The five most cited NDT articles from 1993 to 1999

Eberhard Ritz

Dept. of Nephrology, University of Heidelberg, Heidelberg, Germany

Correspondence and offprint requests to: Eberhard Ritz; E-mail: prof.e.ritz@t-online.de

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Introduction

Prior to 1986, the European Renal Association/European Dialysis and Transplant Association (ERA/EDTA) had published for several years the presentations at its annual meetings in the format of ‘Proceedings of the European Dialysis and Transplant Association’. As time went by, it had been increasingly felt, however, that this format was no longer adequate to reflect the depth and breadth of renal research in Europe. Therefore, the society decided to start a journal. After long discussions, it was named: ‘Nephrology, Dialysis, Transplantation’. This title was felt to reflect the main targets of clinical research on the kidney in Europe. In its fledgling years—and even during its puberty when I was in charge, assisted by my successors Tilman Drueke and Norbert Lameire—NDT had to fight one handicap that was devastating for the impact on the renal community: only few libraries across the Atlantic had NDT on their shelves. It was not available in most libraries outside of Europe, and as a result, it was not widely read outside Europe. Consequently, its impact was limited. In discussions with the ERA/EDTA executive committee, the editorial team adamantly insisted that, under these circumstances, the impact factor was certainly not an adequate criterion to evaluate scientific standing and the clinical importance of our journal.

During the years as Editor-in-Chief, I was not at all discouraged by the impact factor issue because I was absolutely convinced that we produced a high-class journal. It
was at that time, beyond our reach to spread the contents of our journal worldwide; but this problem was eventually overcome by the electronic revolution and the ensuing easy accessibility via PubMed.

Another problem faced by the editor was the limited familiarity of many European and non-European authors with the English language; this forced us to offer linguistic improvement by a native English speaker whom we had hired. More than once, I had to implore the authors to send me their contribution in their language which I then translated into what I believed was decent English.

I have been asked to comment on the five most cited articles during my tenure as Editor-in-Chief. Although we are aware that the most cited articles are not necessarily always the scientifically most valuable ones, nonetheless, they certainly serve as barometers to indicate what the most controversial issues were or the most highly relevant issues for the understanding and management of kidney disease during this time period. These five most quoted articles certainly reflect ‘hot’ issues during this period when in clinical nephrology, dogmas were challenged, and the basis was laid for much of today’s understanding of kidney disease. It is of interest that four of the five papers came from Europe: in the early years, ND7 was almost entirely, for the aforementioned reasons, an exclusively European journal. Part of the explanation, however, is that this Euro-centric sample reflects the fact that on the ‘old continent’, clinical nephrology had been on a very high level.

Outcome and risk factors for left ventricular disorders in chronic uraemia

Nowadays, the prognostic importance of the results of echocardiographic evaluation of the heart in dialysis patients is baseline knowledge for first-year nephrologists, but it was only in 1996 that Parfrey et al. provided the evidence for this in a widely quoted (269 times) prospective multicentre study. In retrospect, it is amazing that until 1996, only two poorly controlled studies reporting echocardiographic findings in dialysis patients had been available. Parfrey and collaborators followed a cohort of 432 patients with end-stage renal disease who survived at least 6 months on dialysis. The patients were treated in university centres; they received 5.2 transfusions per year at the start of the study and later EPO became available. The patients received 1.2 ± 2.1 antihypertensive agents, most frequently calcium channel blockers, followed by beta-blockers, ACE inhibitors, and centrally acting agents. Cardiac morphology and function were assessed by echocardiography, using M-mode and two-dimensional ultrasonography at baseline and on average 18 months after start of dialysis. At the end of the study, the results were related to outcome. The dialysis patients were categorized according to presence or absence of left ventricular (LV) hypertrophy, LV dilatation (with or without LV hypertrophy) and systolic dysfunction.

The study of Parfrey et al. documented that only 16% of the 462 patients had normal echocardiograms at the start of ESRD therapy. No less than 16% had systolic dysfunction (low fractional shortening of the left ventricle), 41% had concentric LV hypertrophy and 28% had LV dilatation (the authors wisely acknowledged the difficulty in distinguishing hypervolaemia from cardiogenic LV dilatation).

