Today's Treatment

Diseases of the Urinary System

Management of chronic renal failure by dialysis and transplantation

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British Medical Journal, 1977, 1, 1585-1588

Conservative treatment of patients with progressive renal disease often minimises and sometimes postpones the onset of symptoms of uraemia, but death will ultimately occur unless long-term treatment by dialysis is available. The annual death rate from chronic renal diseases in England and Wales is about 125 per million, of which roughly 36 per million fall between the ages of 15 and 55 years.

Over the past decade dialysis units have proliferated throughout the world, and at present there are at least 50 in Britain. Hospital-based haemodialysis alone would provide treatment for only a few deserving patients, a fact that became obvious to some nephrologists in the mid-1960s. Consequently the idea of home dialysis was conceived and was shown to be so successful that in Britain most patients are now treated by self-dialysis in their own homes.

Patients at the extremes of life pose many therapeutic problems that render dialysis treatment difficult. In young children the main problems are related to retardation of growth and sexual maturation, whereas in the elderly degenerative diseases weigh heavily against a successful outcome. Despite these problems, the age barriers are being gradually pushed back and particularly in the case of children continued research into the metabolic problems of renal failure should produce improved results.

The presence of multisystem involvement in which chronic renal failure is but one facet—for instance, diabetes mellitus, systemic lupus erythematosus, etc—used to be considered a contraindication to long-term treatment but with increasing experience such patients are nowadays often accepted for treatment, with encouraging results.

Emphasis must be towards transplantation, for not only is it less expensive than dialysis but it also results in a better degree of rehabilitation. The complete interchange of the two forms of treatment should be the aim, so that if transplantation fails the patients are returned home with minimal delay.

The management of chronic renal failure should be continuous. Sensible diet control undoubtedly contributes to the continued wellbeing of many patients with slowly progressive renal failure, but it may be less effective when function declines rapidly. This decline may be a feature of the underlying disease, but in many cases it may be due to inadequate control of blood pressure, infection, and electrolyte balance or even as the result of drug treatment—for instance, tetracyclines.

Ideally, any patient who is no longer able to lead a normal life because of "uraemic" symptoms should be considered

ready for dialysis. Biochemical abnormalities consistent with his symptoms usually add weight to this decision. In practice, however, though preparation for dialysis is made when the endogenous creatinine clearance approaches 5 ml/min, because of extreme pressure for dialysis spaces patients who remain relatively well may have to soldier on beyond this stage, or be temporarily treated by peritoneal dialysis. Complications, such as uraemic pericarditis and peripheral neuropathy, are absolute indications for starting dialysis as further delay may well result in a dead or permanently crippled patient.

Long-term dialysis treatment was made possible by the development of the arteriovenous shunt by Quinton *et al*¹ in 1960. The modified Kiil artificial kidney was adopted by the Seattle group because it had the advantages of a low priming volume and low internal resistance over existing coil dialysers. Seventeen years later we are using the same basic dialysis principles, though equipment has become more sophisticated and safer so that patients may be trained to dialyse themselves with confidence. Arteriovenous shunts made of Teflon and Silastic rubber, though very simple to handle, unfortunately have a limited life span because of their tendency to clot and become infected, so that the arteriovenous fistula as described by Brescia and his colleagues² in 1966 was a welcome innovation. Expertly created by a surgeon, such a fistula may function for many years without appreciable complications. The standard shunt, however, is still useful in treating children and adults who need prompt haemodialysis, for an arteriovenous fistula ideally needs to be left to develop for several weeks before being cannulated.

