Modern nephrology – new methods, new treatments and still numerous difficult challenges

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Abstract: In the current decade, 2001 to 2010, the number of patients undergoing renal replacement therapy worldwide will increase from 1.5 to 2.5 mln. This requires considerable financial input, thus limiting treatment access in 90% to the inhabitants of North America, Europe and Japan, that constitutes less than 20% of the world's population. It is presumed that about 1mln people die every year, a death rate which could be avoidable, were the proper funds for renal replacement therapy obtained. Over the last five years, Poland has joined the elite group of countries fully covering the needs in this respect. Modern nephrology gradually focuses on reducing the incidence of end-stage renal disease, through more effective treatment of diabetes, glomerulonephritis and polycystic kidney disease. Reducing morbidity and mortality rates in dialysis treatment and post-kidney transplant follow-up is another key issue. This overview discusses the modern options and perspectives to face those challenges.

Key words: diabetic nephropathy, end-stage renal disease, glomerulonephritis, morbidity and mortality, polycystic kidney disease, renal replacement therapy

Kidney Diseases – an Oncoming Epidemic of End-Stage Renal Disease

In 2001, 1.5 mln people with end-stage renal disease lived worldwide thanks to renal replacement therapy. Seventy-seven percent of this population were enrolled in dialysis programs (hemodialysis – 69%, peritoneal dialysis – 8%), while patients the remaining received a kidney transplant. In patients with end-stage renal disease, the annual population growth rate exceeds 5 times the world population growth rate (7% vs. 1.3%). Thus, the forecast stating that, by 2010, the number of people requiring renal replacement therapy will have achieved the number of 2.5 mln, is being confirmed. Benefits arising from the prevalence of renal replacement therapy are accessible in 90% to the inhabitants of North America, Europe and Japan, constituting less than 20% of the world population. This territorial concentration of renal replacement therapy obviously does not result from dissimilar needs, but from the different opportunities of fulfilling them. It is estimated that over the next 10 years, world expenditure on renal replacement therapy will have surpassed 1 trillion USD, with an increase from 14 to 28 billion USD in the United States alone in the years 2001–2010. The magnitude of these costs condemns to death over 95% of those patients with end-stage renal disease coming from countries with lower national incomes (Africa, parts of Asia and Latin America). According to estimates, 1 mln people die every year, deaths which could be avoided were the proper funds for renal replacement therapy obtained [1-4]. Over the last five years, Poland has joined the group of countries fully covering the needs in this regard.

By the end of 2004, the total number of people undergoing renal replacement therapy in Poland amounted to 17500, which, at 495 persons per million inhabitants, places us among highly developed countries in Europe [5]. It is estimated that 70.5 % of patients underwent dialysis (91.4% – hemodialysis, 8.6% – peritoneal dialysis), while 29.5% lived with a kidney transplant. This undoubtedly is a major success of the nephrology, transplant surgery and other specialistic circles, including those from the laboratory and transplant coordinating backgrounds, which shape the modern face of renal replacement therapy in Poland. The role of the financial payer cannot be underestimated either.

For logical and obvious reasons, nephrology circles would like to implement into renal replacement therapy all the novelties which lengthen patients' lives and improve the life quality. Therefore, in the patient's interest, attempts are made to overcome the payers' resistance and obtain an increase in refunding the costs of renal replacement therapy. It must, however, be kept in mind that, even with current under-financing, a considerable increase in expenditure per single hemodialysis procedure will be needed, if the tendency is kept up to start hemodialysis in 4000 new patients a year (ca. 100/mln inha-

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Received: March 22, 2007. **Accepted in final form:** March 30, 2007
Conflict of interest: none declared.
Pol Arch Med Wewn. 2007; 117 (3): 95-101

bitants). This requires an increase in expenses by 60 mln USD a year. Additional costs must also be accounted for: the costs of creating vascular access for the purpose of hemodialysis (according to American data – 10% of the total costs of hemodialysis in the first year of treatment) and the growing costs of treating complications in hospital. It is also worth noting that ca. 45% of patients starting dialysis in Poland are over 65 years old, while close to 33% of all dialyzed patients suffer from diabetes.