The main observation was the finding that by echocardiography, a close correlation exists between cardiac morphology and function on the one hand and survival on the other hand:

- The median time to development of heart failure was 19 months in patients with systolic dysfunction, 38 months in patients with concentric LV hypertrophy and 38 months in patients with LV dilatation.
- The median survival was 38 months in patients with systolic dysfunction, 48 months in patients with concentric hypertrophy, 56 months in patients with LV dilatation and 66 months in patients with normal echo findings.

Not surprisingly, the degree of concentric LV hypertrophy on follow-up was independently related to hypertension, older age and anaemia, while LV dilatation was related to ischaemic heart disease, anaemia, hypertension and hypoalbuminaemia; finally, the degree of systolic dysfunction was associated with ischaemic heart disease and anaemia during follow-up.

This was a pioneer study which directed the attention of nephrologists to the heterogeneity of cardiac morphology and function.

Predictive value of dialysis adequacy and nutritional indices for mortality and morbidity in CAPD and HD patients. A longitudinal study

The frequent occurrence of dialysis inadequacy and poor nutritional status and their impact on patient survival motivated Maiorca et al. to perform this 3-year prospective comparative study of CAPD and HD patients which was widely taken note of and cited 195 times. At that time, many investigators struggled to identify predictors of patient survival in order to optimize treatment quality. There was also a religious belief in the validity of Kt/V—such enthusiasm has diminished in subsequent years.

The authors included 68 CAPD and 34 haemodialysis patients who were followed up for 3 years. The study enrolled new patients but—somewhat interfering with the strictness of the protocol—also patients already on dialysis for 3–120 months. The aim of the study was to quantify age and 13 pre-treatment risk factors, e.g. serum albumin, transferrin, normalized protein catabolic rate, Kt/V, residual renal function (weekly Ccr) and subjective global assessment of nutritional status as well as morbidity and survival. In this small study of relatively short duration, survival did not differ between CAPD and HD, i.e. the Kaplan–Meier survival curves were not different for CAPD and HD, but in the early months of treatment, residual renal function was still relatively well preserved.

Cox hazards regression analysis revealed age, peripheral vascular disease, low serum albumin (<3.5 g/dL), and Kt/V <1.0 on HD and <1.7/week on CAPD as independent factors adversely affecting survival. Of note, gender, treatment modality (at least in this short-term observation),
normalized protein catabolic rate and subjective global assessment of nutritional status were not predictive. Confirming other studies, persistence of residual renal function was associated with significantly improved survival.

The authors questioned the validity of serum albumin as a marker of nutritional status because conflicting results had been obtained in cross-sectional studies, and they stated that their own data as well raised doubts concerning the validity of albumin as a direct marker of nutritional status. This concern has been fully vindicated by later observations that serum albumin is, to a large extent, also a reflection of inflammation. Serum albumin was predictive in the study of Maiorca et al., but the significance was lost when survival was adjusted for age and co-morbid conditions. Based on the results of this small study, the authors made the then heretical statement that the relationship between Kt/V and PCRN was the result of a mathematical artefact. Interestingly, neither serum albumin concentration, percentage of malnourished patients, hospitalization days nor patient survival differed between patients with low and high PCRN. The study was too small to give definite answers but served as an important catalyst to abandon simplified concepts.

Longitudinal changes in peritoneal kinetics: the effect of peritoneal dialysis and peritonitis

In this widely quoted (186 times) study, Davies et al. addressed the issue of peritoneal infection and poor ultrafiltration as major causes for failure of CAPD treatment. They adopted the peritoneal equilibration test (PET) to quantify longitudinal changes of low-molecular-weight solute transfer (D/P\text{creat}) and assessed ultrafiltration in a remarkably large cohort of 233 patients, apparently from one centre, treated with CAPD.

