The five most cited NDT papers from 2005 to 2009

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Introduction

In contrast to the previous period (1999–2004), where all five papers covered topics related to a common theme, i.e. cardiovascular problems in kidney failure, the topics covered in the five papers with the highest citation rate of the most recent period (2005–2009) show a much wider diversity. Another difference is that the most cited paper is in fact an ‘extended case report’ describing the careful observation of an astute clinician, working in a non-academic setting, of the syndrome of systemic nephrogenic fibrosis complicating gadolinium exposure. This syndrome attracted much attention beyond nephrology in the subsequent years, being relevant to radiological, cardiological and dermatological practice [1].

The second paper is an evidence-based evaluation by the EUTOX group of the relationship between kidney failure and cardiovascular risk, a review of the literature obtained from a PubMed search using pre-defined keywords related to both conditions and covering 18 years (1986 until the end of 2003) and including data of more than 500 000 patients [2].

The third paper reported on a study comparing intermittent haemodialysis with continuous haemofiltration as a renal replacement modality in critically ill patients with acute kidney injury [3], a topic that at the time of publication was hotly debated. Subsequently, much larger trials have been published which have largely confirmed the conclusions of Uehlinger et al., i.e. that it is not the selection of the dialysis modality per se that determines clinical outcomes in these patients.

The fourth paper covers a topic that up to this day has not been entirely resolved, namely the optimal equation for estimation of glomerular filtration rate in normal and chronic kidney disease (CKD) populations [4]. This topic is of great importance in the classification of CKD and in the development of simple screening strategies.

The last paper describes the long-term effects of enzyme replacement therapy on kidney function in patients with Fabry’s disease [5]. Although this disease is a rare cause of CKD, the fact that enzyme therapy has become available could dramatically change the outcome of these patients.

This editorial review briefly summarizes these five papers, explaining their background, and puts them in the...
context of later developments in the relevant areas. We also explore how these papers contributed to better management of patients with kidney disease.

**Gadolinium and nephrogenic systemic fibrosis**

**Nephrogenic Systemic Fibrosis**

This disease, initially called nephrogenic fibrosing dermopathy (NFD) was described for the first time by a dermatologist, Shawn Cowper and colleagues from the University of California-San Francisco in *The Lancet* [6]. Thirteen patients on chronic dialysis or who had received kidney transplants developed painful, erythematous, firm papules and plaques with geographic borders on the limbs, associated with the joints. The histopathologic findings showed a unique fibrosing disorder that had not been described previously. In the subsequent years, it became clear that the skin lesions may be linked to fibrosis of deeper structures leading to a devastating and debilitating disorder. Systemic involvement of the liver, heart, lungs, diaphragm and skeletal muscle was subsequently reported, and the disease became known as nephrogenic systemic fibrosis (NSF) (for reviews, [7–13]).

The cause of NSF is currently unknown, although there is now little doubt that exposure to Gd chelates is probably the most important pathogenic trigger. It was the 2006 NDT paper by Grobner that first described the association between NSF/NFD and previous exposure to gadolinium-containing contrast agents used for magnetic resonance imaging (MRI) in five of nine haemodialysis patients with the condition [1].

It has since been established that the most important risk factors for the development of NSF are chronic or acute kidney disease (usually necessitating dialysis) and the administration of Gd-containing contrast agents (Gd-CAs).

Recently, Perazella has summarized the pharmacokinetics of gadolinium (Gd) chelates [14]. These have small volumes of distribution, a normal mean terminal half-life (T1/2) of approximately 1.3–1.6 h and are eliminated unchanged via glomerular filtration. In end-stage renal disease (ESRD), T1/2 is prolonged to up to 30 h in patients with a glomerular filtration rate (GFR) <5 mL/min. However, the relatively small molecular weight (500 Da), small volume of distribution (0.28 L/kg) and negligible protein binding make the Gd chelates ideal for removal by haemodialysis. The T1/2 of Gd chelates in non-dialysed patients with ESRD was prolonged at 34.3 h but decreased significantly to 2.6 h in those receiving haemodialysis [8,10]. Peritoneal dialysis, in contrast, is not effective for Gd chelate removal [15]. In view of the accumulation of Gd in kidney failure, it might be prudent to employ the lowest Gd chelate dose possible to achieve adequate image quality in these high-risk patients. There is no evidence that such precautions are efficacious, but the similarities between Gd chelate ‘nephrotoxicity’ and that associated with iodine contrast medium makes these suggestions tenable.

Whether higher doses of Gd chelates (>0.3–0.4 mmol/kg) or the use of higher osmolality Gd chelate agents increase the risk of nephrotoxicity (as is noted when using iodine contrast medium) has not been systematically studied.

