry. Signed .... 25.

prescribing fluids for children who understand the absolute basics of the physiology of salt and water balance so poorly that children are at risk of being harmed by the use of inappropriate fluids, and this needs to be rectified.

In my view, the solution to this difficulty lies with improving the education of this group of doctors, rather than restricting the availability of any particular type of intravenous fluid. There are some very simple basic physiological principles which in my view need to be applied in a more logical manner than they frequently are at present. I have outlined this view in some detail in a paper I wrote in 2008 in response to the National Patient Safety Agency recommendation before then to strictly limit the availability of 0.18% saline in paediatric wards (Appendix 4). Please note in particular that I have entitled one section "A logical fluid management system for all situations: think like an engineer". The message is intended to encourage doctors to think logically about their patients fluid needs, rather than applying simple guidelines or protocols to all children and expecting them to always work.

I have since become aware that this NPSA document may have been triggered in whole or in part by the events that this inquiry is investigating. I disagree with its recommendations, as I explain in my paper. In many situations, 0.18% saline is the perfect solution to use, and it is possible to do harm by using 0.45% to all children across the board, especially those with a limited ability to concentrate their urine. In other words, changing from one fluid to another has the potential to cause a different complication in a different category of vulnerable children.

The important principle is that if fluid is administered which is expected to be retained within the body, it must always have a sodium concentration close to that of plasma, otherwise it will dilute the plasma sodium concentration. This message needs to be made the basis of an education campaign for paediatric doctors. If enough 0.45% saline was administered to a child like Adam, it would also have produced hyponatraemia, though not so extreme.

Withdrawing the availability of a useful and logically-based fluid such as 0.18% saline, which has been of value over many years, in case somebody misuses it to treat hypovolaemia or to 'fill' the vascular compartment is not the right approach. Far better to emphasise the correct use of fluids, and to have the full range of appropriate ones available, than to think a problem can be solved by banning one fluid.

(25)   The book *'Clinical Management of Renal Transplantation'* which was edited by Mary G. McGeown and published 1992, was, as far as the Inquiry team is aware, the only text regarding renal transplantation. Please address the following:

    (a)   Your comments on the following sections:

        (i)   Chapter 13 – *"Insertion of the kidney"*
        (ii)   Chapter 14 – *"Management of the recipient during the operation"*
        (iii)   Chapter 16 – *"Nursing care of the patient with a renal transplant"*
        (iv)   Chapter 20 – *"Early medical complications after renal transplantation"*

    (b)   Please state whether there are any other sections of the book which you would like to see to comment further on (see contents page at Ref: 070-023i-245 to 251)

This book is nearly 20 years old. It is out of date, and irrelevant in 2011. Doctors within the speciality of paediatric nephrology would be expected to read up-to-date texts on both paediatric and adult transplantation during their initial training, and thereafter to keep up-to-date with the changing issues and debates from evidence-based peer-reviewed publications in the medical literature, discussion with colleagues, academic meetings, and so on. I can see no point in spending time reviewing this tome.

(26)   Please find attached further statements as follows:

     (a)   Dr. Savage (WS-002-01 dated 22nd July 2005)
     (b)   Dr. Savage (WS-002-02 dated 14th April 2011)
     (c)   Addendum from Dr. Savage to WS-002-02 (dated 9th September 2011)
     (d)   Dr. Savage (WS-002-03 dated 28th September 2011)
     (e)   Dr. Savage (WS-002-04 dated 28th September 2011)
     (f)   Dr. O'Connor (WS-014-01 dated 19th July 2005)
     (g)   Dr. O'Connor (WS-014-02 dated 11th April 2011)
     (h)   Dr. O'Connor (WS-014-03 dated 22nd September 2011)
     (i)   Dr. O'Connor (WS-014-04 dated 22nd September 2011)

Please provide your comments on the conduct of Drs. Savage and O'Connor in the light of your view as to what could and should have happened. If those statements provoke further amendment or comment to your previous reports, please outline any such amendments or comments

I consider that both Drs Savage and O'Connor provided a degree of care to Adam both before and during his admission for a renal transplant that was appropriately high, and at the level that would be expected from competent and caring consultant paediatric nephrologists. I am aware that I have made minor observations which may appear critical in detailed responses to some questions, but these do not alter my overall view.

     I am quite certain that if they had had any prior doubts or insights about Dr Taylor's abilities to appropriately manage Adam's salt and water balance, they would have intervened in a way that would have prevented this tragedy.

Expert Witness Declaration

I Malcolm Coulthard DECLARE THAT:

1) I understand that my duty in providing written reports and giving evidence is to help the Court, and that this duty overrides any obligation to the party by whom I am engaged or the person who has paid or is liable to pay me. I confirm that I have complied and will continue to comply with my duty.

2) I confirm that I have not entered into any arrangement where the amount or payment of my fees is in any way dependent on the outcome of the case.

3) I know of no conflict of interest of any kind, other than any which I have disclosed in my report.

4) I do not consider that any interest which I have disclosed affects my suitability as an expert witness on any issues on which I have given evidence.

5) I will advise the party by whom I am instructed if, between the date of my report and the trial, there is any change in circumstances which affect my answers to points 3 and 4 above.

6) I have shown the sources of all information I have used.

7) I have exercised reasonable care and skill in order to be accurate and complete in preparing this report.

8) I have endeavoured to include in my report those matt ers, of which I have knowledge or of which I have been made aware, that might adversely affect the validity of my opinion. I have clearly stated any qualifications to my opinion.

9) I have not, without forming an independent view, included or excluded anything which has been suggested to me by others, including my instructing lawyers.

10) I will notify those instructing me immediately and confirm in writing if, for any reason, my existing report requires any correction or qualification.

11) I understand that;

     11.1) my report will form the evidence to be given under oath or affirmation;

     11.2) questions may be put to me in writing for the purposes of clarifying my report and that my answers shall be treated as part of my report and covered by my statement of truth;

     11.3) the court may at any stage direct a discussion to take place between experts for the purpose of identifying and discussing the expert issues in the proceedings, where possible reaching an agreed opinion on those issues and identifying what action, if any, may be taken to resolve any of the outstanding issues between the parties;

Report by Dr Coulthard for Adam Strain death inquiry. Signed ....   27.

11.4) the court may direct that following a discussion between the experts that a statement should be prepared showing those issues which are agreed, and those issues which are not agreed, together with a summary of the reasons for disagreeing;

11.5) I may be required to attend court to be cross-examined on my report by a cross-examiner assisted by an expert;

11.6) I am likely to be the subject of public adverse criticism by the judge if the Court concludes that I have not taken reasonable care in trying to meet the standards set out above.

12) I have read Part 35 of the Civil Procedure Rules and the accompanying practice direction including the "Protocol for Instruction of Experts to give Evidence in Civil Claims" and I have complied with their requirements.

13) I am aware of the practice direction on pre-action conduct. I have acted in accordance with the Code of Practice for Experts.

Statement of Truth

I confirm that I have made clear which facts and matters referred to in this report are within my own knowledge and which are not. Those that are within my own knowledge I confirm to be true. The opinions I have expressed represent my true and complete professional opinions on the matters to which they refer.
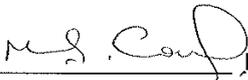
Signed _____ Dr Malcolm Coulthard

Dated _____ 07/11/2011

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

Appendices

1. Coulthard MG, Crosier J. Outcome of children who reach end-stage renal failure under 2 years of age. *Archives of Disease in Childhood* 2002;87:511-17.

2. Newcastle Paediatric transplant protocol, 1999.

3. Dr Coulthard's completed fluid balance form.

4. Coulthard MG. Will changing maintenance intravenous fluid from 0.18% to 0.45% saline do more harm than good? *Archives of Disease in Childhood* 2008;93:335-40.
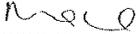
ORIGINAL ARTICLE

Outcome of reaching end stage renal failure in children under 2 years of age

M G Coulthard, J Crosier, on behalf of the British Association for Paediatric Nephrology

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Aims: To determine the outcome of children who reach end stage renal failure before the age of 2 years.
Methods: Using a retrospective questionnaire, 10 years' data were collected from the paediatric nephrology units in Britain and Ireland (1988 to 1997, follow up 1.3–11.5 years).
Results: A total of 192 children were identified; 0.31/million/year. Most had congenital or inherited conditions, and there were more boys. Latterly, half were diagnosed antenatally. Ninety per cent were dialysed initially, most using home peritoneal cyclers, some by haemodialysis through central lines. Five per cent recovered sufficient function to come off dialysis. Most required tube feeding (often gastrostomy) and erythropoietin; some needed growth hormone. A total of 56% received a transplant (2% without prior dialysis) at (medians) 2.6 years and 12.3 kg. The 2 and 10 year survival of first kidneys was 78%. Growth improved following transplantation. Fourteen per cent died because treatment was not started or was withdrawn. Most had particularly complex renal conditions, or additional major non-renal diagnoses. Typically, decisions not to treat were made mutually between clinicians and families. When treatment was continued, 71% survived, and few had serious non-renal conditions. Most attended normal schools, and by 6 years of age, less than 10% still required dialysis. Infants starting treatment under and over 1 month of age fared equally well.
Conclusions: By school age, most infants treated for end stage renal failure will have a functioning transplant, reasonable growth, and will attend a normal class, regardless of the age at which they commence treatment. Treatment is seldom sustained in children who have serious additional medical conditions. It is reasonable to treat infants with uncomplicated renal failure.

See end of article for authors' affiliations
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Accepted 21 July 2002
....

Early reports of treating very young children with end stage renal failure were discouraging.[1–4] Graft losses and mortality were high, and developmental outcomes sometimes poor.[5] Despite substantial recent improvements in outcome for transplanted children, younger ones have continued to fare worse,[6–9] though more optimistic views have been expressed recently.[10] More controversially, increasing numbers of babies with end stage renal failure are now being treated. Paediatric nephrologists worldwide hold strikingly differing views about whether this is appropriate.[11] They are only two thirds as likely to treat a baby aged under 1 month as an older infant, and are twice as likely to accept a parent's decision to refuse treatment.

Few infants with end stage renal failure were treated in Britain or Ireland until the late 1980s, but all the regional centres have participated since then. The British Association for Paediatric Nephrology felt it was important to review their outcome nationally (some of these infants from one centre having been reported previously).[12–15] We consider every child under 2 that reached end stage renal failure during a 10 year period, whether they were treated or not.

PATIENT AND METHODS
Data were collected from all the regional paediatric nephrology units in Britain and Ireland on every child under the age of 2 who had reached end stage renal failure from January 1988 to December 1997 inclusive. The total population rose from 60.7 to 62.6 million during those 10 years (mean 61.7 million). Information was acquired during early 1999, giving a follow up period of 1.3–11.5 years. All cases were reviewed, including children that recovered sufficient function to come off dialysis later, and those who were not treated. All units could identify every affected infant, but few could identify women who chose to have a termination of pregnancy because an antenatal scan had predicted infantile renal failure.

