

Special Features

Special feature on the occasion of the 25th anniversary of *NDT*

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Introduction

The first issue of *NDT* was published in 1986, so we are very pleased to present you this anniversary issue celebrating the 25th anniversary of our journal.

Nephrology, Dialysis, Transplantation, as the journal was called in those days, now abbreviated to *NDT*, is the official journal of the European Renal Association/European Dialysis Transplant Association (ERA/EDTA).

Spanning these 25 years, four Editors-in-Chief have served the journal. Instead of writing a rather 'traditional' historical overview of the journal, we asked our publisher, Oxford University Press, to provide us with the five most cited *NDT* papers in each editorial period. Each editor then summarized these papers and put them in the context of later developments in the relevant areas. We also tried to

explain why these papers received such a high citation number and how they may have contributed to improving the care of our patients suffering from kidney diseases.

We believe that these four contributions reflect the importance of *NDT* not only as a leading European but also as a truly major international journal in nephrology. We hope that our readers will enjoy reading these short papers as much as we all enjoyed writing them.

At this occasion, the editors also want to express their sincere thanks to all the authors, reviewers, editors and readers of *NDT* for their interest in the journal. We also wish to acknowledge the continuous support over all these years of the ERA/EDTA council, the collaborators in the respective editorial offices and our publisher, OUP.

Ad multos annos, *NDT* and *NDT Plus*.

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The five most cited *NDT* articles from 1985 to 1993

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The five most cited *NDT* articles from 1985 to 1993

¹Raine AEG, Margreiter R, Brunner FP et al. Report on the management of renal failure in Europe, XXII, 1991. *NDT* 1992; 7 Suppl. 2: 7–35 (285 citations, end 2009)

²Hasslacher C, Ritz E, Wahl P et al. Similar risks of nephropathy in patients with type-I or type-II diabetes-mellitus *NDT* 1989; 4 (10): 859–863 (176 citations, end 2009)

³Schillinger F, Schillinger D, Montagnac R et al. Post catheterisation vein stenosis in haemodialysis: comparative angiographic study of 50 subclavian and 50 internal jugular accesses *NDT* 1991; 6 (10): 722–724 (175 citations, end 2009)

⁴Sundal E, Kaeser U Correction of anaemia of chronic renal failure with recombinant human erythropoietin: safety and efficacy of one year's treatment in a European multicentre study of 150 haemodialysis-dependent patients *NDT* 1989; 4 (11): 979–987 (152 citations, end 2009)

⁵Neumayer HH, Junge W, Kufner A et al. Prevention of radiocontrast-media-induced nephrotoxicity by the calcium-channel blocker nitrendipine: a prospective randomised clinical trial *NDT* 1989; 4 (12): 1030–1036 (135 citations, end 2009)



Introduction

The change from the Proceedings to a Journal

The European Dialysis and Transplant Association (EDTA) was founded in 1964 in response to the expansion of dialysis and transplantation in the treatment of what was referred to at the time as end-stage renal failure. At a meeting on acute renal failure and its treatment by dialysis, held at the Royal Free Hospital in London, it was suggested that an association be formed relating to dialysis therapy, and this was later expanded to include transplantation. It was therefore in the following year that the three co-founders, Willem Drukker, David Kerr and Stanley Shaldon, established the EDTA and the subsequent annual meetings of members to exchange experiences and ideas. The presentations at the meetings were published as the Proceedings of the European Dialysis and Transplant Association (*Proc EDTA*) and during the early phase articles were either in English or French, and the comments made in free discussions were included until the publication of Volume VI in 1969. Over the years, the size of the publication increased year for year until in 1985 the Proceedings had become a volume of 1284 pages including 187 papers, 11 guest lectures, 9 reports from workshops and the annual report from the adult and paediatric registry. All the papers were edited for uniformity of style and language, typeset, proof read, printed, and published in less than 6 months from the end of the annual congress. This was unsustainable, and the Council of the Association determined to change the format to a journal from 1986, and thus *Nephrology Dialysis Transplantation* was established.