Haemodialysis

Haemodialysis is a process of selective diffusion through an artificial kidney membrane of toxic molecules from the blood to a specially prepared dialysate solution. The concentrations of solutes in this solution are much the same as normal plasma with the exception of a low potassium concentration and the absence of phosphate ions. Specially designed proportionating machines are now available that mix a concentrated solution of these salts with softened or deionised tap water to produce the dialysate solution. The concentration of potassium is purposely kept low, and acetate is substituted for bicarbonate so as to avoid precipitation with calcium and magnesium. The resulting fluid is warmed to body temperature, ideally deaerated, and checked for conductivity before being pumped through the artificial kidney. Inside the artificial kidney or dialyser the patient's blood is separated from the dialysing fluid by a thin synthetic membrane, which allows exchange of molecules across it. In this way toxic metabolites from the blood are removed and washed away. Acid-base balance is corrected by the passage across the membrane into the blood of basic anions.

The controlled transmembrane pressure between blood and dialysate allows ultrafiltration of excess water from hypervolaemic patients.

A new approach in dialysate supply has been developed recently. A small volume of prepared dialysate (5.5 l) is continuously recirculated through a sorbent cartridge, which contains layers of active chemicals designed to remove dialysed toxins thus providing a continuous purified supply of dialysate. Unfortunately the system is expensive and running costs are high but it has the advantages of portability, economy of water usage, and needs minimal rearrangement of the room should it be installed in the patient's home.

DURATION OF DIALYSIS

Opinions vary about the ideal duration of dialysis. Nevertheless, most people would agree that dialysis should be performed in such a way and at such a time that it will interfere least with a patient's life and that it should be sufficiently effective to maintain good health, a good haematocrit, and prevent long-term complications such as peripheral neuropathy and renal bone disease. Frequent short dialysis—for example, three hours daily—would keep the concentration of small molecular weight toxins under good control but those who believe in the toxicity of middle molecular weight substances, which are dialysed only slowly, advocate longer and less frequent dialyses. As a compromise most people practice a regimen of six to eight hour dialyses every other night or three times weekly and long-term studies have shown that this is adequate.

CHOICE OF DIALYSER

The ideal dialyser should have a low priming volume, a low internal resistance, good clearance values for small and middle molecules, good ultrafiltration and washback characteristics, low blood leak rate, and a low cost. If it is disposable, all the better.

Many good models are now available, designed on a coil principle, parallel plates, or made of hollow capillary fibres. The high cost of these disposable kidneys precludes their universal use, so that, at least in Britain, many units still use the Meltec Multipoint dialyser, the disadvantages of which are only their size and the need to strip and rebuild them at intervals.

GENERAL MANAGEMENT

Dietary restrictions should be lifted as soon as a patient is established on dialysis. A normal protein intake is allowed to offset amino-acid losses by dialysis and maintain positive nitrogen balance. Calorie intake should be adequate so as to make the most efficient use of protein, but overenthusiastic carbohydrate and lipid intake will induce hyperlipoproteinemia. Electrolyte and fluid allowances must be judged on crude balance studies coupled with a thorough clinical assessment—for example, a hypertensive patient with evidence of fluid retention will need a low sodium intake, and fluid allowance should be judged on his total output. Some potassium restriction is usually necessary. Folic acid and vitamin B supplements are needed to replace dialysis losses. Phosphate restriction is necessary and is a safer method of controlling plasma phosphate than using aluminium hydroxide, but the latter may be needed intermittently. To replace blood losses a total of 2 g of iron are given over the course of a year. Blood transfusions are rarely necessary on dialysis and then only to replace losses due to bleeding.

Periodic monitoring of plasma urea, electrolytes, creatinine, calcium, phosphate, alkaline phosphatase, and proteins concentrations will provide a reasonable idea as to the patient's

metabolic state and the quality of dialysis. Once a patient is stabilised excessive investigations of this sort should be discouraged in order to conserve blood.

COMPLICATIONS OF DIALYSIS

The clinical course of long-term dialysis patients is usually reasonably smooth. Nevertheless, problems arise from time to time.

Dialysis disequilibrium may occur from over-efficient treatment when a very uraemic patient is first introduced to dialysis. Treating patients earlier and careful lowering of uraemic toxin levels by a series of short dialyses or by peritoneal dialysis will avoid this.