The questionnaire sought the renal (and other) diagnoses, whether it had been predicted antenatally, the age at reaching end stage disease, the modality and difficulties of dialysis, and

Table 1 The annual numbers of children that reached end stage renal failure under the age of 2, the numbers treated and not treated, and the percentage diagnosed antenatally

	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	All
Total	18	19	16	17	21	20	21	18	15	27	192
Treated	18	17	14	16	19	17	21	17	13	25	177
Not treated	0	2	2	1	2	3	0	1	2	2	15
Antenatally diagnosed (%)	25	23	23	27	28	39	44	47	36	54	–

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Table 2 The diagnoses of children that reached end stage renal failure before the age of 2 during the 10 years 1988–97 inclusive

Diagnosis	Treated	Not treated	Antenatal diagnosis (%)
Renal dysplasia	57	7	40
Posterior urethral valves	44	0	84
Finnish congenital nephrotic syndrome	26	2	8
Cortical necrosis	12	1	
Diffuse mesangial sclerosis and nephrotic syndrome (2 Drash)	8	1	
Recessively inherited polycystic kidney disease	6	2	25
Prune belly syndrome	4	0	50
Renal vein thrombosis	4	0	
Nephronophthisis	3	0	
Haemolytic uraemic syndrome	3	0	
Hyperoxaluria type 1	2	2	
Interstitial nephritis	2	0	
Wilms's tumour	2	1	
Cloaca, aortic thrombosis, glomerular fibrosis, glomerulonephritis	1 each	0	
Total	177	15	

whether erythropoietin, growth hormone, or nasogastric or gastrostomy feeding were given. The age and weight at transplantation, patient and graft survival, and the most recent graft function, weight, and height were recorded. For dialysed children, the current weight and height were noted. The educational status of survivors was reported for older children, and predicted for children attending nursery. The age and cause of death was recorded where appropriate. When treatment was not started or withdrawn, the reason and mechanism of the decision was sought.

RESULTS
Incidence
A total of 192 children under the age of 2 reached end stage renal failure, or 0.31/million annually. There was little suggestion of an increasing incidence (table 1). Congenital and inherited diagnoses predominated (table 2). The high ratio of boys to girls (2.6:1) was mainly caused by the frequency of sex specific conditions (posterior urethral valves, Drash and prune belly syndromes in boys, cloacas in girls), and the male preponderance of reflux associated dysplasia. Excluding these, the ratio was 1.3:1.

Initially, about a quarter were diagnosed antenatally, rising to about half latterly (table 1). Dilated urinary tracts were detected most easily (table 2); every boy with posterior urethral valves was identified in the last four years.

One unit caring for 3.1 million people reported that four women had opted for termination of pregnancy because their fetus had posterior urethral valves and severe oligohydramnios. No other data were available. Figure 1 summarises the outcomes for all the children, and each subgroup is considered separately below.
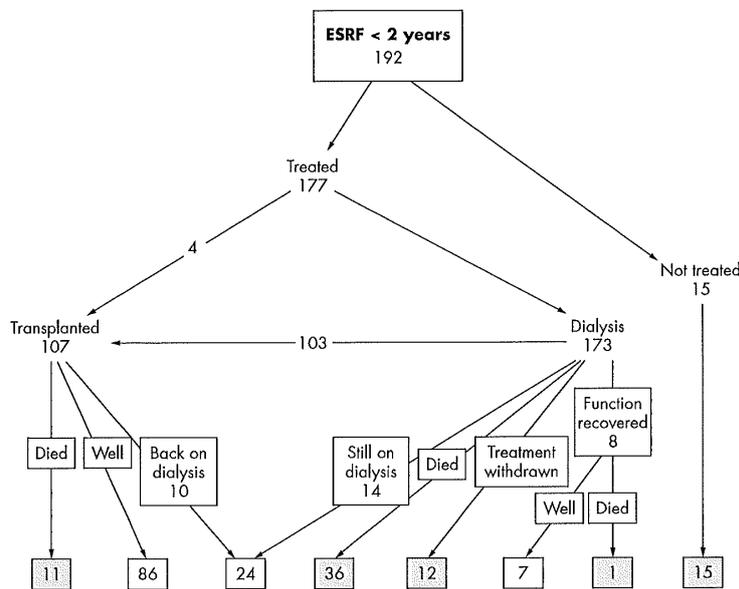

Figure 1 The outcome of 192 children who reached end stage renal failure under the age of 2 in the UK. In the bottom line the figures in plain boxes represent live children, and those in shaded boxes children that have died.

Table 3 Percentages of children on dialysis that received nasogastric or gastrostomy tube feeding, growth hormone, or erythropoietin during each year of the study

	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997
Nasogastric feeds	73	47	39	43	50	38	48	44	50	56
Gastrostomy feeds	7	27	39	21	39	44	38	50	42	36
Not tube fed	20	27	23	36	11	19	14	6	8	8
Growth hormone	27	13	15	7	5	19	14	19	25	*
Erythropoietin	47	50	46	71	89	88	91	75	82	84

Not all the tube feeding percentages add up to 100 because of rounding.
*The growth hormone numbers are not given for 1997 because the follow up period is too short.

Children dialysed

Of 177 children given renal replacement, 173 were dialysed initially, and four were transplanted first. Some babies were born with end stage renal failure; 15% were dialysed within a fortnight, and over a third within four months.

Most dialysed children had complications of treatment; 81% had automatic cycling peritoneal dialysis initially, and 10% had chronic ambulatory peritoneal dialysis. Peritonitis was their commonest complication, and was the reason that 23% changed to haemodialysis. Virtually all of the children initially haemo-dialysed had access through central venous lines, many of which blocked or became infected; 33% were converted to peritoneal dialysis. The initial mode of dialysis was determined by centre preference rather than specific clinical indications.

Most dialysed children were also tube fed. This proportion increased with time, especially those with gastrostomies (table 3). Erythropoietin treatment also increased; over three quarters received it latterly (table 3). The variations in growth hormone use in the first few years were caused by children participating in a national therapeutic trial. Subsequently, about one fifth received growth hormone (table 3).

Many dialysed children were failing to thrive. In 64% their height, and in 36% their weight was below the 2nd centile: height standard deviation score (mean (SD)) −2.73 (1.80); weight standard deviation score −1.56 (1.52).

Eight children recovered sufficient renal function to come off dialysis. One died suddenly at 20 months. The others were well, aged 3.4–11.3 years, but had declining renal function; two have since been transplanted.
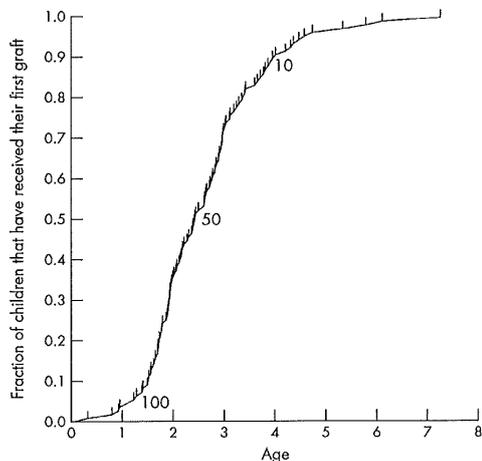
Children transplanted

A total of 107 children were transplanted, 103 with prior dialysis. The median age at transplantation was 2.6 years (90% between 1.2 and 4.7), and the median weight was 12.3 kg (90% between 7.4 and 17.4). Only four were transplanted before their first birthday, and 87% were transplanted between 1 and 4 years (fig 2).

Twenty two kidneys were lost: eight from rejection, two from haemorrhage, and one each from sepsis, oxalosis, cyclosporin nephrotoxicity, and respiratory distress, possibly triggered by cyclosporin. Eight were lost from venous thrombosis, four in the first two years, and four during the last eight. First graft survival was 78% at 2 and 10 years, with about half the lost kidneys surviving for less than one month (fig 3). Thirteen children received a second kidney: seven are functioning, one had a successful third graft, two are back on dialysis, and three have died. Altogether, 11 transplanted children died (fig 3).

All eleven (10%) kidneys donated by a parent are functioning well. By contrast, 11 of 96 children died after a cadaveric graft (89% patient survival, p = 0.29, Fisher's exact test), and 24 lost the kidney (75% graft survival, p = 0.05).

The heights and weights of children with transplants were on higher centiles than those of dialysed children (fig 4). Their height was below the 2nd centile in 17% (height standard deviation score (mean (SD)) −1.14 (1.28)), and their weight was above the 98th centile in 8% (weight standard deviation score 0.01 (1.56)).

Two transplanted children had major non-renal medical problems from birth, one with transposition of the great
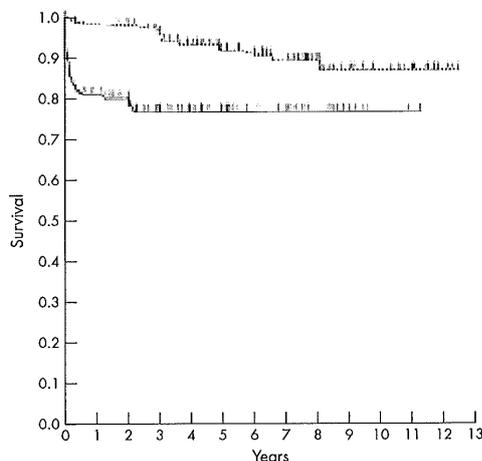

Figure 2 Kaplan-Meier plot of children who reached end stage renal failure before the age of 2, showing the age at which the transplanted children received their first graft. The numbers of cases available for analysis are indicated by the vertical bars and numbers.

Figure 3 Patient and kidney survival curves after the first graft into 107 chilren who reached end stage renal failure before the age of 2. The numbers of cases available for analysis are indicated by the vertical bars.
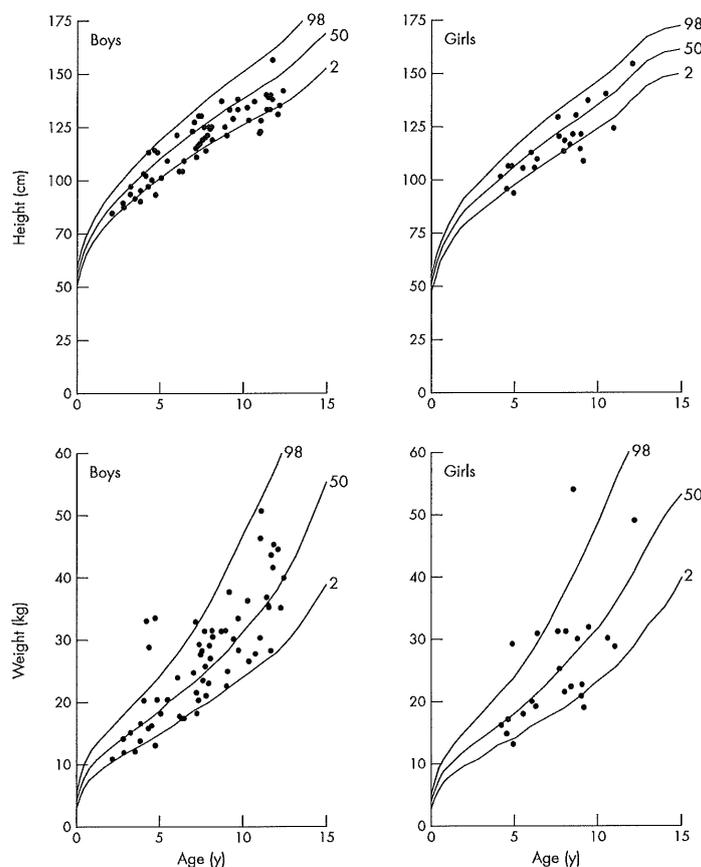
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Figure 4 The most recent height and weight values for 63 boys and 23 girls who currently have a functioning transplant, compared to the normal 2nd, 50th, and 98th centiles.

arteries (since surgically corrected) and one with VATER syndrome who will require surgical stomas to provide continence. Two developed problems later, one with sensory-neural deafness, and one with a mild hemiparesis. One transplanted child was repeatedly salt poisoned by his mother, but sustained no long term physical harm.