The first volume consisted of six issues composed of papers on nephrology, dialysis and transplantation, hence the name of the journal which quickly became known as *NDT*. As the change to a more structured journal had been widely

discussed, there was no shortage of papers to be considered for inclusion in the new journal. As with the previous *Proc EDTA*, the registry reports were published as were the accepted abstracts for the annual congresses. There were many difficulties to overcome including the composition of the editorial board—there needed to be a wide spread of expertise and, for a European Association, adequate geographical representation. A major problem was to gain acceptance for inclusion in ‘Current Contents[®]’, but the initial proposals were rejected as the journal was reported to have ‘no geopolitical influence’ and the editorial board was considered to be composed of unknown people (here I am being polite by not using the actual phrase used!).

It is interesting to look back and try to consider why particular papers were accepted and why some achieved significant citation. It is always difficult to look back, but on an occasion such as this, it is well worthwhile, as such retrospection serves as a reminder of how much has changed and how much progress has been made—usually in small steps rather than any giant leap forward. It is also interesting to see how the style of the papers has changed. Twenty-five years ago there was a fairly rigid structure to scientific papers, which now look somewhat stilted and constrained, but that was the style of the time. This is very much a personal recollection of the papers and of nephrology at the time of publication. I have not listed references, as anyone interested can easily find these in the original articles.

Registry report

Report on the management of renal failure in Europe, XXII, 1991

The early volumes of *Proc EDTA* contained details of activity in centres throughout Europe. The first report on regular dialysis treatment throughout Europe involved 65 centres and included such data as the number of patients accepted for treatment (277) and the number of patients ‘expired while on RDT’ (regular dialysis treatment) (117). The registry was established in 1970 by Willem Drukker and subsequently published annual reports as the Combined Report on Regular Dialysis and Transplantation in Europe which gave valuable information regarding the number of treatment centres, acceptance rates, modes of therapy and survival of patients in the countries involved in the EDTA. These annual reports provided valuable information for the development of renal failure services as well as useful data on specific conditions.

The report did not go through a stringent review process as it was the policy of the EDTA Council that such reports were an integral part of the activity of the Association to which members contributed and had a right to benefit. This does not imply that the reports were not carefully written nor of lesser scientific value—quite the contrary, they were carefully written and subjected to the very careful scrutiny of the Registry committee. The report for 1991 is of value as it provided demographic information to service planners and specific information to clinical providers.

The demographic data was obtained from 73% of the 2541 known dialysis centres throughout Europe. This in-

licated an increasing acceptance rate, mainly of elderly patients, and there was no evidence of a steady-state situation. Not all countries had similar acceptance rates indicating a degree of selection. Bicarbonate dialysis was on the increase. Erythropoietin was by 1991 an established therapy in ~33% of patients. Although use varied considerably between countries, being >77% of patients in Belgium but much less in the UK, Germany and France, this may have been a reflection of differing reimbursement policies. There was an increase in testing for hepatitis C infection, but <50% of the centres were testing all or most of their patients. The report indicated a wide variation in the incidence of hepatitis C with an incidence of ~50% of patients in Poland whilst in the region of 2% in the UK. There were significant differences in the modes of therapy throughout Europe with the UK having twice as many patients on CAPD than any other country. Again, this may have been a reflection of financial policies.

The report of 1991 also contained the results of specific studies of value to the practising clinician. Cardiovascular disease was widespread in the dialysis patient population, but there was significant geographic variation in the incidence, being three to four times more common in the UK than Italy. In Northern Europe, there were also variations with Finland having a much greater incidence than Norway or the UK. Hypertension was the subject of a specific questionnaire employing a random sample of 5% of the dialysis patients. This showed that bilateral nephrectomy was diminishing, although it had been undertaken in 38% of patients in Norway, a practice which nowadays, I suspect, is rare.

There was a report on pregnancy which indicated that, in general, gestation was shortened with 56% of pregnancies being delivered at <37 weeks. Interestingly, perinatal mortality was similar to the general population with a similar gestational age. In transplant patients, there did not appear to be any increase in the incidence of congenital malformations, although the duration of gestation and birth weight was markedly influenced by graft function.