Peripheral neuropathy may result from inefficient or inadequate dialysis, but this can often be halted or even improved by increasing the frequency of dialysis. Renal osteodystrophy sometimes worsens and may even develop during dialysis. The use of vitamin D analogues are now available and may improve dietary calcium absorption and bone mineralisation, but careful control of plasma phosphate is necessary to prevent metastatic calcification.

Dialysis osteomalacia has been described in hypophosphataemic patients, and some units have observed a progressive dementia in some of their patients. Both these complications may be related to aluminium hydroxide treatment.

Dialysis alone controls most cases of hypertension, but some patients may need additional hypotensive agents. Despite adequate dialysis about 5% of all patients have severe uncontrollable hypertension owing to high plasma renin activity and may need bilateral nephrectomy.

Septicaemia may result from infection introduced during cannulation of arteriovenous fistulae or from infected shunts. Prompt treatment with appropriate antibiotics is necessary, and revision of the fistulae or shunts may also be needed.

In areas with hard water, failure to soften the water supply to the dialyser will result in acute hypercalcaemia and hypermagnesaemia, causing acute hypertension, tachycardia, vasodilatation, headaches, and vomiting. In some cases the plasma amylase concentration may be increased as a result of the hypercalcaemia.

Air embolus due to inadvertent entry of air into the extracorporeal blood circuit has led to deaths but with modern equipment this complication is rare. In such an emergency, immediate lowering of the head of the bed, turning the patient to the left lateral position, and administering oxygen may be life saving.

Hypotension due to over-ultrafiltration may be corrected by fluid replacement. Patients with uraemic pericarditis should be regionally heparinised to protect them against haemorrhagic effusion with the risk of tamponade. Febrile reactions on dialysis are unpleasant. Usually no bacterial infection in shunts or blood stream can be found and consequently they are attributed to pyrogens. Certainly, organisms may sometimes be isolated from water supplies, and possibly their exotoxins may be responsible. Regular complete sterilisation of the dialysate and water circuits usually eliminates this problem.

Serum hepatitis is a potential hazard in any dialysis unit but careful screening, limitation of movement between units, screening of essential blood transfusions, and isolation of carriers has reduced the incidence almost to nil.

Renal transplantation

Renal transplantation is no longer regarded as experimental and when performed in close conjunction with haemodialysis units it will provide satisfactory treatment. A successful graft will restore patients virtually to normal health, but unfortunately only about half of all cadaver kidneys are capable of this. The

success rate in well-matched related living grafts is considerably superior to cadaver grafts (80%, five-year-graft survival). Unfortunately, in Britain relatives rarely offer to donate kidneys, so that one depends almost entirely upon cadavers.

Well-dialysed patients withstand transplant surgery satisfactorily, and with good anaesthetic administration and careful fluid and electrolyte control mortality is low. It is depressing that after more than 10 years' experience, 30-40% of all grafts are still lost during the first six postoperative weeks from irreversible rejection, infection, or technical problems.

TISSUE MATCHING

In tissue matching ABO compatibility is always observed. HLA typing of recipients may be performed prospectively, but donors have to be typed just before transplantation. Direct crossmatching of donor cells and recipient serum is usually performed to detect cytotoxic antibodies and to avoid second-set rejection. Though the value of HLA matching is not altogether clear in primary renal transplants, an attempt should always be made to select the closest matching pairs for if rejection does occur the range of antibodies induced will be confined to as few specificities as possible. When patients are selected for second grafts previous antigenic incompatibilities will have to be avoided and closer matching will be necessary.

PREOPERATIVE MANAGEMENT

Careful preparation of patients for transplantation surgery is essential to minimise postoperative risks.

(1) Infection should be eliminated so far as possible. Particular care of the skin, teeth, and upper respiratory and urinary tracts should be taken. Patients with chronic infection such as bronchiectasis or tuberculosis may cause considerable problems in the face of immunosuppressive treatment and are best excluded from transplantation.

(2) Barium meal and enema examinations should be performed to detect peptic ulcers or diverticular disease. A penta-gastrin test may be an additional investigation worth doing.