Children who died
Deaths fell into three groups. Some babies were not offered renal replacement, some were treated and had this withdrawn, and some died despite treatment (fig 5).

Children not treated
Fifteen infants (8%) were not treated, and died. There was no trend with time (table 1). In 14, the parents and clinical team agreed on the no-treatment option. One family wanted their baby dialysed, but the clinicians felt this was not feasible because he also had a large diaphragmatic hernia; he died very quickly.

Several non-treated babies had diagnoses with potentially complicated management problems, two with Finnish nephrotic syndrome, and two with hyperoxaluria-1 which typically requires kidney and liver transplantation. Four had

serious additional diagnoses: microcephaly and blindness, Down's syndrome with a congenital heart defect, Alagille's syndrome, and extensive necrotising enterocolitis. Two children had complications linked to the renal diagnosis: severe pulmonary hypoplasia, and a preterm infant with Drash syndrome and a Wilms's tumour. Seven babies died within a month, seven more by six months, and one at 18 months (fig 5, curve a).

Treatment withdrawal
Twelve children (7% of those treated) subsequently had dialysis withdrawn. These, too, were usually mutual decisions by parents and clinical teams. Several children had additional medical problems, either recognised at birth (Down's syndrome), or later, including cystic fibrosis, cerebral infarction following hypovolaemia, major seizures, global delay and microcephaly, with and without blindness, and a combination of hypertrophic cardiomyopathy, cerebellar hypoplasia, and autism. Some children had treatment withdrawn because the renal failure management alone had produced an unacceptably poor quality of life. Most of these children died under 1 year of age, and all died before 3 years (fig 5, curve b).
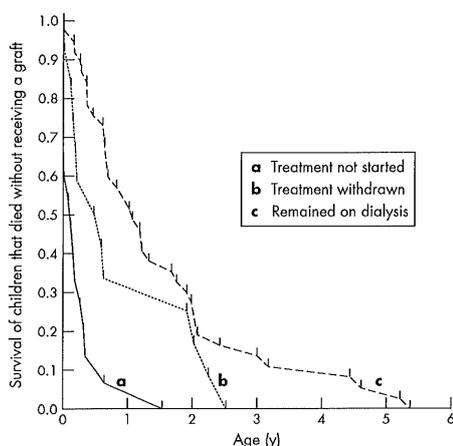
Figure 5 Survival curves for children who reached end stage renal failure before the age of 2, and died (a) because treatment was not started, (b) because treatment was withdrawn, or (c) despite remaining on dialysis.

Table 4 Numbers and percentages of the 192 children reaching end stage renal failure under 2 years of age, according to their survival and current treatment

Patient status	Number	%
Alive		
Recovered function	7	4
Functioning transplant	86	45
On dialysis	24	13
Total	117	61
Dead		
Never treated	15	8
Recovered function, but died later	1	1
Dialysis treatment withdrawn	12	6
Died while on dialysis	36	19
Transplanted, then died	11	6
Total	75	39

Not all the percentages add up to 100% because of rounding.

Deaths despite treatment

Forty seven children (27% of those treated) died on dialysis (n = 36) or following transplantation (n = 11). In four cases, death was a result of non-renal diagnoses specifically associated with infantile renal disease: two had pulmonary hypoplasia, and two developed liver failure with recessively inherited polycystic kidney disease. Most deaths had similar causes to those seen in older patients receiving renal replacement.

Most dialysis deaths were infective, including septicaemia following Tenckhoff or central venous line infections. Fluid imbalance caused one case each of cerebral and pulmonary oedema. Hyperkalaemia killed four children, probably caused a cardiac arrest in another, and may have contributed to four cases labelled as sudden infant death syndrome. One boy with inferior vena cava and renal vein thrombosis at birth had a pulmonary embolus at 3 months. Another boy died from septic shock and haemorrhage after a fundoplication. Figure 5, curve c, shows the ages at death of dialysed children.

Among transplanted children, four deaths occurred within one week, from haemorrhage, heart failure, septicaemia, and hyperkalaemia following hyperacute rejection. Later deaths were from gastrointestinal bleeds (n = 2), immunosuppression linked infections (one each, cytomegalovirus and *Pneumocystis carinii*), transplant artery haemorrhage following angioplasty (n = 1), recurrence of oxalosis (in one child given only a kidney), and one unexplained sudden death. Figure 3 shows their survival curve.

Overview of the survivors

Table 4 summarises the present status of all the children. The 117 survivors are 61% of the total cases, 66% of those treated, and 71% of those where it was continued. The currently dialysed children are younger than those with transplants (mean 3.6 *v* 7.6 years); it is likely that several of these will be transplanted eventually. Cross sectional data on the survivors (table 5) show that most preschool children, but very few schoolchildren are dialysed.

Of the 105 surviving children old enough to assess, 91 attended a normal school, or were expected to, but 16 of these required a classroom helper's support. Fourteen children attended special schools, 11 for their developmental and emotional needs, and three for physical reasons.

Effect of age at starting treatment

Table 6 compares the outcomes of children treated in the first month of life with those treated up to a year, or during their second year. A significantly larger proportion of children treated early went on to recover function. The higher mortality among children dialysed before 1 month did not reach statistical significance. Fewer children that started treatment early have a transplant compared to those dialysed from their second year of life (p < 0.001), probably because the data were collected when they were younger (though they are also slightly younger and lighter when transplanted). The age of starting treatment made no difference to graft survival, or post-transplant height or weight standard deviation scores, or to those requiring special education.

DISCUSSION

We show that each year in Britain and Ireland, one child aged under 2 years will reach end stage renal failure per three million people. It is perhaps surprising that the incidence was so stable. We had expected it to gradually rise because several British paediatric nephrologists had expressed reservations about treating babies at a national conference within a year of

Table 5 Current treatment modalities of patients alive at the time of the study, according to age

Treatment modality	Age groups of patients (y)											
	0–2		2–4		4–6		6–8		8–10		Over 10	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Dialysis	5	(100)	10	(53)	4	(17)	2	(8)	1	(5)	2	(9)
Recovered function	0	(0)	1	(5)	2	(9)	1	(4)	1	(5)	2	(9)
Transplanted	0	(0)	8	(42)	17	(74)	23	(88)	19	(90)	19	(83)

Not all the percentages add up to 100% because of rounding.

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Table 6 Outcomes compared according to the age that the children commenced renal replacement

Patient status	Age at reaching end stage renal failure		
	<1 month (n=31)	1–12 months (n=76)	1–2 years (n=70)
Of those treated:			
Recovered function (%)	16	3*	1**
Died (%)	45	37	26
Transplanted (%)	36	55	77***
Of those transplanted:			
Age at transplant (years)	2.1	2.4	2.8‡
Weight at transplant (kg)	11.0	11.8	12.8†
Duration of transplant (years)	3.8	3.4	4.1
Current graft survival (%)	91	76	80
Height standard deviation score	−1.67	−1.55	−1.33
Weight standard deviation score	−0.83	−0.26	−0.04
Of surviving children at time of study:			
% attending a special school	20	27	14

The symbols indicate that there are statistically significant differences between the children commencing renal replacement within that age group and the children treated under 1 month of age. *χ^2, p<0.05; **χ^2, p<0.02; ***χ^2, p<0.001.
†Mann-Whitney U, p=0.05; ‡Mann-Whitney U, p<0.01.

the period studied. We believe that the figures are reliable; the paediatric nephrology centres are confident of their complete recall, and it is unlikely that infants will have been diagnosed in district hospitals and not referred, especially latterly. It is a pity that there was so little data on termination of pregnancy because anecdotal experience suggests that it may have a major impact, halving the number of babies born with severe renal impairment as a result of posterior urethral valves in one centre. The improvement in antenatal diagnosis makes this option available to more women. A prospective study would be valuable.

Many more infants were offered renal replacement than might be expected, given the views expressed by paediatric nephrologists worldwide in 1998.[11] In almost every case the decision on whether to treat was made mutually by parents and the clinical team. Generally, dialysis was started unless the infants had an additional serious medical diagnosis. Several had treatment withdrawn after extra clinical problems emerged, and there were few children with multiple medical problems among the long term survivors. The fact that peritoneal dialysis was the modality of choice was similar to other reports,[9 16] and not a surprise, given the fact that haemodialysis necessitates technically demanding hospital based treatment. Further, adequate clearances are seldom produced in small children,[17] probably because of the widespread use of double lumen vascular access lines which limit the blood flow that can be achieved.[18]

Managing end stage renal failure in young children involves much more than just dialysis. As well as dietary modifications, fluid restrictions, and oral medications, other treatments are increasingly used, including overnight gastrostomy feeding, and subcutaneously administered erythropoietin and growth hormone. Though these undoubtedly improve general health and nutrition, they can make life arduous for the children and their families alike. Despite that, few families opted to withdraw treatment unless there were other adverse factors. The higher than expected incidence of sudden infant deaths among dialysed children was probably caused by acute biochemical disturbances, such as hyperkalaemia. These, and the fluid imbalances implicated as a cause of some of the morbidity and mortality, probably reflect the near impossibility for families of constantly having to maintain strict regimens for their small children.

Survival in these children is lower than in those who reach end stage later. However, some cases should be excluded from

our calculations, namely those whose deaths result from a careful decision not to start or to withdraw treatment, or from a specific infantile renal failure syndrome. Survival among the remainder compares closely with that in older children. The fall in graft thrombosis rates during the decade was probably mainly related to vascular anastamoses being created more proximally. Our first graft survival rates compare well to those for North American children who were transplanted when significantly older, but during a similar time period. Our two and 10 year kidney survival rates of 78% were almost identical to the five year North American figure for live donors,[19] and much higher than their cadaveric graft figure of 64%.[20] One centre has reported almost 100% two year graft survival in children weighing less than 15 kg at transplantation.[21]

The fact that most of our survivors already have a functioning transplant before they start school minimises the social impact of their illness compared to those children still needing dialysis and associated therapies. Also, our children show significant catch up growth. This is encouraging but not surprising; most children's growth deteriorates still further after transplantation, except for the youngest.[9 19 20] It has been argued that dialysing rather than transplanting under the age of 2 gives a lower mortality, but that transplanting soon after that maximises the growth potential.[9] This is the strategy that has been followed in Britain and Ireland, with some success. Our assessment of their social and educational functioning is crude but encouraging, with most children coping well at normal schools. Ultimately, a detailed psychological assessment of every child and a review of their educational achievements would be very valuable.

Many paediatric nephrologists believe that only older infants with end stage renal failure should be treated, and not those under a year, and certainly not those under one month.[11] Our data provide no evidence to support their view. Though the mortality is higher in babies treated from under 1 month of age, most that recover function are also from this group. These babies are ones who are believed to be in end stage irrecoverable renal failure, but who subsequently improve sufficiently to come off dialysis. It is clearly difficult, but extremely important, to make a confident diagnosis of end stage in the very young; eight of our cases only needed temporary dialysis, but would have died if they had not been treated. Babies that are ultimately transplanted have the same graft function and survival, and better growth than those from the older groups. It is, therefore, illogical to plan a renal

replacement policy based on the patient's age at entry. Many physicians have a fear of doing harm by enabling the survival of children whose only reward is to suffer, either by undergoing physical discomfort and pain, or by being severely handicapped by a poor quality of life. The clinical policy pursued in Britain and Ireland has been to treat children of any age unless they have overwhelmingly serious additional diagnoses, or seem to their parents and the clinical team to be suffering excessively. The quality of life of the survivors appears to justify this approach.

