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NEPHROLOGY

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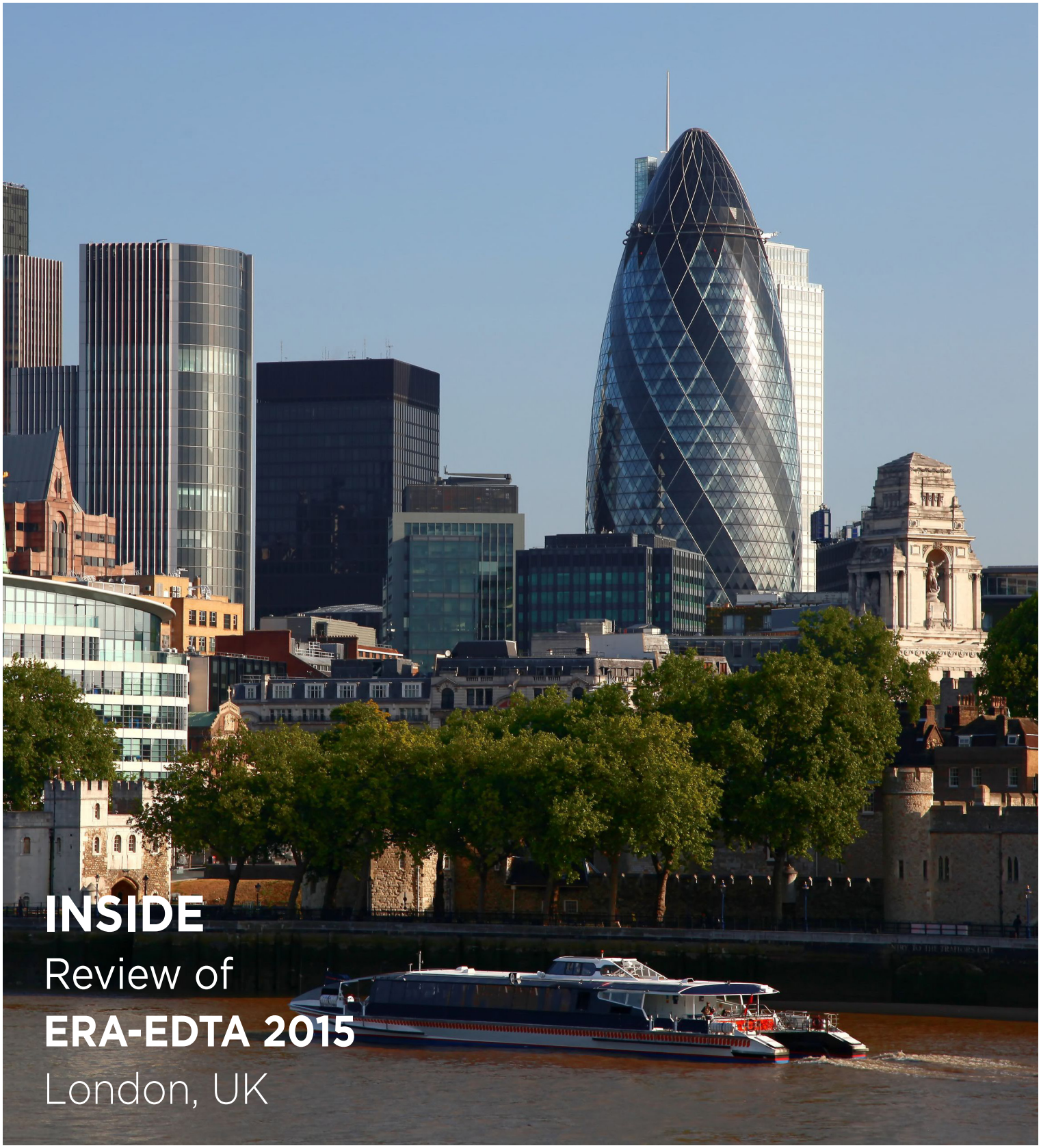

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ERA-EDTA 2015

London, UK

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Welcome

Hello and a very warm welcome to the 2015 edition of *European Medical Journal Nephrology*: home to the latest innovations and discoveries in the field. As always, our editorial team has been working tirelessly, not only to compile our usual selection of timely reviews, but also to bring you in-depth coverage of one of the most important events on any nephrologist's calendar: the 52nd Annual Joint Congress of the European Renal Association and the European Dialysis and Transplant Association (ERA-EDTA).

The EMJ team were there in London to cover all of the action, and our expansive report, brought to you straight from the congress floor, is the perfect refresher for those lucky enough to be there and an invaluable resource for those unable to attend. Inside, you will find coverage of all of the major news and developments from the event, including symposium reviews, reports on some of the most important presentations, and interviews with prominent delegates that we hope will build a comprehensive picture of the prestigious event.