(3) Skeletal surveys and studies of calcium metabolism should be done to assess the parathyroid state.

(4) Careful control of hypertension is essential.

(5) Investigation of the lower urinary tract should be performed to assess bladder neck function and to detect ureteric reflux.

(6) Cervical smears should be examined.

Appropriate surgical correction of gastrointestinal tract abnormalities, the removal of infected, refluxing kidneys and ureters, and gynaecological problems should be dealt with before transplantation.

CADAVER DONORS

The ideal kidney donor should have a normal blood pressure and renal function before death, be aged from 10 to 50 years, and should not have suffered a long period of premortem hypotension. Evidence of localised or generalised antemortem infection should be regarded suspiciously and treated energetically if time allows. Many donors result from road traffic accidents and time for assessment of function is not usually available so that much will have to depend on the appearances of the kidneys on removal and their perfusion characteristics assessed by the surgeon. Patients dying of cerebrovascular accidents or cerebral tumours may often be suitable donors, but those with extracranial tumours should never be considered. Evidence of pre-existing renal disease should naturally exclude the potential donor.

The time from circulatory arrest to removal and perfusion of

the kidneys should be as short as possible and certainly not longer than one hour. Permission for kidney removal from next of kin or coroner, or both, is essential, and this may take considerable time in unexpected death. Many suitable organs are inevitably lost because permission is unobtainable in this limited time. Cold perfusion will retard metabolic deterioration of the organs so that time is available to prepare suitable recipients once the kidneys have been cooled.

If living related donors are considered normal, renal function, blood pressure, intravenous urography, and renal arteriograms are mandatory. HLA identity and a negative mixed lymphocyte reaction are desirable for the best results.

THE OPERATION

The actual transplant operation is now a relatively routine procedure, the kidney being placed extraperitoneally in one or other iliac fossa. The vascular connections are made between the renal vessels and the iliac vessels and the ureter implanted into the bladder through a submucosal tunnel.

IMMUNOSUPPRESSIVE TREATMENT

Corticosteroids and azathioprine are usually started at the time of operation. Dose regimens vary but moderately large doses of steroids are usually given initially (100-200 mg prednisone) and are gradually reduced to a maintenance dose of 10-20 mg per day. Azathioprine is given in the highest possible dose tolerated by the individual as judged by the leucocyte and platelet counts. Doses are curtailed when renal function is poor. Antilymphocyte globulin is used by some departments.

Rejection episodes are treated by increasing the steroid dose temporarily with or without the addition of actinomycin D, cyclophosphamide, and sometimes local irradiation.

COMPLICATIONS

The complications of transplantation are related to four main factors: (a) the quality of the donor kidneys, (b) technical problems at operation, (c) graft rejection and (d) immunosuppressive drugs.

In the early postoperative period a degree of ischaemic renal failure is not uncommon. Diuresis follows within one to three weeks unless other complications supervene. Acute rejection, unfortunately, often occurs during this oliguric period and may be difficult to diagnose with certainty. Other complications such as ureteric obstruction or leakage and vascular thrombosis may be masked and should always be remembered. Dialysis treatment with regional heparinisation must be continued during this period and constitutes a further potential hazard. When immediate diuresis occurs, complications are more easily diagnosed, for any deterioration in urinary output and renal function can be immediately investigated.

We have found percutaneous needle biopsy to be a relatively safe and reliable investigation in cases of suspected rejection.³ The histological changes of acute rejection are well known and include: (a) mononuclear cell infiltration, (b) interstitial haemorrhage, (c) arterial and arteriolar necrosis, and (d) glomerular thrombosis and necrosis.

When the immunological reaction is aggressive and severe vascular changes are seen, there is little hope of success with present antirejection treatment, so that the graft should be removed and the patient re-established on dialysis.