ACKNOWLEDGEMENTS

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RENAL TRANSPLANT PROTOCOL
Jan.1998

Patient's Name: ....

Contents

Dr N D Plant

1

RENAL TRANSPLANT PROTOCOL

URGENT ON CALL TEAM'S DUTIES,
A 10 POINT PLAN

Once the patient has arrived undertake the following without delay:

1. **Insert largest possible cannula. Take pre-operative bloods.** All results are required urgently.

PRE-OPERATIVE BLOODS

- **FBC (0.5 ml in EDTA bottle)**

- **Clotting screen (2 ml Citrate)**

- **Ionised calcium, magnesium, SMAC (2 ml Brown Vacutainer)**

- **X-match 2 units if < 30 Kg or 3 units if > 30 Kg. (1 ml EDTA to RVI Blood Bank). CMV negative blood is required for CMV negative transplant recipients.**

- **Cytotoxic X- match, FACS (20 ml Li-hep, 10 ml clotted and 5ml EDTA to Tissue Typing, Regional Blood Transfusion Service)**

- **Viral Screen: HBsAg, HIV, CMV, Hep C, EBV (2 ml clotted to Virology, NGH - extn 22801 or on-call Virologist)**

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2. **Give po dose of cyclosporin A 300mg/m^2 and azathioprine 60mg/m^2.** (See chart for body surface area calculation on p.15). **Give calcium heparin 75 units/Kg sc.** Administer these as soon as possible after the patient's arrival. (**Tacrolimus** and **mycophenolate mofetil** are alternative drugs used in selected patients - see "Further notes on transplant drugs" p.8).

3. **Commence pre-operative hydration with iv fluid.** Give the patient's measured daily urine output (volume is recorded in patient's notes on blue flow sheet) plus another 25% (i.e. estimated output = 100%, total fluid required = 125%). Give fluid as 0.45% NaCl. Divide total by 24 to give the hourly rate required. Administer for a minimum of 6 hours pre-operatively. **Also, ensure 100 ml/Kg of 4.5% HAS is ordered (using a Blood Bank form) and taken to the recovery room for use in the immediate post-operative phase.**

4. **Microscope the patient's urine and dialysis fluid.**

5. **Clerk and examine the patient.** Check for evidence of PD catheter exit site infection. Document your findings clearly in the notes.

6. **Write up the pre- and post-operative drug charts.** Drugs should be prescribed on separate "Pre-operative" and "Post-operative Drug Charts". Once the patient has returned from theatre cross out and file the pre-operative chart.

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7.   **Write up the pre-operative drugs**

PRE-OPERATIVE DRUGS

- **Cyclosporin A 300 mg/m^2 po and azathioprine 60mg/m^2 po (or tacrolimus and mycophenolate mofetil)** as soon as possible after the patient's arrival. (See 2. above.)

- **Amoxycillin 30 mg/Kg iv, flucloxacillin 30 mg/Kg iv and ceftazidime 15 mg/Kg iv.** Give all antibiotics immediately before going to theatre. If the donor died of infection e.g. meningococcaemia, then continue appropriate ones iv for 10 days

- **Methyl prednisolone 300 mg/m^2 iv** at the time of the arterial anastamosis Send drug to theatre with patient. It will be administered by the anaesthetist.

- **Calcium heparin 75 units/Kg sc.** Give as soon as possible after the patient's arrival. (See 2. above)

- **Acyclovir 10 mg/Kg po.** Necessary only if the recipient is CMV negative and donor is CMV positive. Give as near to 6 hours pre-operatively as possible.

---

8.   **Write up the post-operative drugs.**

3

POST-OPERATIVE DRUGS

- **Calcium heparin 75 units/Kg sc.** Give bd for 7 days (in those >30Kg) or 10 days (if <30Kg).

- **Methyl prednisolone 300 mg/m² iv. Single dose.** Give 24 hours after returning from theatre.

- **Prednisolone 5 mg/m² po bd.** Start on day 1 post-op.

- **Cyclosporin A 300 mg/m² po bd for 48 hours. Give the first dose 12 hours post-op.** Give the second 300 mg/m² dose at 0800 or 2000, whichever is the closest to 12 hours after the first 300mg/m² dose. CyA levels are performed after the third post-operative dose. **After 48 hours change to cyclosporin A po 150 mg/m² bd.**

- **Azathioprine 60 mg/m² po od.**

- **Co-trimoxazole 12 mg/Kg po od.**

- **Acyclovir 10 mg/Kg po if required.** The dose interval is as follows:
  - If on dialysis (PD or HD) give *twice a week*.
  - If off dialysis and GFR <10 ml/min/1.73 m² give *od*.
  - If off dialysis and GFR =10-25 ml/min/1.73 m² give *tds* and if GFR >25 ml/min/1.73 m² give *qds*.
  GFR is calculated using the "Paediatric Creatinine Chart" on p.16.

- **Morphine infusion.** 1 mg/Kg morphine made up to 50ml of 5% Dextrose. Infuse at 1 ml/hour. Reduce dose when possible. Older patients may need a PCA. This is usually prescribed by the anaesthetic team.

** CHECK THE DOSE OF PRE- & POST-OPERATIVE DRUGS WITH THE CONSULTANT BEFORE ADMINISTRATION **

9. **Write up the post-operative fluids.**

POST-OPERATIVE FLUIDS

1. **0.45% NaCl & 5% Dextrose at 300ml/m²/day = 12.5ml/m²/hour. This is to replace the patient's insensible losses.**

2. **0.45% NaCl & 5% Dextrose to replace the patient's urine output ml per ml each hour.**

- The crystalloid used may change depending on the plasma and urine electrolytes.

- **Additional fluid in the form of colloid may be required to maintain an appropriate intravascular volume - see p.5.**

Children are maintained on this post-operative fluid schedule until they are able to tolerate significant volumes of oral fluid. This is usually day 3 or 4 post-op.

10. **Contact the anaesthetic staff on call.** They should be reminded that the standard paediatric transplant protocol is to be followed. This entails the peri-operative

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administration of methyl prednisolone and a radial arterial and central venous line being sited. The CVP is to be maintained between 7 and 15 cm of water during the operative procedure using colloid boluses (see p.5).

The central venous line will be sent to theatre with the child. This is either a **15** or **20 Vas-cath "Vasaccess single lumen catheter with Y"**. The type of catheter depends on the patient's size and will be organised by either the consultant or renal nurse.

ADDITIONAL PRE-OPERATIVE NOTES

The family will be contacted at home by the consultant Paediatric Nephrologist on call. They will be told to bring in the child promptly with EMLA cream applied and, if being dialysed at the time of the call, a sample of dialysis fluid.

The Transplant Co-ordinators inform the Renal Team of kidneys from donors of at least 15Kg, with an age gap between donor and recipient of no greater than 40 years. No more than a total of 2 mismatches on the B and DR loci is acceptable. The decision to accept the kidney is taken jointly by the nephrologist, transplant co-ordinator, specialist renal nurse and transplant surgeon.

Most children having peritoneal dialysis do not need to have any changes made in their dialysis prescription prior to theatre. If the child is being haemodialysed, a session may be required pre-transplantation. This will be organised by the consultant and the specialist renal nurse.

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IMMEDIATE POST-OPERATIVE CARE

The children are met from theatre by the consultant paediatric nephrologist and the specialist renal nurse on call and a member of the ward nursing staff. Junior doctors are always welcome.

In Recovery the patient is assessed and standard post operative fluids commenced. The patient's CVP will be measured promptly in the recovery room as will the blood pressure via the arterial line. Additional colloid is given in order to maintain an appropriate intravascular volume (see **"Maintaining an adequate circulating volume"** below).

Plasma & urinary electrolytes and a FBC should be taken as soon as possible in the recovery room. The results are required urgently.

Once the patient has been stabilised they will return to the ward.

ON RETURN TO THE WARD ....

Maintaining an adequate circulating volume.

This is essential and in the context of post renal transplantation care is defined as

- **a CVP between 7 and 15 cm of water**

- **a toe-core gap of less than 1.5 °C.**

- **and a systolic blood pressure between the 50th and 95th centiles for age (See chart on p.17).**

These findings should be interpreted in conjunction with a clinical assessment of the patient.

If the child appears **hypovolaemic** by virtue of a low CVP, a wide toe core gap, hypotension or clinical judgement then **5 ml/Kg of 4.5% human albumin solution should be administered over 5 minutes**. This should be repeated if the patient remains under-filled. Packed red cells would only normally be given if the patient's haemoglobin was below 6 g/dl. The patient would also need to be normokalaemic. The use of blood **must** be discussed with the consultant on call.

In the presence of an **appropriate intravascular volume** the patient's **urine output should be in excess of 2 ml/Kg/hour**. If the urine output falls and there is evidence of hypovolaemia then colloid should be administered. If the urine output falls and the child is adequately filled then a single intravenous dose of **frusemide (2mg/Kg)** should be administered. If there is no response, the consultant on call should be contacted.

If a patient is **over-filled** they may develop a degree of pulmonary oedema. Pulse oximetry is thus always continued for the first 2 post operative days and a CXR should be performed if pulmonary oedema is suspected. Frusemide is the usual first line treatment (2mg/Kg iv).

Hypertension, defined as a systolic blood pressure greater than the 95th centile for sex and age, and its treatment is to be discussed with the consultant on call.

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POST-OPERATIVE BLOODS

Biochemistry

- *Blood and urine* biochemistry (including plasma glucose) is required promptly 4 hourly for the first 24 hours. This is reduced to 6 hourly on day 2. Thereafter the frequency will be determined by the Renal Team depending on the child's progress.

Full blood count

- This should be performed with the biochemical tests above on days 1 and 2. Thereafter a daily full blood count is required unless there are untoward circumstances.

Cyclosporin level

- This should be performed after the 3rd post-operative dose and then daily until discharge. A strict 12 hour trough level is required prior to the 0800 dose.

  Send 0.5ml EDTA to Biochemistry, FRH - extn 26437 or 31017. The specimen must be sent in a taxi arranged from Peacock Hall to arrive in the lab before 10am. Routine assays are performed Monday to Saturday. Inform the lab of levels required on a Sunday as far in advance as possible.

Plasma magnesium

- This should be checked every third day beginning on day 2.

Cytotoxic antibody screen

- This should be undertaken routinely on day 14 post graft. (If the patient is to receive ATG or ALG (see p.12) a screen is also required *before* starting the course. The results of cytotoxic antibody screening are not interpretable for 6 weeks after a course of ATG/ALG and testing should not be undertaken during this period.)

  NB. Further routine serum samples for cytotoxic antibody screens are required at 3 and 6 months post graft.

CMV

- If negative pre-operatively, the patient's CMV status should be assessed fortnightly by PCR and antigenaemia tests. (7ml Li-hep to Virology, NGH - extn 22801)

MAINTAINING NORMAL ELECTROLYTES

- The type of intravenous fluid needed post-operatively to maintain normal sodium, potassium and bicarbonate will depend on the concentrations of these being lost in the urine, and is adjusted according to urine and blood biochemistry.

Sodium

- Use the urine biochemistry as the initial guide to the best intravenous fluid to use. Select the standard fluid bag with the sodium concentration nearest to that in the urine to replace the urine volume.

- Standard bags are as follows:

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Normal saline	= 0.9% NaCl	= 150 mmol/l
Half normal	= 0.45% NaCl	= 75 mmol/l
One fifth normal	= 0.18% NaCl	= 30 mmol/l

- Use the blood biochemistry to monitor how well this system is working.