This report followed along the lines of previous reports from the registry and provided much useful information. The highlighting of differences in provision and practice between the European countries served a very useful purpose in that it made countries and individual centres examine their practices critically, thereby improving the management of patients with end-stage renal failure. This aspect of the registry is a continuing valuable function.

Diabetes mellitus

Similar risks of nephropathy in patients with type I and type II diabetes mellitus

The accepted teaching for many years was that the risk of developing the disabling microvascular complications of long-term diabetes mellitus was much less in those patients with type II diabetes mellitus when compared with those with type I. The concept was that juvenile onset insulin-dependent diabetes was type I and the late-onset oral hypoglycaemic controlled type was type II. In general, it

was considered that patients with the former type were more liable to experience the vascular complications such as retinopathy and nephropathy whereas those with the latter type were less likely to develop such pathology, although it was known for many years that patients with type II could progress to renal failure. The belief was that renal disease was more benign in type II when compared with type I. The expansion of dialysis facilities, however, and the findings of the EDTA Registry indicated that a significant number of patients commencing dialysis had an underlying aetiology of diabetes, and the majority was on insulin, suggesting support for the greater risk in type I patients. It was found that although most were on insulin, not all had a diagnosis of type I. This prompted this careful single-centre study of the incidence of nephropathy in patients attending an outpatient clinic over a 15-year period from 1970 to 1985.

There were 496 type II patients with no proteinuria or elevation of serum creatinine at the time of the first visit. Type II was defined as age at the time of diagnosis of greater than 40 years and treatment for at least 2 years with diet alone or in combination with oral hypoglycaemic agents. The diagnosis of nephropathy was based on persistent proteinuria (four consecutive urine samples over a 6-month period) in the absence of any other detectable renal disease such as infection and the absence of cardiac failure, cirrhosis or other systemic diseases. The study was therefore carefully designed to ensure accuracy of diagnosis and exclude other causes of renal impairment which is particularly important in the elderly population.

The findings indicated that the cumulative risk of nephropathy and the evolution of renal failure is similar in patients with type II or type I diabetes mellitus, in spite of the fact that the onset date of the disease is much easier to determine in type I disease than in type II. It is a most interesting finding that once nephropathy is detected, the progression is remarkably similar in both groups of patients.

The findings of the study were valuable to nephrologists planning dialysis provision, as it was becoming obvious that type II diabetes was an increasing problem due to increasing incidence of obesity in the general population. In addition, there were implications for those providing diabetic services as it demonstrated the importance of screening all patients with diabetes for renal disease instead of concentrating mainly on those with type I disease.

Vascular access

Post-catheterisation vein stenosis in haemodialysis: comparative angiographic study of 50 subclavian and 50 internal jugular accesses

Repeated and effective vascular access is a prerequisite for successful haemodialysis. When first introduced, vascular access was achieved by cut-down cannulation of the peripheral arteries and veins. This was very successful for short-term treatment, and particularly suited to the management of acute reversible renal failure, but quite unsuitable for the long-term management of chronic irreversible renal failure. Such procedures resulted in loss of vessels and, as there are

limited suitable sites in the limbs, it was possible for patients to reach the point where vascular access was no longer viable. The introduction of the teflon-silastic shunt was a significant advance in vascular access, but this also was found to have a limited lifespan. In many patients, infection and/or repeated thrombotic episodes destroyed the vessels and resulted in a search for suitable access technology. A variety of artificial vessels were developed including umbilical veins and synthetic materials. All had significant disadvantages. The development of the arteriovenous fistula was an improvement which provided significant benefit to many patients and was very quickly adopted as the access of choice for the majority of patients.