Repeated high doses of immunosuppressive drugs may lead to dangerous complications. These are principally infective in nature and may be due to bacterial, fungal, viral, or protozoal organisms, often complicated by bone marrow depression. Treatment is difficult for specific chemotherapeutic agents such

as amphoterecin B and pentamidine can be toxic. Immunosuppressive drugs may have to be withdrawn.

Gastrointestinal complications may be extremely serious because of exsanguination and infection, and need prompt surgical intervention. Ureteric obstruction or leakage also demand prompt and expert surgical correction. Localised or systemic infections sometimes lead to rupture of the vascular anastomosis with consequent loss of the graft.

Further, though less dramatic, complications of treatment include Cushingoid features, hirsutism, diabetes mellitus, erythraemia, pelvic lymphocoeles, and steroid psychosis.

Later complications develop several months or years after successful grafting and include alopecia, thinning of the skin, recurrent infections, myopathies, hyperlipidaemia, osteoporosis, avascular necrosis of weight-bearing joints, cataracts, glaucoma, and neoplastic diseases.

Despite these many complications, a considerable number of patients benefit from successful renal transplantation. Although 40-50% of kidney transplants fail during the first six months, the rate of loss of function after the end of the first year is slow, and in our series 20-25% are still functioning at 10 years. Three of our women patients have had normal babies since transplantation and six of the men have successfully fathered normal children. As the combination of dialysis and transplant treatment has improved over the years, so has the survival of

patients. The long-term life expectancy from combined treatment of patients with chronic renal failure is currently above 70%.

To treat more patients economically in the future, home dialysis and transplantation units must continue working closely together with a greater emphasis on transplantation. More donor kidneys both from living relatives and cadavers are desperately needed. A change in the law regarding cadaver donation may well help to solve the problem of donor shortage. Immunosuppressive treatment has not improved for over 10 years, furthermore one must strive to improve immunological methods of selection since HLA matching as such has not contributed as much to graft acceptance as was originally hoped. Multicentre sharing of kidneys as practiced by the National Organ Matching and Distribution Service, Eurotransplant, etc, theoretically should help to ensure better HLA matching, but this has to be weighed carefully against the possible disadvantages of increasing ischaemic time intervals.

References

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Clinics in General Practice

A case for the gynaecologist?

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British Medical Journal, 1977, **1**, 1588-1590

The trainee's problem

The patient is 31 and has two children aged 9 and 7. She was sterilised after the birth of the second child and has no regrets about this. Her husband is a foreman joiner and so far as we know there are no material family problems.

The problem is of deciding management of a three-year history of low bilateral abdominal pain that has occurred almost every day for periods of sometimes several hours at a time. The pain is constant, eased by paracetamol, and not apparently related to any specific event. It rarely but occasionally occurs through the night and when it does it prevents sleep. The patient has been investigated already at the surgical outpatient department, where the only abnormality noted was an enlarged uterus on ultrasound examination. The surgeon recommended her referral to a gynaecologist six months ago but the patient

did not come to see us over the summer when her children were at home.

She is back wanting help. She has heavy but regular periods and a periodic offensive vaginal discharge. (Vaginal swab grew a normal vaginal flora with some coliforms present.) She is "allergic" to penicillin, and a week's treatment with co-trimoxazole has succeeded only in adding nausea to her other symptoms. She is genuinely tender in both iliac fossae.

Last week she looked and admitted to being depressed. She says she is depressed because of the pain and not the other way round. I feel inclined to believe her and not start psychotropic drugs—which could easily become long-term treatment—but equally feel referral to a gynaecologist is passing the buck. I don't really see what he could do as the symptoms do not really suggest gynaecological disease to me. How much should I be influenced by the ultrasound findings (which don't seem reflected by much abnormality on clinical examination) and surgical advice (which appears to reflect lack of anything better to suggest).

General practitioner's comments

Some patients and their problems fill me with anxiety even when they are not in my care. Such a case has just been described. There is a feeling of despair in the doctor and dependency in the patient, with a pattern of chronicity that forbodes ill for the future. I wonder if this is the type of case

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