- If the plasma sodium is on the high side, use a fluid replacement bag with a sodium concentration below that of the urine sodium, and vice versa.

Bicarbonate

- If the plasma bicarbonate is low, **some** of the intravenous sodium can be given as sodium bicarbonate. Calculate the hourly bicarbonate infusion rate as:

(required rise in concentration (mmol) X body weight (Kg)) / 40 = rate in mmol per hour.

- This will correct the deficit in about 12 hours. To calculate the concentration needed in the infusion bags, use this value and the approximate infusion rate being used at the time. Add the bicarbonate as an 8.4 % solution which has 1 mmol of sodium and 1 mmol of bicarbonate per ml. Do not assume that this formula will give a precise correction, but check progress every four hours.

Potassium

- This is seldom needed in immediate post-transplant infusions, but a rapidly functioning new transplant may lose a lot of potassium into the urine which will need replacement. Adjustment is by the same principal as for sodium - measure the potassium concentration in the urine and infuse with a fluid containing a similar potassium concentration. Standard pre-mixed bags contain 20 or 40 mmol/l. Extra may be added as "Strong Potassium Chloride" (2 mmol/ml) which must be mixed thoroughly after addition. Monitor the results of this by looking at the blood potassium achieved.

Phosphate

- There may also be large tubular losses of both phosphate and magnesium in the post-graft period.

- Hypophosphataemia is usually treated with po Phosphate Sandoz (Starting dose: 1 soluble tablet tds if < 5 years of age, 2 tablets tds if > 5 years. Each tablet contains 16 mmol phosphate, 20 mmol sodium and 3 mmol potassium). If parenteral phosphate is required use Neutral Sodium Phosphate Injection (1 mmol phosphate/ml and 1.8 mmol sodium/ml). Give 0.15-0.33 mmol/Kg phosphate over 6 hours. Maximum infusion rate is 0.05 mmol/Kg/hr. Dilute 1 in 10 with 5% Dextrose or 0.9% NaCl. Adjust the treatment according to response.

Magnesium

- Hypomagnesaemia is almost always corrected with oral magnesium supplementation. If the plasma magnesium is <0.4 mmol/l give magnesium chloride 0.15 mmol/Kg/dose qds. Each MgCl (Slo-Mag) tablet contains 2.5 mmol magnesium.

- Convulsions associated with hypomagnesaemia are the only indication for iv magnesium treatment. Give 20-40 mg/Kg iv magnesium sulphate 20% solution (20 mg in 0.1 ml) at a rate no greater than 150 mg/min. Dilute *at least* 1 in 2 with 5% Dextrose. This can be repeated 4-6 hourly if necessary.

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POST-OPERATIVE IMAGING

Renal ultrasound scan with Doppler assessment

- A baseline ultrasound of the renal tract is required once any perinephric drains have been removed.

- A scan should be undertaken the day following the transplant if there is primary non-function.

- An ultrasound scan is mandatory if rejection is suspected (see below).

DMSA

- A baseline DMSA is required around the 10th post-operative day. Undertake earlier if there is a suspicion of a perfusion defect.

FURTHER NOTES ON TRANSPLANT DRUGS

Cyclosporin A (Neoral).

- After the initial cyclosporin A level these are to be performed daily. Cyclosporin should be administered at 0800 and 2000 the level is taken as close to 12 hours after the previous dose as possible.

- *Intravenous cyclosporin A* is seldom used. If oral administration is not possible, give iv cyclosporin A 12 hourly as an infusion over 4 hours. *The iv dose is a third of the po dose.*

- Acceptable cyclosporin A levels are as follows:

M'ths Post Tx	CyA Level (ng/ml)	M'ths Post Tx	CyA Level (ng/ml)
0-3	200-250	6-12	100-150
3-6	150-200	>12	100-125

Prednisolone

- The initial dose of 5 mg/m^2 bd po is given for 1 month. This is reduced to 5 mg/m^2 od for the next month and then to 5 mg/m^2 on alternate days thereafter.

Azathioprine

- The dose of 60 mg/m^2 od does not change.

Co-trimoxazole (Septrin)

- This is given for the first 6 months post transplant at a dose of 12 mg/Kg od, or while cyclosporin A levels are being maintained at >150 ng/ml.

Acyclovir

- If indicated, po acyclovir is continued for 12 weeks post transplantation. The dose is adjusted as the patient's GFR changes. This occurs most rapidly in the first few days after the transplant.

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Tacrolimus (Prograf or FK506)

- This is a macrolide immunosuppressant with a similar mode of action and adverse effects to cyclosporin A. It is occasionally used instead of cyclosporin A. The starting dose is 0.15mg/Kg bd po. Give 2 hours after food at 1000 and 2200. Tacrolimus levels need to be checked as a trough, 12 hours after the previous dose. Send by taxi 0.5ml EDTA to *Microbiology*, FRH - extn 26291. Routine assays are at 1400 Monday to Friday and 0930 Saturday and Sunday.

- Trough tacrolimus levels should be 5-10ng/ml at all times post graft.

Mycophenolate mofetil (CellCept)

- This is a cytotoxic immunosuppressant closely related to azathioprine. It is used in selected cases as an alternative to azathioprine. Give 600mg/m^2 bd po immediately after food. This can be changed to 300mg/m^2 qds po if diarrhoea, a common adverse effect, is troublesome.

LIVING RELATED DONOR TRANSPLANTATION (LRD)

This is an elective procedure. The recipient is usually admitted 2 days before the operation date.

The only deviations from the standard **pre-operative** protocol are given below. **The post-operative management is unaltered.**

Pre-transplant drugs and fluids

The recipient will **already** be taking po cyclosporin A and po azathioprine. The pre-operative hydration iv fluids should be commenced the night before the graft.

Bloods

Bloods are to be taken as per the "10 Point Plan" on the day of arrival.

The **donor** should also be bled at this time for cytotoxic X-match and FACS - 60ml Li-hep (*note* larger volume than for recipients), 10ml clotted and 5ml EDTA. The X-match result is required as soon as possible in order to cancel the procedure in good time if the result is positive.

A **recipient cyclosporin A level** should also be checked on the morning of admission and the morning of the transplant. A level of 200-250ng/ml is desired.

Donor

The donor is admitted by the transplant surgeons the day before the procedure. Apart from the X-match bloods the donor is under their *exclusive* care.

SUBSEQUENT POST-OPERATIVE CARE

Mobilisation

- Patients are encouraged to sit out and mobilise as soon as is practical post operatively.

Temporary Central Venous Line

- This usually remains in situ until after the patient's discharge.

PD catheter or permanent haemodialysis line

- These are usually removed surgically 3 months post graft. Typically **this procedure is combined with the removal of the ureteric stent.**

Urinary catheters

- Children return from theatre with either a urethral or suprapubic catheter. Catheter urine should be microscoped on a daily basis.

- The urethral catheter is usually removed on day 5. A suprapubic catheter is clamped on day 7 and removed on day 21 (often after discharge).

IMMUNISATIONS

After renal transplantation the following live vaccines are <u>contraindicated</u> :

- BCG

- Measles, mumps and rubella (MMR)

- Oral poliomyelitis, live (Sabin)

The following inactivated/detoxified exotoxin vaccines <u>can be given</u>:

- Diphtheria, Pertussis, Tetanus (Triple vaccine)

- Diphtheria and Tetanus (Booster)

- Haemophilus influenzae type b (Hib)

- Influenza - but this is **not necessary** for children after transplantation

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POST-OPERATIVE FEVER

Infection and **rejection** are the main diagnoses to be considered. Discuss a post-operative pyrexia with the Paediatric Nephrology Consultant on call.

Investigations

In all febrile patients perform the following urgently:

- plasma creatinine (unless measured within the last 8 hours)

- FBC

- microscope the urine

- if a Tenckhoff catheter is in situ, even if they are not dialysed, microscope the dialysate

- venous blood cultures should be taken from the central line

- other investigations such as a chest x-ray, wounds swabs etc. need to be considered

- USS of the renal tract*

- check CMV status urgently*

- if recipient CMV negative and check cytotoxic cross match*

* Can be deferred until the following morning if the episode occurs after 1700.

Diagnosis

If a focus of *infection* is acutely found, a diagnosis of infection can be made. Infection, however, can trigger rejection.

Rejection is typically seen between days 5 and 10. It is usually diagnosed on 2 or more of the following:

- rising creatinine
- reduced urine output
- fever
- hypertension
- graft tenderness

In some patients it may be impossible to distinguish between infection and rejection and treatment with both antibiotics and increased immunosuppression is required

Treatment

- **Treatment of infection**

  If the patient is unwell and blind antibiotic treatment is necessary, use

  Augmentin 30 mg/Kg/dose qds iv for 5 days **or** **ceftazidime 25 mg/Kg bd iv** for 5 days (give 25 mg/Kg od iv if GFR 15-30 ml/min/1.73 m^2 or 4.5 mg/Kg iv od if GFR less than 15 ml/min/1.73 m^2).

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- **Treatment of rejection**

  First episode of acute rejection occurring within 6 weeks of transplantation: treat with *3 days of iv methyl prednisolone 300 mg/m²* (This may be extended to 5 days on the judgement of the renal team). If the creatinine has not returned to baseline after this course, the following "tail" of oral prednisolone may be used: *3 days of 2 mg/Kg po prednisolone then 3 days of 1.5 mg/Kg, then 3 days of 1 mg/Kg.,* then return to standard maintenance prednisolone dose.

  Second acute rejection episode within the first 6 post-operative weeks: treat in the same manner.

  Rejection episodes occurring greater than 6 weeks post operatively: treat with *3 days of 3 mg/Kg of po prednisolone.* The same indications for "tail" applies.

  A **transplant biopsy** will be considered if the creatinine does not a return to baseline with glucocorticoid therapy **or** if it is the 3rd episode of acute rejection.

  <u>*NB*</u> During episodes of rejection it is essential that daily cyclosporin A levels are monitored to ensure they are within the therapeutic range.

SECOND LINE IMMUNOSUPPRESSANT AGENTS

These are occasionally used in the treatment of rejection resistant to intravenous steroids. They include ATG, ALG and OKT3.

Second line therapy is initiated by consultants only.

<u>Anti-Thymocyte Globulin (ATG) (Merieux) 25mg in 5ml.</u>

Anti-thymocyte globulin is an anti-T cell preparation. Periodically the availability of this product changes and its sister compound Anti-Lymphocyte Globulin (ALG) is employed.

Take blood for cytotoxic cross match before the initial dose.

Dose:

- 80mg/m² for 10 days, occasionally extended to 14 days. Must be given via a *central venous line*. Dilute each 1mg of ATG in at least 2ml of 0.9% NaCl. Infuse over 8 hours. The first dose should be given during the day as allergic reactions are not uncommon and consist of fevers, rigors and malaise. For this reason the initial infusion is to be given when a larger number of medical/nursing staff are available.

- Treat allergic responses with 0.2mg/Kg Chlorpheniramine iv (maximum dose 10mg) and 8mg/Kg of Hydrocortisone iv (maximum dose 200mg). These doses can be used prophylactically for future infusions.

- After the first infusion, ATG is usually administered overnight.

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Anti-Thymocyte Globulin (ATG) Continued

Side Effects:

- See allergic reactions above.

Monitoring:

- The absolute T cell count needs to be measured each day. This involves sending a 0.5ml EDTA sample to Haematology for a FBC and differential and a 2 ml Li-Hep. sample to the Department of Surgery FACS lab (extension 24368) for T cell subsets.