The arteriovenous fistula had a major drawback in that it takes time for the venous drainage to dilate and arterialise sufficiently to make it suitable for repeated vascular access puncture; therefore, it must be established prior to haemodialysis becoming necessary. This is now standard practice in those patients known to have deteriorating renal function, but there are many patients who are referred late to the nephrology service and who require dialysis as a matter of some urgency. In these situations, there are a number of options: insertion of a shunt, peritoneal dialysis, vascular access using repeated puncture of a major vein, or the insertion of an indwelling venous catheter. For many, the latter was the method of choice as it preserved limb vessels for the formation of an arteriovenous fistula.

The site of choice in many instances was the subclavian vein as the catheter could be strapped to the chest and thereby hidden from view. In addition, the subclavian vein was usually easy to cannulate. Once the patient was established on treatment, an arteriovenous fistula could then be formed as a planned procedure, and once developed, the cannula could be removed, and the fistula used.

In a number of patients, following fistula formation, oedema of the arm developed if the fistula had been inserted in the ipsilateral arm to the subclavian cannulation. The cause of this was stenosis or thrombosis of the subclavian vein at or around the area of the cannula puncture. Once a fistula had been formed, the increased blood flow resulted in increased arm venous pressure if there was any restriction to centripetal blood flow. This varied from minor oedema to massive swelling and the development of collateral venous drainage.

The study of Schillinger *et al.* was carefully conducted with the angiographic examination of 50 patients in whom the subclavian-brachiocephalic vein had been used for catheter access and a further group of 50 patients in whom the internal jugular had been used. The groups were similar in all other respects. The results revealed a stenosis in 42% of patients in whom the subclavian vein had been cannulated and only 10% in the internal jugular group. This demonstrated the superiority of the internal jugular vein, as stenoses were less frequent, but also where stenoses developed there was no resulting limb oedema.

Many patients are referred late for dialysis treatment for a wide variety of reasons. This paper provides sound basis for management by the use of an internal jugular catheter as temporary vascular access until an arteriovenous fistula can be formed and allowed to develop. This is significant

for the reduction of patient morbidity, and thus of value to both clinicians and their patients.

Anaemia and erythropoietin

Correction of anaemia of chronic renal failure with recombinant human erythropoietin: safety and efficacy of one year's treatment in a European multicentre study of 150 haemodialysis-dependent patients

Anaemia in patients with chronic renal failure is a major cause of morbidity. The aetiology of the anaemia is multifactorial including dietary factors, impaired production of erythropoietin, a possible reduced effect of erythropoietin, reduced red cell survival and, for patients on haemodialysis, the small repeated blood loss to the dialyser at each treatment session. Prior to the cloning of the gene for human erythropoietin and the subsequent availability of recombinant erythropoietin (r-HuEPO), many patients endured an haemoglobin level consistently in the region of 6 g/dL.

Treatment strategies mainly revolved around ensuring an adequate supply of iron, either orally or intravenously, and essential vitamins. Attempts to increase endogenous erythropoietin secretion included cobalt and androgens, but these measures were not particularly successful, and androgens were associated with unacceptable side effects in many patients. Repeated blood transfusion was an option, but this was at a time when tissue typing was in its infancy, and there was the distinct possibility of the resulting sensitivity limiting further transfusions and seriously impairing the chance of successful transplantation in addition to the risk of iron overload.

The development of r-HuEPO paved the way in alleviating the anaemia of chronic renal failure and significantly enhancing the lives of patients on dialysis therapy. There were problems with the introduction of this potentially effective therapy including costs and the development of safe and effective treatment regimens. The paper of Sundal and Kaeser reported on a Europe-wide multi-centred industry-funded (Cilag) study of intravenous r-HuEPO. Twelve centres in six countries contributed 150 patients, and the study was open-label and non-randomised. It is interesting to note the small number of patients and the relatively large number of centres reflecting how little was known about the clinical use of r-HuEPO. Furthermore, there were 37 patients who dropped out of the study, mainly as a result of transplantation, but one developed uncontrolled hypertension, three had seizures and one dropped out due to myocardial infarction. This experience was similar to that which other centres found in the initial stages of r-HuEPO introduction.

r-HuEPO was effective in the correction of anaemia and, not surprisingly, those with more severe anaemia required larger doses and longer treatment time to achieve correction (as defined by an Hb of 10–12 g/dL).

r-HuEPO was considered to be safe, but 48 of the 150 patients experienced 104 hypertensive episodes as defined by an increase in or introduction of anti-hypertensive medication. It did not appear that the hypertension was

causally related to the rate of correction of anaemia. Significantly, a number of patients experienced clotting problems with their vascular access.