In February 2007, the European Medicines Agency (EMEA) contraindicated the use of gadodiamide in patients with a GFR <30 mL/min. Four months later, a caution for its use was added in patients with a GFR between 30 and 60 mL/min [16].

Thus, for the first time in the history of radiology, kidney function was mentioned in the datasheet of a radiology product. This was a new concept for European radiologists who needed to know the GFR in all patients before using the Gd-based agents. In the USA, the US Food and Drug Administration, on 23 May 2007, requested that vendors add warnings about the risk for developing NSF to the full prescribing information on the packaging for all Gd-CAs (gadopentetate dimeglumine, gadodiaimide, gadoversetamide, gadoteridol, gadobenate dimeglumine) [17]. The new labelling highlighted the risk for NSF following exposure to a Gd-CA in patients with acute or chronic kidney disease with impaired kidney function (GFR <30 mL/min/1.73 m²), patients who had acute kidney injury (AKI) of any severity due to hepato-renal syndrome or patients who had received a liver transplant. In such patients, the use of a Gd-based agent should be avoided unless the diagnostic information is essential and/or is not obtained by use of non-contrast-enhanced MRI.

Demonstration of significant quantities of insoluble Gd in the skin of NSF patients, months after Gd-based contrast exposure (even after extensive tissue processing), suggests that Gd might have undergone transmethylation in vivo. This is supported by the fact that the overwhelming majority of NSF cases reported thus far have been associated with linear MRI contrast agents (for review, [18]) that have inferior thermodynamic stability and a kinetic or conditional stability that favours transmethylation. However, a first case of NSF in a dialysis patient after exposure to a macrocyclic chelate has recently been described, and at least two additional cases are known [19,20]. All three cases have all been described in publications in NDT or NDTPlus.

In practice, informed consent must be obtained and documented before a patient receives an MRI investigation, and recommendations to maximize the safety of the procedure have been developed [10].

**CKD and cardiovascular risk**

That patients treated by chronic renal replacement therapy are exposed to cardiovascular problems and suffer from accelerated and severe atherosclerosis was proposed in a seminal paper by Lindner et al. in 1974 [21]. Studies on the epidemiology of cardiovascular disease in the dialysis population showed that, even after stratification by age, gender, race and the presence or absence of diabetes, cardiovascular mortality in dialysis patients is 10–20 times higher than in the general population [22], although much of the excess risk is accounted for by cardiovascular pathologies that are not directly related to atherosclerosis.
Many studies in recent years, some of which were discussed in a previous contribution to this anniversary issue [23], showed that patients with chronic renal disease should be considered in the highest risk group for subsequent cardiovascular events.

It became evident that the association between chronic kidney disease and cardiovascular morbidity and mortality is observed early during the evolution of renal failure [24].

Vanholder et al., on behalf of the EUTOX working group [2], reviewed the literature obtained from a PubMed search using pre-defined keywords related to cardiovascular disease (CVD) and CKD and covering 18 years (1986 until the end of 2003). Eighty-five publications, covering 552,258 subjects, were summarized. All three studies support a link between kidney dysfunction and cardiovascular risk. The review confirmed that the association is observed very early during the evolution of kidney failure: an accelerated cardiovascular risk appears at varying GFR cut-off values, which were ≥60 mL/min in at least 20 studies. Although many reviewed studies lacked a clear definition of cardiovascular disease and/or used a single determination of serum creatinine or GFR as an index of kidney function, in six studies, chronic kidney dysfunction and cardiovascular disease were well defined, and these studies confirmed the relationship between early kidney dysfunction and increased cardiovascular risk, independent of geographic or ethnic factors.

This paper was frequently cited because it provided for the first time an evidence-based evaluation of the link between cardiovascular link and chronic kidney disease in CKD stages much earlier than 5D. In addition, the authors formulated a number of recommendations for increasing the awareness of this major health problem among the general public and the non-nephrological medical community.

**Intermittent haemodialysis versus continuous renal replacement in patients with acute kidney injury**

The choice of dialysis modality has been one of the most frequently debated topics in the field of AKI. Intensivists and ‘intensive care nephrologists’ have attempted to prove the superiority of one type of renal replacement techniques (RRT) over another in an intensive care setting [25]. Recent attention has focussed on the relative merits of continuous RRT (CRRT) versus intermittent haemodialysis (IHD). Before the NDT paper of Uehlinger et al. [3] was published, only two randomized controlled trials comparing continuous versus intermittent dialysis in AKI patients in need of RRT had been published.