- From the differential and subset counts the absolute number of T cells can be calculated. If the T cell count is less than $0.05 \times 10^9/l$ ATG should not be administered that day. The count should obviously be repeated the following day.

- Quite often children only require ATG on alternate days during their course.

Other drugs:

- Cyclosporin A is *discontinued* during the ATG course and recommenced at the previous dose 3 days before the end of ATG. Prednisolone and azathioprine are continued throughout.

- If not already on co-trimoxazole, start 12 mg/Kg po od and continue for 2 months after completing the course of ATG. This is as prophylaxis against *pneumocystis carinii*.

Anti-Lymphocyte Globulin (ALG) (Merieux) 100mg in 5ml.

NB. The dose of ALG is <u>four times</u> that of ATG.

Dose:

- 240mg/m^2 for 10 days.

Other than the dose, all of the above applies equally for ALG.

OKT3 (Janssen-Cilag) 5mg in 5ml

This is a CD3 murine monoclonal antibody. It can be given through a peripheral cannula. A central venous line is not required. The patient must be normovolaemic and have a normal chest x-ray prior to treatment, as pulmonary oedema is a recognised but rare acute adverse reaction.

Dose

- 5mg/Kg iv for 10 days, occasionally extended to 14 days. Give as a fast bolus.

- Do **not** administer if patient's temperature exceeds 37.8℃.

Side Effects

- Usually seen with 30 minutes to 6 hours of the *first* dose. Include: chills, fever, dyspnoea, nausea, vomiting, pulmonary oedema (see above - treat with prompt IPPV) and wheezing.

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<u>**OKT3 Continued**</u>

Monitoring

- Samples as for ATG/ALG. Within a day the CD3, CD4 and CD8 counts will fall.

  The CD4 and CD8 counts increase between days 2 and 7, but the CD3 count remains low.

Other drugs

- Give methyl prednisolone 1mg/Kg iv before each of the first 3 doses of OKT3. Give hydrocortisone 100mg po 30 minutes after the first 3 doses. No further steroid doses are required after day 3 in the absence of adverse reactions.

- Cyclosporin A is *discontinued* during the OKT3 course and recommenced at the previous dose 3 days before the end of OKT3. The dose of prednisolone is reduced to 0.5mg/Kg od po and the dose of azathioprine is halved.

- If not already on co-trimoxazole, start 12 mg/Kg po od and continue for 2 months after completing the course of OKT3. This is as prophylaxis against *pneumocystis carinii*.

CHART TO ESTIMATE SURFACE AREA FROM BODY WEIGHT

weight (kg)	BSA (m2)	weight (kg)	BSA (m2)	weight (kg)	BSA (m2)
0.4	0.049	8	0.422	40	1.27
0.5	0.058	9	0.458	42	1.32
0.6	0.066	10	0.493	44	1.36
0.7	0.074	11	0.526	46	1.40
0.8	0.082	12	0.559	48	1.44
0.9	0.089	13	0.591	50	1.48
1	0.096	14	0.622	52	1.52
1.2	0.110	15	0.652	54	1.56
1.4	0.123	16	0.681	56	1.60
1.6	0.135	17	0.710	58	1.63
1.8	0.147	18	0.739	60	1.67
2	0.159	19	0.767	62	1.71
2.2	0.170	20	0.794	64	1.75
2.4	0.181	21	0.821	66	1.78
2.6	0.191	22	0.848	68	1.82
2.8	0.201	23	0.874	70	1.85
3	0.212	24	0.900	72	1.89
3.2	0.222	25	0.925	74	1.92
3.4	0.231	26	0.950	76	1.96
3.6	0.241	27	0.975	78	1.99
3.8	0.250	28	0.999	80	2.03
4	0.259	29	1.02	82	2.06
4.5	0.282	30	1.05	84	2.09
5	0.304	32	1.09	88	2.16
5.5	0.325	34	1.14	92	2.22
6	0.345	36	1.19	96	2.29
7	0.384	38	1.23	100	2.35

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APPENDIX 3   Adam's perioperative fluid balance. (Assumes weight of 19 kg; surface area = 0.8 m²) Dr COULTHARD

Adam's usual daily intake (known)	Enteral intake = [2100] ml
Adam's usual daily output (estimated)	Urine output = [1500] ml; insensible loss = [240] ml; dialysis loss = [up to 292] ml; faecal loss = [68] ml. Total = [2100] ml

	Time between ward admission & start of preoperative fasting 2200-0500 = 7 h	Time between start of preoperative fasting period & anaesthesia 0500-0700 = 2 h	Time between induction of anaesthesia & start of surgery 0700-0800 = 1 h
Fluid losses			
a) Insensible losses	[300] ml/m²/d = [10] ml/hr = 70 ml	[300] ml/m²/d = [10] ml/hr = 20 ml	[300] ml/m²/d = [10] ml/hr = 10 ml
b) Urine output	[62] ml/h = 434 ml	[62] ml/h = 124 ml	[62] ml/h = 62 ml
c) Blood loss	0 ml	0 ml	0 ml
d) Dialysis loss	Likely to be much less than 292 ml: *See Note B	0 ml	0 ml
Total fluid losses	Between 500 and 800 ml, most likely approximately 600 ml. *See Note B	144 ml	72 ml
Actual fluid input	952 ml	0 ml	750 ml
Est. fluid (+ =excess; - = deficit)	+152 to +452 ml	-144 ml (cumulative =+8 to +308)	+678 ml (cumulative =+686 to +986)
Comments + Estimated SODIUM BALANCES	**Input**=Dioralyte; 953 ml = 57 mmol Na⁺ **Output**=Insensible Na approximately 0, + urine likely to be 75/1 = 33 Na loss, + dialysis likely to be 130/1 = <38 Na loss. **Na balance**=Less than 14 mmol deficit (PD loss likely to be much less than 38, so probably in POS Na balance)	**Input**= 0 mmol Na⁺ **Output**=Insensible Na approximately 0, + urine likely to be 75/1 = 9 Na loss. **Na balance**=-9 (Thus, cumulatively, likely to be overall approximately 0, ie, WENT TO THEATRE IN SODIUM BALANCE)	**Input**= 31 mmol/l = 23 mmol Na⁺ **Output**=Insensible Na approximately 0, + urine likely to be 75/1 = 5 Na loss. **Na balance**= +28 (If accept arrival in theatre in approx Na balance, now cumulative Na balance = +28 ml)
Reasons why planned fluid infusion (content or infusion rate) should change due to change in estimated loss	• Overall, the estimated water balance pre-op is close to ZERO from +12 to 312 ml • Overall, the estimated Na balance pre-op is also quite close to ZERO, given the unknowns including the UF value and the urine sodium concentration. • It is therefore reasonable to assume that Adam went to theatre in approximately normal salt and water balance.		The cumulative Na and water balance since induction of anaesthesia, assuming he was in balance on arrival in theatre, IS: Water = +678 Na = +28 The concentration of the accumulated fluid therefore = 28/678 = 41 mmol/l.

APPENDIX 3   Adam's perioperative fluid balance. (Assumes weight of 19 kg; surface area = 0.8 m²) Dr COULTHARD

	Time from start of surgery until vascular clamps on (0800-1000)	Time while vascular clamps applied (1000-1030)	Time from when clamps released until end of surgery (1030-1130)	Time from end of surgery until arrival in ICU (1130-1215)
Fluid losses				
a) Insensible losses	20 ml	5 ml	10 ml	7 ml
b) Urine output	up to 124 ml *See Note A	up to 31 ml *See Note A	up to 62 ml *See Note A	up to 46 ml *See Note A
c) Blood loss	600 ml	200 ml	328 ml	0 ml
Total fluid losses	up to 744 ml *See Note A	up to 236 ml *See Note A	up to 400 ml *See Note A	up to 53 ml *See Note A
Actual fluid input	2300 ml *See Note C	200 ml *See Note C	250 ml *See Note C	0 ml *See Note C
Estimated fluid excess	+1556 ml (cum =+2242 to +2542)	-136 ml (cum =+2106 to +2406)	-150 ml (cum =+1956 to +2256)	-53 ml (cum =+1903 to +2203)
Comments + Estimated SODIUM BALANCES	Input = 226 mmol Na+ Output= blood 78 *See Note D + urine = approx 9 mmol total. Na balance=+139	Input = 26 mmol Na+ Output= blood 26 *See Note D + urine = approx 2 mmol total. Na balance=-2	Input = 33 mmol Na+ *See D Output= blood 43 *See Note D + urine = approx 5 mmol total. Na balance=-15	Input = 0 mmol Na+ Output= urine = approx 4 mmol Na balance=-4
Reasons why planned fluid infusion (content or infusion rate) should change due to change in estimated loss	The cumulative Na and water balance since induction of anaesthesia, carrying forward the 07:00 to 08:00 values above, is therefore: • Minimum water excess = +1956 • Sodium excess = +150 • The concentration of the accumulated fluid therefore = maximum of 150/1948 = 77 mmol/l. • This is equivalent to retaining 1071 ml of fluid with a physiological Na concentration of 140 mmol/l AND AN EXTRA 885 ml of WATER.			

Will changing maintenance intravenous fluid from 0.18% to 0.45% saline do more harm than good?

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ABSTRACT

The recommended change in maintenance intravenous fluid in children from 0.18% to 0.45% saline might cause more children to develop hypernatraemia than it would prevent children from developing hyponatraemia, and thus could do more harm than good. There is no simple formula that will guarantee to prevent either hyponatraemia or hypernatraemia in all children, and it is impossible to decide on a safe fluid regimen merely by knowing the plasma sodium concentration and estimating the degree of dehydration, as is often done. Changing which fluid is used for routine maintenance therapy will not compensate for using a too-simple approach to fluid replacement. Instead, it is necessary to base the fluid regimen on an assessment of the child's physiology. A vital part of that assessment includes measuring the urinary volume, sodium and creatinine, and using them to calculate the fractional excretion of water and sodium. This enables fluid replacement to be decided using a logical approach in which plasma sodium measurements are just used for fine-tuning. Also, 0.18% saline provides a more physiological standard replacement than 0.45% saline, equivalent to normal oral intakes, and should remain the basic maintenance fluid.

The National Patient Safety Agency has recommended changing the standard paediatric intravenous maintenance fluid from 0.18% to 0.45% saline to prevent children from developing serious hyponatraemia.[1] It recommends that only 0.45% saline should be available for maintenance in most clinical areas ("half-normal dextrose–saline", sodium concentration 75 mmol/l, hereafter called N/2), and that the previously widely used 0.18% saline ("one-fifth-normal dextrose–saline", sodium concentration 30 mmol/l, hereafter called N/5) should be restricted to specialist areas, such as paediatric intensive care and nephrology units. However, I believe that this is the wrong solution (literally!) to the problem. I will argue that N/5 is the physiologically most appropriate standard fluid, and that hyponatraemia is much more likely to be due to its misuse than to its inherent properties. Most fluid-prescribing guidelines lack a logical base and appropriate monitoring, and make unjustified pathophysiological assumptions which will inevitably lead to perturbations of plasma sodium in some children, whatever range of fluids is available. Changing from N/5 to N/2 will reduce the cases of hyponatraemia, but increase the cases of hypernatraemia; I fear that, on balance, it may do more harm than good. What is needed is physiologically based fluid prescribing.