The main focus of nephrology is increasingly on restricting the number of patients requiring renal replacement therapy through more effective prevention of renal insufficiency in conditions which most often lead to end-stage renal disease: diabetic nephropathy, glomerulonephritis and polycystic kidney disease. High mortality rates, mostly due to cardiovascular lesions, still cast a shadow on the successes in renal replacement therapy. The risk of cardiovascular mortality in 25–35 years dialyzed patients increases 375 times in comparison with the general population, while in patients over 75 years it does 5 times so. The life expectancy of a 49-year-old patient with end-stage renal disease is 7.1 yrs compared to 8.6 yrs for a patient with colon cancer, 12.8 yrs for a patient with prostate cancer and 29.8 yrs for the general population [4-9]. Kidney transplantation creates further challenges. Patients back on dialysis due to loss of graft function account for the third, as to frequency, group of patients enrolled in chronic dialysis programs in the United States, preceded only by those with diabetic nephropathy and glomerulonephritis. Selected aspects of the above key issues in modern nephrology will be presented in further parts of this overview.

Diabetic Nephropathy

The number of patients suffering from diabetes in 2000 was estimated at 171 mln (2.8% of the world population, in 90% of the cases – type 2 diabetes), with the prediction of an increase to 366 mln by 2030 (6,5% of the world population). Careful calculations show that 30 – 40% of patients with type 1 diabetes and 10–20% of patients with type 2 diabetes are at risk of end-stage renal disease development after 20–25 yrs of disease duration. These catastrophic forecasts do not have to and should not turn into actual facts. Even today, significant differences are observed between countries concerning the incidence of diabetic nephropathy-related end-stage renal disease.

In the U.S., diabetic nephropathy is by far the leading cause of dialysis implementation, occurring in 45% of patients, while in Great Britain, with a share of 16%, it is visibly second to glomerulonephritis (30%) [4]. These differences cannot solely be explained by dissimilar ethnic structure. Greater accessibility to effective treatment methods in the United Kingdom is a more probable cause. Randomized clinical trials have unequivocally indicated two key factors in the prevention and inhibition of diabetic nephropathy development: adequate carbohydrate metabolism balance and proper hypertension treatment with the use of inhibitors of the renin-angiotensin system: angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor antagonists (ARA), which show particular nephroprotective properties.

The long-term (6.5-year follow-up) Diabetes Control and Complications Trial has provided data on the significance of proper glycaemia control in type 1 diabetes. It has proven that intensive insulin therapy (mean glycated hemoglobin – HbA_{1c} 7.2%), compared to conventional insulin therapy (2 injections daily, mean HbA_{1c} – 9.2%), reduced the risk of onset of microalbuminuria by 39% and of progression to macroalbuminuria by up to 54% [10]. Similar findings were provided by the UK Prospective Diabetes Study, which demonstrated that a difference of 0.9% in HbA_{1c} levels (7% vs. 7.9%) was linked, over an 11-year observation period, with lowering the risk of micro- and macro-albuminuria development by 25–30% [11].

An equally important factor is rigorous hypertension control, with target values at ≤130/80 mmHg, and ≤120/75 mmHg in the macroalbuminuric stage. In hypertension treatment, the lead role is assigned to inhibitors of the renin-angiotensin system, responsible for the development of intraglomerular hypertension and stimulating fibrosis processes through the intermediary of the transforming growth factor β (TGFβ). First reports about the benefits of such treatment date back to the early 1990s. The Collaborative Study Group Trial demonstrated that captopril intake in patients with type 1 diabetes in the macroalbuminuric stage and decreased glomerular filtration rate (serum creatinine concentration >1.5 mg/dl), significantly reduced the risk of doubling in serum creatinine level and occurrence of the so-called combined endpoint, concluding in either renal replacement therapy or death.

This target was reached, in comparison with a group of study subjects with similar hypertension control, but receiving hypotensive drugs which did not inhibit angiotensin II function [12].

Another trial (HOPE) has shown that ramipril intake (10 mg once daily) in type 2 diabetes, lessened the risk of diabetic nephropathy development by 24% and significantly reduced cardiovascular mortality [13]. Another ACEI, trandolapril, has also proven effective in preventing the development of microalbuminuria in patients with type 2 diabetes [14]. This function was additive to excellent metabolic control, mean HbA_{1c} at 5.8%.

A number of studies, conducted on thousands of study subjects, concern the nephroprotective properties of ARA. Observations were issued that irbesartan (best effect at 300 mg tdd) and valsartan (mean 120 mg tdd) do not only lessen the risk of microalbuminuria progressing to clinically manifest nephropathy in patients with type 2 diabetes, but also, in some patients, reverse the process to normal range values [15,16]. In two further studies, the significantly beneficial influence of irbesartan (up to 300 mg tdd) and losartan (mean 85.5 mg tdd) on macroproteinuria in type 2 diabetes became evident. A significant deceleration in the decrease of glomerular filtration rate was observed, with consecutive lengthening of progression to end-stage renal disease by a mean of 2 yrs [16,17].