Past studies, both retrospective and prospective, had found that peritonitis rates were a risk factor for ultrafiltration failure and a cause of morphological damage. The authors argued that, although many authors had stated that peritonitis was a major cause of ultrafiltration failure, the documentation for this was variable, and the underlying mechanisms remained poorly defined. In order to provide more definitive evidence so as to base therapeutic strategies on solid data, the authors started this prospective observational study in a large unselected cohort of patients. Peritoneal kinetics were measured at baseline and remeasured after every isolated or recurrent episode of peritoneal infection. This permitted the authors to present the first prospective longitudinal study linking deterioration of peritoneal transport kinetics with bacterial peritonitis over an observation period of 5 years. In their cohort, the authors had observed 281 episodes of peritonitis, 87 of which were single episodes, 58 double episodes and 136 multiple infections. Clustering in individual patients explains the fact that 67% of infections occurred in <10% of patients, while in contrast, 86 patients had no episodes of peritonitis at all.

One goal of the study was to identify the outcome of peritoneal transport kinetics after single peritonitis episodes or peritonitis clusters, addressing the concern that a substantial proportion of CAPD patients are, in the long term, unable to deliver an adequate dialysis dose once residual renal function is gone. In the past, it had been postulated that this was mainly, but not exclusively, the result of progressive peritoneal damage in response to peritoneal microbial infections. In the present study, single infectious episodes failed to affect D/P\text{creat}, while recurrent infections caused significant increase in D/P\text{creat} and reduction in ultrafiltration (UF). To further address the potential causes, the authors monitored leucocyte counts in the effluent; cumulative dialysate leucocyte counts were predictors of D/P\text{creat} and reduction in UF regardless of infecting organism. Not surprisingly, the greatest changes in peritoneal transport characteristics were observed in patients with the highest leucocyte counts and specifically for infections with Staphylococcus aureus and Pseudomonas. The impact of infections on peritoneal kinetics is reflected by the observation that treatment drop-out due to death or technical failure occurred twice as frequently in individuals who had higher D/P\text{creat} and lower UF up to 24 months into the study. Nevertheless, with respect to transport kinetics, patients with single peritonitis episodes caught up with time, i.e. developed similarly abnormal transport kinetics. The authors postulated that—apart from peritonitis—other factors also influence peritoneal transport kinetics. The finding that, with time, structural and functional changes of the peritoneal membrane were noted even in the absence of peritonitis episodes suggested to the authors that microbial infections are not the only cause for deterioration of peritoneal transport characteristics. The authors postulated that this was mainly the result of biocompatibility, and this has been documented in more detail in subsequent years.

As a working hypothesis, the authors proposed that continued low-grade activation of the peritoneal immune system is a potential trigger (or one of the triggers) for long-term changes in peritoneal vascularity, which led them to postulate that the development of more bio-compatible dialysates remained an important goal for the long-term use of peritoneum as a dialytic membrane—a postulate which has definitely been addressed and taken care of with updated methodology in subsequent years.

Incidence and risk factors of atherosclerotic cardiovascular accidents in predialysis chronic renal failure patients: a prospective study

At a time when the risk factor profile associated with cardiovascular complications on dialysis had already been well identified, it had had not been well documented at which stage of chronic kidney disease the cardiovascular risk started to increase and to what extent the cardiovascular risk was magnified by chronic kidney disease. The excellent 10-year follow-up of a relatively small cohort of 147 patients with an average Ccr of 30 mL/min followed up in a single centre (Hôpital Necker Paris) allowed the authors to assess cardiovascular risk factors relative to the French background population (data provided by the Nationwide Epidemiological Enquête Nationale sur l’Infarctus du Myocarde study).
At that time, the issue of risk factors leading to atherosclerotic complications had been assessed in haemodialysis, peritoneal dialysis patients and renal transplant patients, but up till then, there had been no study in predialysis patients with progressive chronic renal failure. The objective of the authors was to find out whether accelerated atherogenesis was the result of the dialysis procedure per se and/or of the uraemic state.