CHOOSING AN APPROPRIATE MAINTENANCE FLUID

Intravenous maintenance fluids need to replace the water and salt that would normally be taken orally in healthy children (table 1). Typical oral intakes would have an average sodium concentration of 20–27 mmol/l, which is similar to the 30 mmol/l in N/5, but only about one-third of that present in N/2. Potassium intakes are similar.

Ignoring growth and stool losses, all the sodium and potassium ingested each day is excreted in the urine. Because water evaporates through the skin with minimal electrolytes (except in cystic fibrosis), the urine electrolyte concentrations average slightly higher than those in the intake fluid. Box 1 gives an example of the likely urine osmolality (UOsm) that would result from providing intravenous maintenance for a 1-year-old girl, as N/5, N/2 or normal saline (150 mmol/l, NS), plus potassium. Because the kidneys of a normal infant can generate a UOsm anywhere between ≈ 50 and 700 mosmol/kg (over 1000 in older children), none of these fluids should disturb their physiology because they can simply adjust the UOsm to the necessary level. However, not all children can be this flexible and adaptive, either because they have inherent defects of kidney control or function, or because acute illness has resulted in their kidneys being re-regulated to produce a fixed urine concentration.

HOW MIGHT REHYDRATION CAUSE HYPONATRAEMIA?

When children are dehydrated, they are nearly all depleted of approximately normal saline, whether their plasma sodium concentrations (PNa) are high, normal or low. For that reason, they should be rehydrated with the same volume of NS. The use of bags of NS + 4% glucose allows glucose to be administered simultaneously. If the circulation is compromised, protein can be given with the saline (ie, plasma).

Once rehydrated, most children can receive their maintenance fluid, which I have argued should normally be N/5 + 20 mmol/l potassium because it is nearest to the intake they would receive if they were switched to oral fluids. If the rehydration phase is managed with a hypotonic fluid (N/2 or N/5), or if children are switched to maintenance fluids too soon, they may develop hyponatraemia. Feedback I receive from teaching sessions indicates that both practices are common.

HOW MIGHT MAINTENANCE FLUIDS PERTURB THE PLASMA SODIUM?

The kidneys of normal children are able to independently vary the amount of water and

Table 1 Typical daily intakes of water and sodium in healthy normal children

Age	Daily intakes		Sodium concentration (mmol/l)
	Water (ml/kg)	Sodium (mmol/kg)	
Newborn	150	3	20
1 year	100	2.5	25
5 years	75	2	27
12 years	50	1	20

solutes they can excrete so widely that they can maintain the plasma volume and PNa within the normal range despite widely varying intakes. A child with a very-low-salt diet, or maintained only on intravenous dextrose, will produce urine almost free of electrolytes, and thereby avoid hyponatraemia for a long period. Similarly, a child on a high-salt diet, or receiving maintenance NS, will produce urine loaded with salt.

Therefore, problems only tend to occur if there is a particular reason, such as having lots of extra osmoles to excrete (eg, diabetes mellitus) or an inability to adjust UOsm. If the kidney cannot synthesise urine at the right strength to maintain fluid and chemical balance, then the PNa will be affected. Even a moderate limitation of UOsm can induce hypernatraemia—for example, a fixed maximum capacity of 200 mosmol/kg may result in a daily rise in PNa of 7 mmol/l using N/2, and of 25 mmol/l using NS (box 2).

WHY MIGHT KIDNEYS PRODUCE A LIMITED OR FIXED UOSM?
Some children can only produce a dilute urine because of renal disease, including dysplasia (box 2), renal impairment, nephrocalcinosis, nephronophthisis and nephrogenic diabetes insipidus (where the maximum UOsm may be „100 mosmol/kg), or from central diabetes insipidus. The number of children affected may be higher than is generally appreciated, and many will not be recognised until they happen to require intravenous fluids. Most will maintain a normal PNa on N/5, but many receiving N/2 will not.

Sometimes children can only produce a highly concentrated urine, regardless of the PNa. Mostly this is due to the massive release of antidiuretic hormone (ADH) in response to intravascular hypovolaemia, usually because of dehydration. It may also occur in relapsed nephrotics, after haemorrhage, and in septic

shock. Hypovolaemia can induce greater ADH release than can occur with changes in plasma osmolality, so normal kidneys conserve water avidly in shock. Because shock over-rides the hormonal control of plasma tonicity, severely dehydrated children produce small amounts of very strong urine, irrespective of their PNa. If the child's physiology has a conflict between defending the plasma volume and defending the PNa, volume always wins. In parallel, hypovolaemia induces maximal tubular sodium reabsorption by stimulating renin, and thence aldosterone release.

The fact that hypovolaemia may induce ADH secretion, and thereby the production of a concentrated urine in the face of hyponatraemia (which is appropriate for protecting the child's volume status), often leads to the incorrect diagnosis of the syndrome of inappropriate excretion of ADH (SIADH). This should only be diagnosed when ADH is secreted in excess by an extraneous release mechanism, rather than a physiological drive (in this case, the presence of hypovolaemia). True SIADH is very rare, and, in my experience, about 10 cases are falsely diagnosed for each real case. The management is completely different.

Although restoring the circulating volume by rehydration typically reverses the hormone drives that led to a fixed high UOsm, this may take hours; I have seen it take several days in infants. Even infusing maintenance NS during this period will lead to hyponatraemia, and more dilute fluids will lead to profound hyponatraemia, with almost no benefit of substituting N/2 for N/5 (box 3).

A LOGICAL FLUID MANAGEMENT SYSTEM FOR ALL SITUATIONS: THINK LIKE AN ENGINEER
Most paediatricians will prescribe fluids to rehydrate a hypernatraemic dehydrated child solely from knowing the PNa and estimated degree of dehydration. The fluids and rates prescribed will vary, but most will avoid rapid infusions. Mostly, it works, but not always. Try asking an engineer how to manage this situation reliably, and the answer will be very different. First, explain the physiology: a tank of cells is bathed in saline which has become too concentrated, and the level of which has fallen; the challenge is to replenish the volume relatively quickly and correct the concentration slowly and evenly. Water evaporates from the surface, and a tap normally drains out water and salt independently, within defined limits. Some models are faulty and always lose water and salt in a fixed

Box 2 Daily sodium imbalances in a 6-year-old boy with dysplastic kidneys (urine osmolality (UOsm) limited to 200 mosmol/kg) while receiving maintenance intravenous fluids

Weight 30 kg
Daily water intake at 60 ml/kg = 1800 ml
Daily insensible losses at 300 ml/m², and surface area* of 1.0 m² = 300 ml
Urine output needed to maintain water balance = fluid intake – insensible loss = 1500 ml
Non-electrolyte osmolar losses (urea, etc) = 60 mosmol
Maximum UOsm (because of renal dysplasia) = 200 mosmol/kg

Infusing N/5 + 20 mmol/l potassium
Electrolyte intake (and therefore excretion) = 54 Na + 36 K + 90 Cl = total 180 mmol
Resultant UOsm = 60 + 180 = 240 mosmol, in 1500 ml = 160 mosmol/kg
Sodium accumulating, as cannot be excreted = 0 (capacity to excrete 60 mmol/day more)

Infusing N/2 + 20 mmol/l potassium
Electrolyte intake (and therefore excretion) = 135 Na + 36 K + 171 Cl = total 342 mmol
Resultant UOsm = 60 + 342 = 402 mosmol, in 1500 ml = 268 mosmol/kg
Sodium accumulating, as cannot be excreted = 102 mmol/day
Resultant rise in PNa (assuming sodium space of 50%) = 6.8 mmol/l

Infusing NS + 20 mmol/l potassium
Electrolyte intake (and therefore excretion) = 270 Na + 36 K + 306 Cl = total 612 mmol
Resultant UOsm = 60 + 612 = 672 mosmol, in 1500 ml = 448 mosmol/kg
Sodium accumulating per day, as cannot be excreted = 372 mmol/day
Resultant rise in PNa (assuming sodium space of 50%) = 24.8 mmol/l
*Boyd E. The growth of the surface area of the human body. Minneapolis: University of Minnesota Press, 1935

ratio, and, in some, the ratio becomes transiently jammed. Engineers always conclude that it is not possible to ensure a smooth recovery if only the saline level (% dehydration) and concentration (PNa) are known, and that it is essential to know the rate and salt concentration of the tap losses (urine volume and sodium concentration, UNa). With that, they can then guarantee to always manage every situation safely.

This is their solution. First, top the tank up with NS fairly quickly because restoring the fluid volume will provide important benefits and NS will alter the PNa only slightly.

Then, determine the fluid regimen according to the measured salt and water losses, and only use the PNa to assess the results and fine-tune the treatment. If the volume and UNa of the urine lost is matched by the fluid infused (and allowance made for evaporative losses), the system would be "clamped". Infusing fluid with a sodium concentration a little lower than the UNa would allow the PNa to fall gently.

In clinical practice, I would suggest that all dehydrated children requiring intravenous rehydration (usually with NS + 4% dextrose) should have their presenting urine sample

Box 3 Daily imbalances in a 2-month-old girl with a persistently raised urine osmolality (UOsm) of 1000 mosmol/kg despite having been fully rehydrated, now on maintenance intravenous fluids

Weight 5 kg
Daily water intake at 130 ml/kg = 650 ml
Daily insensible losses at 300 ml/m², and surface area* of 0.3 m² = 90 ml
Urine output needed to maintain water balance = fluid intake – insensible loss = 560 ml
Non-electrolyte osmolar losses (urea, etc) = 20 mosmol
Fixed UOsm (because of persistent antidiuretic hormone (ADH) release) = 1000 mosmol/kg

Infusing N/5 + 20 mmol/l potassium
Electrolyte intake (and therefore excretion) = 19.5 Na + 13 K + 32.5 Cl = total 65 mmol
At a UOsm of 1000 mosmol/kg, will be able to produce 65 ml/day urine, so retain 495 ml water
With a total body water of 60%, this will dilute a starting PNa of 140 to 120 mmol/l by 24 h

Infusing N/2 + 20 mmol/l potassium
Electrolyte intake (and therefore excretion) = 49 Na + 13 K + 62 Cl = total 124 mmol
At a UOsm of 1000 mosmol/kg, will be able to produce 124 ml/day urine, so retain 436 ml water
With a total body water of 60%, this will dilute a starting PNa of 140 to 122 mmol/l by 24 h

Infusing NS + 20 mmol/l potassium
Electrolyte intake (and therefore excretion) = 98 Na + 13 K + 111 Cl = total 222 mmol
At a UOsm of 1000 mosmol/kg, will be able to produce 222 ml/day urine, so retain 338 ml water
With a total body water of 60%, this will dilute a starting PNa of 140 to 126 mmol/l by 24 h
*Boyd E. The growth of the surface area of the human body. Minneapolis: University of Minnesota Press, 1935

measured for UNa as well as creatinine concentration (UCr) and UOsm while their plasma biochemistry is being routinely measured, and that they should have their initial urine output measured. If by the time the laboratory results are available, the PNa is normal and the child is voiding well, it is clear that their kidneys are fine, and any fluid regimen would be equally likely to work. If, however, the laboratory results are very abnormal, the ongoing fluid management could be decided on according to the engineers' logical approach, and would be certain to be safe and effective. Note that this treatment does not require any knowledge of, or make any assumptions about, the underlying pathology that led to the disturbed electrolyte status.