The CALM trial, on the other hand, has shown evidence of the positive effects of a double angiotensin II blockade, through simultaneous administration of ACEi and ARA (lisinopril 20 mg tdd and candesartan 16 mg tdd). Conjunction of these two drugs enables reaching target blood pressure values and lowering microalbuminuria in those patients with type 2 diabetes, in whom monotherapy remains insufficient [18]. It is worth noting that 60% of angiotensin II is generated in a chymase-mediated ACE-independent pathway. This pathway may be inhibited solely by ARA [19].

Glomerulonephritis

As mentioned previously, glomerulonephritis invariably remains the leading cause of end-stage renal disease in Great Britain. A similar, 30%, share in the epidemiological distribution of end-stage renal disease is observed in Australia, and an even higher percentage in Japan – 47% [4]. In Poland, according to the latest data for the year 2004, glomerulonephritis, at 23%, has for the first time given way to diabetic nephropathy, at 33%, as the leading factor, and currently occupies the second position [5]. A specific element is connected with the prevention of glomerulonephritis-related end-stage renal disease: namely, renal failure mainly occurs in children and young adults. Both individual and social wellbeing are therefore connected with effective glomerulonephritis treatment. Epidemiologically wise, the most frequent clinical presentations leading to renal failure are: membranous nephropathy, focal segmental glomerular sclerosis and IgA nephropathy, which conjoin to form 80% of primary glomerulonephritis in adults. The key to therapeutic success is lowering proteinuria from nephrotic range (>3.5 g/24h) to below 0.2 g/24h while maintaining normal glomerular filtration rate. This finds confirmation in a long-term metaanalysis in patients with membranous nephropathy. From among 190 patients with proteinuria <0.2 g/24h, end-stage renal disease development occurred in only 1 case [20].

As in diabetic nephropathy, inhibition of the renin-angiotensin-aldosterone system is an unseparable component of anti-proteinuric treatment in glomerulonephritis, involving the use of ACEI/ARA [19]. The benefits resulting from a double blockade are shown in the COOPERATE trial, in which trandolapril (3 mg tdd) and losartan (100 mg tdd) reduced proteinuria by 40%, while simultaneous administration resulted in a 76% reduction, a significantly more beneficial effect on glomerular filtration [21].

In the induction of proteinuria remission in patients with glomerulonephritis, glucocorticosteroids and cytostatics are being used (cyclophosphamide, chlorambucil, azathioprin), as well as anti-rejection drugs transponed from renal transplantology: cyclosporin, tacrolimus, and mophetil mycophenolate, an antiproliferative agent.

For instance, in focal segmental glomerular sclerosis, a program consisting of 3 intravenous infusions of methylprednisolone 0.5g tdd followed by oral prednisone 1 mg/kg/24h for 2–3 months and a subsequent dose reduction to 0.5 mg/kg, induced remission in 25–40%.

In about 20% of glucocorticosteroid-resistant FSGS-related nephrotic syndromes, remission was achieved using cyclosporin (initial dose 5–6mg/kg/24h) and prednisone 0.5 mg/kg every other day.

In isolated casuistic reports, if resistance to such a combination occurred, mophetil mycophenolate proved effective. A positive therapeutic response to glucocorticosteroids and immunosuppressive drugs is also obtained in patients with nephrotic syndrome in the course of other, primary glomerulonephritis (membranous nephropathy, IgA nephropathy, mesangiocapillary glomerulonephritis) [20,22,23]. Final answers to substantial questions are however still lacking: In which patient group should glucocorticosteroids and immunosuppressive treatment be implemented? Whether only in the instance of nephrotic proteinuria? How to restrict glomerulonephritis relapse and steroid - or cyclosporin- dependent remission? Should, as in transplantology, long-term supportive treatment be applied? Why is glomerulonephritis treatment by design less intensive (double-drug) than post-transplantation anti-rejection therapy (triple-drug standard), with the use of calcineurin inhibitors, antiproliferative drugs and prednisone? An alternative to not achieving glomerulonephritis remission and developing end-stage renal disease is performing a kidney transplant with the necessity of lifelong immunosuppressive treatment. On the other hand, post-transplant immunosuppression programs do not prevent glomerulonephritis relapse in the kidney graft, although the course of the disease is usually less severe than in native organs, thus limiting the application of imitative immunosuppressive post-transplant treatment programs.