The first of these trials was conducted in the USA and compared IHD with continuous haemodiafiltration (HDF) in an intensive care unit (ICU) setting [26]. In this study, 166 patients were randomized. Using an intention-to-treat analysis, the overall ICU and in-hospital mortalities were 50.6% and 56.6%, respectively. Continuous therapy was associated with an increase in ICU and in-hospital mortality relative to intermittent dialysis. Median ICU length of stay from the time of nephrology consultation was 16.5 days, and complete recovery of renal function was observed in 34.9% of patients, with no significant differences between the groups. However, despite randomization, there were significant differences between the groups in terms of covariates independently associated with mortality, including gender, hepatic failure, APACHE II and III scores and the number of failed organ systems. In each instance, these biased in favour of the intermittent dialysis group, and when using logistic regression to adjust for the imbalances in group assignment, the odds of death associated with continuous therapy were no longer significant. Despite the fact that the authors had expected a survival benefit of the continuous dialysis modalities, the study was thus essentially negative. The second trial, performed in the Cleveland Clinic [27], randomized 80 critically ill patients with AKI after stratification for severity of illness to treatment with continuous venovenous haemodialysis (CVVHD) or IHD. There were no differences in survival or renal recovery between the groups, despite there being a greater net volume removal in the CVVHD group and a significant decrease in mean arterial pressure for patients on IHD therapy, not seen in those on CVVH therapy. The paper by Uehlinger et al. [3] described the first European randomized controlled trial (RCT) comparing continuous venovenous haemodiafiltration (CVVHDF) with IHD in AKI patients admitted to an ICU. The primary end point was ICU and in-hospital mortality, while recovery of kidney function and length of hospital stay were secondary end points. The two groups were comparable at the start of RRT with respect to age, gender, number of failed organ systems, Simplified Acute Physiology Scores, presence of septicaemia, shock or previous surgery. Hospital and ICU mortality rates were not different in the two groups, nor was length of hospital stay in the survivors or duration of RRT required.

All three of these studies (and many others, including two meta-analyses that were subsequently published [28,29]) have been criticized [30] for being underpowered, while in the Uehlinger study, the institution at which the trial was performed had limited access to only two CRRT machines but unlimited availability of HD machines. This limitation mandated an unusual randomization scheme which was dependent on the number of CRRT machines in current use. There were also doubts as to the ‘adequacy’ of the amount of ultrafiltered fluid that was removed from the patients and on the adequacy of the dose of dialysis. For example, the prescribed dose of predilution CVVHDF (the CRRT modality used in the Uehlinger study) was only 27 mL/kg/h, which at that time was considered to be too low. However, in the light of more recent data [31–33] and an earlier study [34] on the dose of ultrafiltration needed in continuous techniques, the dose used in the Uehlinger study could be considered as adequate.

Since the publication of Uehlinger’s study in NDT, two major systematic reviews [29,35] have suggested that the outcomes of death, ICU mortality, in-hospital mortality, length of hospitalization and requirement for chronic dialysis/renal recovery in survivors are similar in haemodynamically stable, critically ill AKI patients receiving either CRRT and IHD. Lins et al. [36] also reported similar outcomes in a larger RCT of 316 patients with regard
to ICU stay, hospitalization, mortality and renal outcomes comparing CRRT and IRRT.

The paper by Uehlinger et al. was published at a time when dialysis modality selection for critically ill patients with AKI was hotly debated. This and other papers have certainly stimulated further interest in this topic and, more importantly, have initiated more robust studies that have confirmed the findings of the NDT paper, namely that the dialysis modality chosen for this type of patient does not determine the patient’s outcome.

Errors in the formulae for the prediction of kidney function

Evidence-based clinical practice guidelines suggest that an estimate of GFR (eGFR) provides the best clinical tool to gauge kidney function. The most common equations used in adults are the Cockcroft–Gault (C–G) [37], estimating a creatinine clearance (eCr), and the simplified equation from the Modification of Diet in Renal Disease (MDRD) Study, estimating GFR [38,39]. In contrast to the Cockcroft–Gault, the MDRD equation does not require knowledge of the patient’s weight. The MDRD-derived eGFR is adjusted to a standard body surface area (BSA) (1.73 m²) within the equation, whereas the eCr (C–G) equation includes body weight as a variable and does not adjust the final value.

The calculation of the eGFR by the MDRD equation is fundamental to the definition (and thereby diagnosis) and subsequent staging of CKD as proposed in the original Kidney Disease Outcomes Quality Initiative-Chronic Kidney Disease (KDOQI-CKD) classification system [40]. In 2004 and 2006, Kidney Disease: Improving Global Outcomes (KDIGO), an independent not-for-profit foundation, endorsed the global use of the KDOQI definition and staging system [41,42].