This pioneer study, which has been quoted 181 times, documented that the cardiovascular risk increases in the relatively early stages of CKD. In both genders, event rates were three times higher than in the general population. The incidence of myocardial infarction was 7.6, 18.2 and 27.8/1000 patients/year in the age brackets 45–55, 55–65 and >65 years compared with 3.4, 8.9 and 10.4/1000 subjects/year in the background population. The strongest risk factors were cigarette smoking, elevated systolic blood pressure, LDL cholesterol, triglycerides, APO B, fibrinogen and homocysteine levels. CRP and other recent hot risk factors were not assessed in those days. The authors also found elevated homocysteine concentrations. This raised the issue (which has remained controversial to this day) of whether hyperhomocysteinaemia is atherogenic. But the authors did not fall into the trap of assuming that correlation is evidence of causality—an assumption from which they prudently refrained.

The authors drew the sensible conclusion that the same factors that favour atherogenesis in the general population are also operative in chronic renal failure, but that their effect is amplified. On the basis of elevated concentrations of type-1 plasminogen activator inhibitor (PAI-1), the authors concluded that this finding pointed to endothelial dysfunction as the primary culprit—an assumption which has been confirmed by a number of recent studies.

This paper was an early breakthrough which has contributed to the modification of the then current concepts and interventions. The clinical interest that this observation provoked was mainly caused by the conclusion of the authors that preventive therapeutic measures against treatable atherogenic risk factors, i.e. both changes of lifestyle and drug interventions, should be initiated early in chronic kidney disease—a concept which is now widely accepted, although unfortunately, evidence based on outcome data to support this conclusion is still scarce.

**Antiproteinuric effect of blood-pressure-lowering agents: a meta-analysis of comparative trials**

The documentation of the blood-pressure-independent antiproteinuric effect of renin–angiotensin system blockade is one of the breakthroughs that have modified current concepts and interventions.

This meta-analysis of Gansevoort et al. on all 41 studies available at that time comprised (only) 1124 patients (558 non-diabetic and 566 diabetic patients)—note the small number of patients in this cohort compared with the gigantic number of individuals included in recent cardiovascular risk studies, e.g. ONTARGET and HOPE). The readouts were the antiproteinuric effect of ACE inhibitors compared with blood pressure lowering by alternative antihypertensive medication. In those early days, the quality of the studies was often suboptimal, to put it politely, and as a result, wide interstudy variation of the antiproteinuric response was noted by the authors. Nevertheless, the antiproteinuric effect was found to be consistently and significantly greater in patients treated with ACE inhibitors compared with the antiproteinuric effect of the comparator antihypertensive drugs (−39.9% vs. −17%), although blood pressure lowering was equal between patients on ACE inhibitors and patients on other antihypertensive drugs (−12% vs. 11.4%). This issue was unresolved at that time because several studies had found that the urinary protein loss obtained with other antihypertensive drugs compared fairly well with that of ACE inhibitors. Another point is that previous meta-analyses had been limited to diabetic nephropathy, while the meta-analysis of Gansevoort et al. documented that this was true in non-diabetic as well as in diabetic kidney disease. It is not surprising that this paper was quoted 176 times.

It is of course a big step to extrapolate from antiproteinuric effects to reduction of the rate of progression—a conclusion from which the authors wisely refrained. Nevertheless, together with other subsequent meta-analyses, particularly of Jafar et al. (Ann Intern Med (2001) 135:73–87), the meta-analysis of Gansevoort was the first major evidence supporting the rationale to use RAAS blockade (more recently also with angiotensin receptor blockers and in the future possibly renin inhibitors) as the number one treatment in patients with proteinuric chronic kidney disease.

**Final thoughts**

The aforementioned papers are examples of papers which had a wide impact within and outside of the ERA-EDTA. As the past Editor-in-Chief, when I served our society, I was proud that we could publish papers which left a mark and had a definite impact on clinical nephrology. In retrospect, it is remarkable that each of the aforementioned top-quoted papers has left its mark on today’s understanding of chronic kidney disease and dialysis treatment.

In retrospect, having invested so much energy and effort into running *NDT*, it is with great pleasure that I acknowledge that our journal has grown further and continued to prosper under the leadership of Tilman Drueke and subsequently Norbert Lameire. Initially, I encountered great difficulty in convincing both to work with me as associates for *NDT*; but luckily, both got hooked and subsequently performed fantastically as chief editors. Today, *NDT* has undoubtedly become one of the worldwide top-ranking clinical journals in our specialty.