The hitherto unsatisfactory effects of glomerulonephritis treatment create the need for further exploration of new treatment methods. Attempts to reach immune tolerance towards DNA in patients with lupus nephritis with the use of LJP 394 (abetimus sodium) are an innovative and interesting approach. This is a molecule consisting of four double-stranded oligodeoxyribonucleotides attached to nonimmunogenic polyethylene glycol, a proprietary carrier platform, showing cross-reactivity with the dsDNA receptor in B lymphocytes, independently of T cell involvement. In the IIIrd phase of an international trial, prolonged remission was achieved in patients with lupus nephritis. A similar method, basing on muted immune response to an initiating antigen (non-collagenous fragment of type IV collagen), was implemented with success in an experimetal glomerulonephritis model of the antibody against glomerular base membrane type (anti-GBM).

Further new perspectives are linked with the removal of B lymphocytes with the aid of rituximab (humanized monoclonal antibody against CD20). Treatment success was reported in the case of resistant lupus nephritis, Wegener's granulomatosis and membranous nephopathy. Clinical attempts to inhibit lymphocyte T costimulation using CTLA4Ig (betalacept) in lupus nephritis are planned, as well as attempts to

inhibit PDGF-activated (*platelet-derived growth factor*) cellular processes with the use of imatinib in patients with IgA nephropathy. The so-called bone morphogenic protein-7 (BMP-7), which reduces TGFβ_1-activated (*transforming growth factor* β_1) fibrosis processes, also seems to be a promising therapeutic agent [24]. In a rat glomerulonephritis model, encouraging results have been obtained using mesenchymal stem cells, administered directly into the renal artery. Accelerated mesangium regeneration was noted, in a paracrine pathway, linked with stem cell-generated anti-inflammatory and angiogenic cytokines [25].

Polycystic Kidney Disease (PKD)

Due to its widespread distribution, it is the most common genetic disease leading to end-stage kidney disease. Millions suffer from this condition, 400 thousand people in the United States alone, while 1800 from among them will start dialysis each year. In Poland, over 940 patients (11.5% of the total number of dialyzed patients) are being dialyzed due to the PKD-induced end-stage renal disease [5]. The course of this hereditary disease is varied, however as much as 50% of the patients develop end-stage renal disease between 57 and 73 years of age. Medicine has hitherto proven unable to provide patients with a treatment which would effectively stop cyst formation and enlargement, leaving them in dreary awaitance of the inevitable progression of the lesions. Glimmers of hope have lately appeared in this dark tunnel, arising from the discovery in animal models of the pathological mechanisms beneath the disease. ADH (vasopressin) was identified as one of the key factors leading to tubular cyst formation. The hormone, activating type 2 vasopressin receptors located in cystic endothelium, leads to water retention in the cysts and mesangial tissues. A study is being planned to investigate the usefulness of vasopressin v_2-receptor antagonists in 1500 patients with PKD using tolvaptan, an agent with high-affinity to that receptor.

Other observations in animal models indicate that cyclic AMP plays a substantial role in cyst diameter growth. CAMP production and cumulation may be inhibited by octreotide - a long acting somatostatin analogue. The first pilot study using octreotide showed promising effects in patients with PKD. Different observations in animal models associate cyst growth with the activity of a kinase, mammalian target of rapamycin – mTOR. Two clinical trials are scheduled, involving the use of respectively everolimus and rapamycin, known immunosuppressive drugs, inhibitors of this protein [26,27].

Morbidity and Mortality in Renal Replacement Therapy Programs – Repair Strategies

High morbidity and mortality rates are weak points of renal replacement therapy, mainly due to cardiovascular disease resulting from both classical and specific renal failure-related risk factors. Accelerated atherosclerotic processes were the subject of another detailed study [28].

In the present work, I focus on morbidity connected with vascular access and anaemia. I also present the possibilities to lengthen graft-recipients' lives as well as prolong graft function through greater individualization of immunosuppressive treatment.

Complications linked with vascular access are the source of significant morbidity rates in patients on chronic dialysis programs, being the cause of 15% of hospital admissions. They most frequently occur in patients with vascular catheters and synthetic arteriovenous fistulas (polytetrafluoroethylene – PTFE), while being rare in patients with native vascular fistulas. For these reasons, the American National Kidney Foundation has stipulated that

This best kind of vascular access should be obtained in at least 50% of all patients starting dialysis. Currently, that percentage does not exceed 30% in most of the American centres [29].