To aid clinicians in their decision-making, it was recommended that laboratories report eGFR routinely for adult patients using these creatinine-based equations. The introduction of automated eGFR calculation has in recent years led to an overall increase in referrals to nephrology services [43–45], in particular among women, older individuals and those with diabetes and stage 3 CKD. In at least one study [45], this increased referral appeared to result in net benefit.

It is beyond the scope of this editorial to discuss the pros and cons related to the DOQI and KDIGO CKD classification systems. It is fair to say that the current classification schema, based on eGFR alone, needs to be applied with some caution, particularly in the elderly without concomitant signs of kidney damage. It is also likely that the presence and magnitude of albuminuria will be added to future classification systems to increase the power to predict cardiovascular and kidney prognosis (for recent reviews [46–48]). Major concerns related to the eGFR equations include their precision, bias and accuracy. Serum creatinine test results can vary between clinical laboratories, a fact that is not always recognized by health care professionals. This variation is greater in the normal and near-normal range of creatinine measurements. Such differences may be of sufficient magnitude to change patient classification when an eGFR is calculated. At higher levels of GFR (eGFR > 60 mL/min/1.73 m²), the MDRD equation tends to underestimate true GFR, thus magnifying ‘overdiagnosis’ of CKD when an absolute threshold is used. Many other equations have in the meantime been proposed, among them the Mayo clinic equation. Investigators at the Mayo were concerned about the low accuracy of the MDRD equation in healthy persons and proposed a new equation (Mayo) for use in healthy individuals and in chronic kidney disease [49].

Another recently developed equation, the CKD–EPI [50], is considered to be an improvement over those in current use. However, the use of these newer equations to identify genuine CKD has not yet been rigorously evaluated in older patient populations, in whom there is a greater possibility of overdiagnosis. Whether cystatin C-based estimations of GFR will become a universal standard remains uncertain at present, but preliminary data based on this biomarker are encouraging, even though its use to diagnose CKD in an older population has not been fully evaluated [51].

Cirillo and his colleagues [4], in their 2005 NDT paper, were among the first to examine the effects of gender, age and body mass index (BMI) on errors in kidney function predictions assessed by C–G, MDRD and Mayo equations in a population of individuals in whom GFR had been formally measured. The relative error (bias) of predictions based on the C–G equation was associated with age and BMI but not with gender and GFR. C–G-based predictions tended to overestimate measured GFR in obesity and underestimate GFR in underweight and older individuals. The MDRD-based predictions showed lower average values when compared with measured GFR. This bias was explained by an underestimate of true GFR in females and in individuals with a GFR > 60 mL/min/1.73 m². The Mayo equation predictions showed higher average values than measured GFR mainly due to overestimates in male gender and in obesity. These findings tended to be similar at any value of GFR. Thus, overall, the effects of gender, age and BMI on errors of prediction were independent of GFR level, with the exception that association between BMI and error when using the Mayo equation was found only in subjects with a GFR > 60 mL/min/1.73 m². GFR level affected the error of predictions using the MDRD and Mayo but not by the C–G equation. Although predictions by both MDRD and Mayo equations had greater error at GFR values >60 mL/min/1.73 m², these errors were opposites, with underestimates using the MDRD and overestimates using the Mayo equation.

The paper by Cirillo et al. has been frequently cited because it was timely and pointed out some of the weaknesses of the proposed GFR estimation equations. The strengths of the study were that a ‘gold standard’ measurement of GFR was used as the comparator (clearance of inulin administered by continuous infusion) and that the target population was a relatively large cohort of non-US individuals. At approximately the same time, Froisart et al. [52], using Cr-EDTA plasma clearances in a cohort of 2095 adult Europeans, found that the C–G and MDRD equations showed very limited bias for the
entire study population. However, analysis of subgroups defined by age, gender, BMI and GFR level showed that the biases of the two equations could be much larger in selected populations. Furthermore, analysis of the standard deviation of the mean difference between estimated and measured GFR showed that both equations lacked precision, the C–G equation being less precise than the MDRD in most cases, with 29.2% and 32.4% of subjects misclassified, respectively, with respect to KDOQI stage.

Both studies [4,52] prompted investigation of the accuracy of these equations, in particular the MDRD when used in non-Caucasian, non-African-American populations.

The data from the study by Cirillo et al. have recently been included in a larger multi-centre European dataset of 2208 subjects with and without CKD, with a broad range of GFR values and diversity of kidney pathology [53]. As was shown earlier, the C–G and MDRD equations showed limitations in their ability to properly estimate the GFR, as measured by continuous inulin infusion. Both equations had an accuracy of approximately 70% of the GFR estimates within 30% of the measured GFR, but only 60% of the population was classified correctly in the five GFR groups defined by the KDOQI-CKD classification.