This study was helpful to clinicians in as much as it demonstrated the relative safety of r-HuEPO and the need for dose titration and a careful monitoring of blood pressure. In addition, it showed that once the anaemia was corrected, as defined, the frequency of administration could be reduced to twice weekly. Furthermore, it drew the attention of clinicians to the fact that there may be a need to increase heparin during dialysis sessions, that vascular access may be compromised and that allergic reactions did not seem to be a problem. Thus, it was helpful to the more widespread introduction of r-HuEPO to dialysis centres and resulted in a significant reduction in the morbidity of patients.

Radiocontrast media-induced nephrotoxicity

Prevention of radiocontrast media-induced nephrotoxicity by the calcium channel blocker nitrendipine: a prospective randomised clinical trial

The increasing use of radiocontrast in the investigation of vascular and other pathologies paved the way to the introduction of techniques such as percutaneous vascular dilatation. However, it was recognised that there was a risk to such investigations and, particularly, to the development of renal injury which could be seen clinically as an acute reduction of the glomerular filtration rate varying from relatively transient and asymptomatic to the development of oliguric renal failure. The mechanism was poorly understood but was considered to be a combination of the direct toxic effects on tubular cells, as evidenced by increased urinary enzyme excretion and alterations to renal haemodynamics with prolonged vasoconstriction. A number of risk factors were identified including pre-existing renal insufficiency, diabetes mellitus, paraproteinaemia and dehydration. Such conditions were frequently present in patients who required radiocontrast investigations and so attention was directed towards the ways and means of reducing the risk of post-contrast acute renal failure.

It was thought that the development of alternative radiocontrast media such as non-ionic and low-osmolality preparations would suffice, but this did not prove to be the case. This prompted investigations into other ways in

which adverse renal effects could be ameliorated. Calcium channel blockers could reduce renal vasoconstriction and had the added advantage of inhibiting intracellular calcium uptake, and it was considered that these two mechanisms could be beneficial in reducing post-contrast ischaemic acute tubular necrosis.

Neumayer *et al.* carefully undertook this prospective randomized double-blind study of 35 patients. The patients did not have a primary diagnosis of renal disease, and renal function was measured by exogenous inulin clearance. The results of the study demonstrated that the prior administration of the calcium channel blocker nitrendipine was accompanied by less reduction in the glomerular filtration rate and less enzymuria (gamma-GT, AAP and beta-NAG) than in control patients.

This study therefore demonstrated a safe, effective and inexpensive way of reducing the possibility of renal injury in patients undergoing radiocontrast studies. It was, therefore, of significant clinical value to both radiologists and nephrologists and provided safer patient investigation as well, particularly in the elderly and those with diabetes mellitus and/or vascular diseases.

Final thoughts

The five papers in this review are the ones most commonly cited from *NDT* that were published during my tenure as Editor-in-Chief. One should ask: 'Where do they stand now?' and 'Are they still relevant to today's practice?' The answer is probably yes and no. The registry report remains a snapshot of renal replacement at a particular time. It is now widely accepted that diabetes mellitus type I and type II are more similar than what was previously accepted; vascular access remains a problem in some patients, and the guidelines of Schillinger *et al.* remain of value. Erythropoietin is a cornerstone of therapy with well-established regimens, and radiocontrast is much safer, while post-contrast acute renal failure is a rarity. Thus, these five papers still stand the test of time and reflect the practice of 20 or so years ago. *NDT*, with its editorial practice, will, no doubt, continue to provide information of value to clinicians, to researchers and, most importantly, to patients whose treatment will be enhanced by the results of the research published within its pages—long may it continue to do so.