Our own experience, as well as the achievements of other European centres prove that, using all the possible variants of native vessel fistulae, it is possible to create an autogenous fistula in 90% of the dialyzed patients, not excluding the "difficult ones" – i.e. those suffering from diabetes and the elderly (over 75 yrs old) [29-35]. A special mention is here due to a method invented in Wroclaw by W. Weyde, consisting of a subcutaneous transposition of a classical arteriovenous fistula in the forearm, between the radial artery and the cephalic vein. This procedure enables using this best possible distal vascular access in obese patients with type 2 diabetes, in whom the deeply located veins are inaccessible for puncturing. A report on this topic was published in the prestigious Kidney International [31] and is one of the three publications concerning vascular access recommended for reading on the American Society of Diagnostic & Interventional Nephrology webpages (http://www.asdin.org).

Another important cause for increased morbidity and mortality in dialyzed patients with end-stage renal disease is anaemia [36-38]. It has been determined that, in patients with hemoglobin levels within low range 8.0–9.99 g/dl, the risk of mortality was 35% higher than in those whose hemoglobin was within recommended range of 1113 g/dl. Twenty years passed last year since the onset of a breakthrough event – the development of synthetic erythropoetin and its implementation in the treatment of anaemia in the course of end-stage renal disease [36]. Modern studies on erythropoiesis stimulating factors focus on the development of long-lasting agents, lengthening intervals between dose intakes up to a month's time, and ensuring greater hemoglobin level stability. The clinical introduction of darbepoetin alfa, with a half life of 24.9h and 48.8h following respectively intravenous and subcutaneous administration, was an important step in this direction. Darbepoetin alfa, used once a week, effectively managed anaemia in dialyzed patients, while administration once every two weeks was sufficient as the supporting dose [39].The newest achievement in this respect is the production of pegzerpoetin alfa, with a 130 h circulating half-life [40]. Clinical trials,

involving a significant number of Polish centres, have demonstrated that this new drug manages anaemia with initial doses administered once every two or even three weeks, while the supporting effect is maintained when administered once a month [41,42].

Kidney transplantation is by far the best renal replacement therapy, providing patients with highest quality of life and lowering mortality rates 5 times in comparison with dialysis. This does not alter the fact that the most common cause for graft loss is the death of the graft-recipient (54%) with maintained kidney function, while the second most frequent cause is chronic graft nephropathy (40%). In each of these transplantation failures, the lack of adequate immunosuppressive treatment (either over- or undertreatment) is being underscored [43,44].

Thus, the individualization of immunosuppressive treatment has become a central issue, aiming to reduce the impact thereof in patients showing signs of allograft tolerance. The search is still on for markers of immune activity, which could indicate anti-graft alloreactivity suppression. Our team's studies have demonstrated that, in patients without acute graft rejection during 18months following transplantation and with coexistent normal glomerular filtration rate, a lower percentage of T CD4+ lymphocytes in peripheral blood expressed CD40L in comparison with graft-recipients with chronic graft nephropathy. Simultaneously, a higher percentage of T CD4+ cells expressing CTLA-4 was noted in those patients.

A clinical suggestion is therefore made, that graft recipients with typical CD40L and CTLA-4 behaviour trends accompanied by adequate glomerular filtration rate and graft function loss characteristic of chronic nephropathy, should be the proper candidates for dose reduction and weaning from nephrotoxic calcineurin inhibitors [45]. Limiting glucocorticosteroid use is another direction in minimizing post-transplant immunosupression. Clinical studies, largely conducted in Polish centres, have shown that in graft-recipients with good graft function and without signs of acute rejection, patients may safely be weaned from prednisone 3 months after transplantation [46]. Another study has found that in a fair share of kidney transplant recipients with average risk of rejection, if using tacrolimus with anti-IL 2-R monoclonal antibody (basiliximab) or tacrolimus with mophetyl mycophenolate, a single perioperative dose of 500 mg methylprednisolone may be sufficient without the follow-up steroid administration [47].

CONCLUSIONS

During the 61 years, which elapsed since the first successful treatment of acute renal failure with hemodialysis by its inventor, Willem Kolff, in the small Dutch town of Kampen, and 52 years since the first pioneer kidney transplant, performed in Boston by the later Nobel Prize winner Joseph Murray, renal replacement therapy has become standard procedure in end-stage renal disease. Millions of saved human lives are a measure of its success. Modern times, however, provide new challenges. Mortality and morbidity reduction in dialysis programs and post-kidney transplant follow-up, further advances in the treatment of diabetes, glomerulonephritis and other renal diseases are just some of the challenges which must be met, in order to obviate the catastrophic prophecy of a looming epidemic of end-stage renal disease, the magnitude of which reminds of the Biblical flood.

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