Long-term treatment of Fabry disease with enzyme replacement

Fabry disease (FD), also called Anderson–Fabry disease (AFD), is an X-linked lysosomal storage disorder caused by deficient activity of the lysosomal enzyme α-galactosidase, A (α-Gal A). This enzyme defect generates progressive accumulation of globotriaosylceramide (Gb3), the principal substrate of the enzyme, and related glycosphingolipids. Accumulation occurs in various tissues and organs including blood vessels, the heart, eye, autonomic nervous system and kidneys, causing a multisystem disorder that leads to progressive tissue damage and associated clinical manifestations. Progressive renal insufficiency is a major source of morbidity, with additional complications resulting from cardio- and cerebrovascular involvement. Survival is reduced among affected males and symptomatic female carriers. The incidence of FD is estimated at 1 in 117 000 live births for males [54], although it may be higher. In a recent survey of a newborn population, the incidence of α-Gal A deficiency was 1 in approximately 3100, with an 11:1 ratio of later-onset disease to the classic phenotype [55]. If only known disease-causing mutations were included, the incidence would be 1 in approximately 4600, with a 7:1 ratio of later-onset, classic phenotype. These results suggest that the later-onset phenotype of Fabry disease is currently underdiagnosed among males with cardiac, cerebrovascular and/or kidney disease.

For a number of years, enzyme replacement therapy has been available for patients with Fabry disease. Two enzyme preparations have been approved by the European Agency for the Evaluation of Medicinal Products (EMEA): agalsidase β (Fabrazyme®, Genzyme Corporation), produced in Chinese hamster ovary cells; and agalsidase α (Replagal®, Shire Human Genetic Therapies, Inc.), produced in human cell lines. Although both proteins are structurally and functionally very similar, with the same amino acid sequence as the native human enzyme, they differ in the pattern of glycosylation which is influenced by the cell line of origin. In the USA, the Federal Drug Administration approved only agalsidase β.

Enzyme replacement therapy is usually administered once every 2 weeks, using a dose of 0.2 mg/kg body weight for agalsidase α compared with 1 mg/kg for agalsidase β.

A very recent Cochrane review [56], based on five clinical trials that enrolled 187 participants, analysed the different formulations of the enzyme; two trials compared agalsidase α with placebo, and three trials compared agalsidase β with placebo. Based on the limited evidence from these five rather small controlled trials of poor quality, no robust evidence to support the use of either agalsidase β and α to treat Anderson–Fabry disease could be found. Intravenous enzyme infusions were reasonably well tolerated, with reported infusion reactions occurring in about 10%, mostly consisting of fever and transient rigours of mild to moderate intensity.

A proportion of patients with AFD receiving enzyme replacement therapy have developed antibodies to α GLA, although such antibody formation did not influence clinical efficacy or outcomes in either of the initial clinical studies undertaken, and antibody titres usually decreased over time. In a few cases, IgE antibodies have been reported after infusion of agalsidase β [57].

The NDT paper of Schiffmann et al. [5] described the long-term open-label follow-up of 25 adult male Fabry patients who had previously participated in a randomized placebo-controlled trial (including 26 patients) for 6 months. The results of the original study had previously been published by the same authors in 2001 [58]. In the follow-up study, all patients were treated every other week with agalsidase α (0.2 mg/kg) infused intravenously over 40 min. During the 4–4.5 years of enzyme replacement therapy, all eligible subjects were transferred to home therapy. Eight patients developed persistent IgG antibodies to agalsidase α, but IgE antibodies were not detected. Estimated GFR remained stable in subgroups of patients with stage I (GFR > 90 mL/min) and stage II (GFR 60–89 mL/min) CKD at baseline. In contrast, in the subgroup of patients with stage III CKD (GFR 30–59 mL/min), the slope of the decline in GFR was reduced compared with comparable historical controls, suggesting that enzyme replacement therapy might slow the decline of kidney function. The NDT paper has been frequently cited because it was one of the first follow-up studies suggesting a long-term positive impact of enzyme replacement on kidney function in Fabry disease patients.

Schiffmann and colleagues also participated in an analysis of 5-year follow-up data collected from 181 Fabry’s disease patients treated with agalsidase α enzyme replacement therapy around the world [59]. This analysis revealed...
that, in addition to a reduction in left ventricular mass (LVM), there were improvements in pain inventory and quality of life scores, and the mean yearly fall in estimated GFR versus baseline was substantially slower than in previous studies of Fabry’s disease patients.

References