This system would correctly lead to a polyuric, dehydrated, hypernatraemic child being treated with a maintenance of just 5% dextrose if their UOsm was only 60 mosmol/kg and UNa only 8 mmol/l, without the need to know that he/she had severe nephrogenic diabetes insipidus. Equally, it would correctly manage an oliguric hypernatraemic child with intravenous maintenance fluid with a sodium concentration of 320 mmol/l (NS + 34 ml/l of 30% NaCl, which contains 5 mmol sodium/ml) because their UOsm was 950 mosmol/kg and UNa was 350 mmol/l. Using either N/5 or N/2 would cause profound hypernatraemia in the first child, and hyponatraemia in the second.

THE RIGHT TESTS TO UNDERSTAND HOW THE KIDNEY IS BEHAVING …

Doctors need to do more than manage the fluids safely; they must also make a diagnosis. To do this reliably in every case, it is necessary to measure the UOsm and the fractional excretions of water (FEH_2O) and sodium (FENa). These are easily calculated from the PNa and plasma creatinine (PCr) and the UNa and UCr of a ''spot'' urine sample taken at about the same time as the blood (box 4). They provide profound insights into how a child's kidneys are handling salt and water.

The FEH_2O is the fraction of the glomerular filtrate volume that appears as urine. In a healthy man with a daily urine output of 1.5 litres and a glomerular filtration rate (GFR) of 150 litres each day, the FEH_2O is 1.5/150 = 1%. If his PCr was 100 mmol/l and his UCr was 10 mmol/l, or 10 000 mmol/l, his FEH_2O is calculated as 100/10 000 = 1%. After heavy drinking, voiding 1 litre per hour would represent an FEH_2O of 1/6.25 litres per hour = 16%, which is close to the physiological maximum. His UCr will have fallen to 625 mmol/l, giving an FEH_2O of 100/625 = 16%.

The FENa is the fraction of the sodium filtered by the glomeruli which appears in the urine. In health, virtually all the

salt eaten each day is excreted in the urine. The sodium filtered is the product of the GFR and the PNa; a man with a GFR of 150 litres/day and PNa of 140 mmol/l will filter $150 \times 140 = 21\ 000$ mmol daily. If his salt intake was 120 mmol, he would excrete 120/21 000 = 0.0057 of the filtered load, or have an FENa of 0.57%. If he ate 600 mmol of sodium daily, he would then need an FENa of 2.85% to remain in balance. For an example of a calculation (box 4), if UNa = 80 mmol/l, PNa = 140 mmol/l, PCr = 100 mmol/l and UCr = 10 000 mmol/l, then FENa = (80/140)×(100/10 000) = 0.57%.

The FE values in health vary because people's water and salt intakes vary; there are therefore no normal ranges. However, under stress, these values respond predictably, so they can be used to understand the pathophysiology. Even mild dehydration causes a release of ADH and renin, and thus avid tubular reabsorption of water and salt, leading to a fall in FEH_2O and FENa. Children with healthy kidney tubules can lower both FE values to ~1%, and often much lower.

By contrast, the UNa cannot be interpreted alone.[2] The UNa falls during dehydration because it is avidly reabsorbed, but rises because water is also avidly reabsorbed, so its final level is unpredictable. Infants with hypernatraemic dehydration have UNa values between 36 and 210 mmol/l,[3] almost identical with dogs dialysed to the same condition.[4] It is widely quoted that the UNa needs to be ~20 mmol/l for hypovolaemia to be diagnosed, but this has no published basis. Thus, UNa is not discriminatory, but FE measurements are.

… AND THEN USING THE TESTS TO MAKE A PATHOPHYSIOLOGICAL DIAGNOSIS

Figure 1 shows an algorithm to determine the pathophysiology of salt and water disturbances. It is not exhaustive, but will apply to most ill children. It starts with UOsm because all dehydrated, hypovolaemic, or hypotensive children produce a concentrated urine if their kidneys are capable of doing so. A low UOsm therefore indicates a failure to generate a concentrated urine. This may reflect chronic problems of the renal tubules (eg, nephrogenic diabetes insipidus, dysplasia) or their hormonal drive (central diabetes insipidus), or acute insults, which may recover (acute tubular necrosis) or be irreversible (cortical necrosis). These can be further distinguished from the history, FENa, and ultrasound appearances.

Most ill children who generate a concentrated urine (UOsm ~600 mosmol/kg) will have compromised renal perfusion, and will therefore be reabsorbing water and salt avidly. Thus, they will have low FEH_2O and FENa values (at least ~1%, often much lower). Sometimes the PCr has only had time to increase a little. The high UOsm and low FE values prove that their renal tubules can function well, and so confirm pre-renal failure. The PNa may be low, normal or high. A low PNa usually means the child had drunk earlier or been given inappropriately hypotonic fluids. A high PNa usually results from diarrhoeal losses containing more water than salt,[5] sometimes exacerbated by dietary supplements.[6] Either way, the immediate treatment is to restore the circulating volume with saline.

Very rarely, children do have SIADH, an increased secretion of ADH which is driven by neither the plasma osmolality nor the circulating volume. For a secure diagnosis, the UOsm and FENa must be high (FENa typically ~3%), and the PNa and FEH_2O low (typically ~1%).

A hypernatraemic child who produces large volumes of a concentrated urine containing lots of sodium (UOsm high, FEH_2O ~1%, FENa ~3%) is excreting a large excess of sodium, and has been salt poisoned.[1]
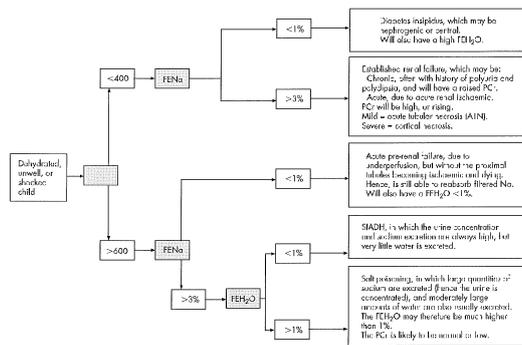
Figure 1 Algorithm to diagnose the pathophysiology of the water and salt balance of unwell children. Note that this is a simplified scheme, and will not apply to every single case; for example, what about the child whose UOsm is between 400 and 600 mosmol/kg, or who has a UOsm of ≥400, but an FENa of 2.9%? However, it defines the vast majority of sick children with fluid and electrolyte disturbances. FEH₂O, fractional excretion of water; FENa, fractional excretion of sodium; PCr, plasma creatinine; SIADH, syndrome of inappropriate excretion of antidiuretic hormone; UOsm, urine osmolality.

HOW SHOULD WE MANAGE CHILDREN IN EVERYDAY PRACTICE?

Most children who require intravenous fluids have simple diagnoses and normal kidneys, do not need complex fluid prescriptions, and will cope with whatever they are given. However, all paediatricians occasionally meet children for whom a diagnostic algorithm to understand the water and salt handling is needed and a tailored fluid prescription. Then, there is no substitute for a logical approach, ideally based initially on pre-intervention measurements and subsequently on ongoing urine volume and UNa measurements.

Practically, I measure UOsm, UCr and UNa on a spot urine and PNa and PCr whenever I start an intravenous infusion on a dehydrated child. Collection pads are reliable for this.[7] Unless I suspect a renal concentrating defect, I start intravenous NS + dextrose in the mean time. Most children then improve clinically, void plenty of urine, and have normal or near-normal PNa and PCr, and no more special attention is needed. In the

Figure 2 Hyponatraemia: algorithm to diagnose the pathophysiology of the water and salt imbalance. In each case, the child produces either no urine or a small amount of concentrated urine, and either continues to take oral fluids or is given inappropriately hypotonic intravenous fluids. Note that this is simplified, but will cover most cases. FEH₂O, fractional excretion of water; FENa, fractional excretion of sodium; PCr, plasma creatinine; PNa, plasma, sodium; SIADH, syndrome of inappropriate excretion of antidiuretic hormone; UOsm, urine osmolality.
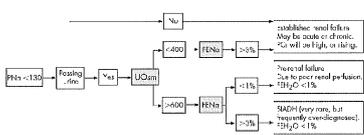
Figure 3   Hypernatraemia: algorithm to diagnose the pathophysiology of the water and salt imbalance. Note that this is simplified, but will cover most cases. FEH$_2$O, fractional excretion of water; FENa, fractional excretion of sodium; PCr, plasma creatinine; PNa, plasma sodium; UOsm, urine osmolality.
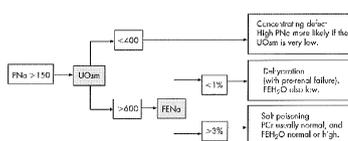
complex cases that do not follow this pattern, having the baseline data allows safe management.

If a urine-concentration defect is known or suspected in a child, I delay starting fluid therapy pending the urgent biochemistry results if this is clinically safe. If not, I only infuse minimal volumes of NS to ensure an adequate circulation. Thereafter, it is reliable and safe to base ongoing fluid management on measured urine volumes and UNa; I know no other way of consistently managing these children safely.

There may be particular circumstances, such as immediately after surgery, when the tendency to ADH release may make N/2 more appropriate than N/5 saline, but this should not lead to a blanket recommendation for all maintenance infusions.

APPROACHING THE DIAGNOSIS AFTER THE PNa IS KNOWN
The most common alarm bell alerting paediatricians to a complex fluid problem is an abnormal PNa. Below, and in figs 2 and 3, I consider making the diagnosis from that perspective.

Hyponatraemia
Children become hyponatraemic after being given relatively more water than salt when they cannot excrete it because they are anuric or are producing a fixed-strength urine. This may be because they have damaged tubules (renal failure) or tubules that are making maximally concentrated urine to conserve fluid volume (pre-renal failure), or, extremely rarely, because of SIADH. Figure 2 shows the diagnostic sequence. Note again the unique findings required to diagnose SIADH.

Hypernatraemia
Children become hypernatraemic because (a) their kidneys cannot make a concentrated urine (low UOsm), (b) they become dehydrated with the loss of more water than salt (predominantly water depletion), or (c) they are salt poisoned (primarily sodium overloaded).[5] Although salt-poisoned children are typically fluid replete from induced thirst, they may be mistakenly thought to be dehydrated if they become generally unwell with poor peripheral perfusion. The diagnostic key (fig 3) is the combination of raised PCr and low FE values in dehydration, contrasting with a normal PCr and high FENa (and often a high FEH$_2$O) in salt poisoning.[5]

SUMMARY
Knowing the PNa, the PCr and degree of dehydration is not enough to reliably diagnose how fluid and electrolyte disturbances have occurred in unwell children. It is sufficient information to manage straightforward cases, but not complex ones, and does not allow logical prescribing of fluids. For complex cases, it is also necessary to measure the initial UOsm, UNa and UCr, and use them to calculate the FEH$_2$O and FENa. Mostly, rehydration can proceed using a variant of NS while the laboratory results are awaited.

In complex cases, subsequent maintenance fluids can be prescribed according to the child's measured urine output and UNa, and fine-tuned by monitoring the PNa, a method that guarantees to be safe, regardless of the type of biochemical and renal dysfunction. In uncomplicated cases, the most appropriate maintenance fluid is 0.18% saline + 4% glucose + 20 mmol/l potassium, because it is closest to the usual oral intake. The suggested change to 0.45% saline has been advised in an attempt to avoid hyponatraemia in a small number of children. However, this is not the best way to prevent this complication. Rather, this should be carried out by paediatricians adopting a fluid prescription formula and diagnostic pathway which will take account of children with disturbed salt and water handling. If half-normal saline is used in the same way that one-fifth-normal saline has been mainly used in the past, without being regulated according to the UNa, I fear that this policy change will result in fewer children developing hyponatraemia, but many more developing hypernatraemia.

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