As well as our congress review, you will also find a wealth of peer-reviewed scientific articles from some of the preeminent minds working in nephrology today, hand-picked for their quality and relevance. In their article *'Chronic kidney disease and endothelium'*, Rebić et al. outline the close relationship between chronic kidney disease (CKD) and the endothelium. The authors discuss how endothelium dysfunction (ED) increases the risk of cardiovascular events in CKD patients, bringing to the fore the need for ED evaluation to bolster diagnosis and treatment.

Significant advances have been made in the knowledge of the pathophysiology of immunoglobulin A nephropathy (IgAN). However, in their paper *'IgA nephropathy: new aspects in pathophysiology and pathogenesis'*, Berthoux et al. describe the need to further understand the pathogenesis of IgAN in order to explain the initiation of the disease and to ascertain the respective role of factors including genetics and the environment. These articles, along with a many others, are sure to make this edition of *EMJ Nephrology* indispensable.

ERA-EDTA was unmistakably a success, and surely a high watermark for this ever-evolving area of medicine. It is our hope that the very palpable sense of innovation and betterment in practice that was evident at the congress can be passed on to you, our readers, positively influencing your practice and the health of your patients. Thank you for reading, and we wish you all the best for the remainder of the year.

Spencer Gore

Team Principal, European Medical Journal

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Foreword

Prof Norbert Lameire

Emeritus Professor of Medicine and Nephrology, Ghent University, Ghent, Belgium

Dear Colleagues and Friends,

This issue of the *European Medical Journal Nephrology* offers interesting information on several aspects of acute and chronic kidney diseases (CKDs), incorporating the latest research and findings in this vital medical area.

This edition includes reviews of the management of refractory lupus nephritis, IgA nephropathy, epidemiology, diagnosis, prognosis, and a general update on acute kidney injury (AKI), the role of complement involvement in renal transplantation, and the state of the art of transplantation in autosomal-dominant polycystic kidney disease, as well as a challenging case report on retrograde intrarenal surgery for complex stones in a toddler with congenital renal anomalies, all of which will certainly be of major interest to our readers.

The 52nd European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) Congress, which took place in London on 28th-31st May 2015, featured a high-quality scientific and international programme that was presented through invited lectures, symposia, and free communications. The whole spectrum of kidney diseases was covered, including basic research, fluid and electrolyte disturbances, renal physiology, hereditary diseases, pregnancy and the kidney, and paediatric nephrology. AKI, intensive care nephrology, and all aspects of CKD and renal replacement therapy were also discussed.

Other highlights from this congress included a particularly interesting symposium in collaboration with the International Society of Nephrology, covering the enormous challenge of AKI facing the global nephrological community, as well as a symposium organised by ERA-EDTA with the Chinese Society of Nephrology, both of which are sure to be of great interest to a large number of medical professionals worldwide.

This is a hugely exciting and innovative time in nephrology, and on behalf of EMJ, the authors, and the editorial board who have worked so hard towards this edition, we hope that the content will be of great interest to you, the reader, and of course contribute towards the ultimate goal of improving patient care.

Yours sincerely,

Norbert Lameire

Emeritus Professor of Medicine and Nephrology, Medical Faculty of Ghent University, Ghent, Belgium; Editor-in-Chief of Acta Clinica Belgica; Past Chairman of the European Kidney Health Alliance.

ERA-EDTA ANNUAL CONGRESS 2015

EXCEL LONDON EXHIBITION & CONVENTION CENTRE, LONDON, UK

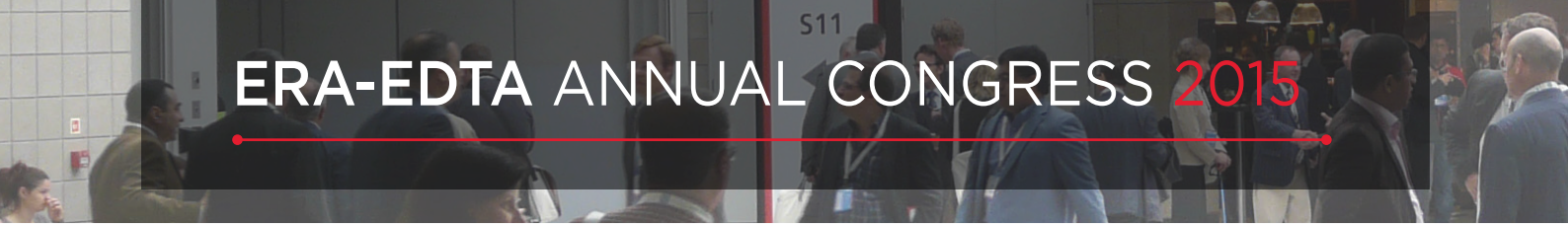
28TH-31ST MAY

Welcome to the *European Medical Journal* review of the 52nd European Renal Association – European Dialysis and Transplant Association Congress 2015

Hello and welcome to the *European Medical Journal* review of the 52nd European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Congress. The congress, which took place on 28th-31st May 2015, was hosted for the second time by London, a city steeped in over 2,000 years of history. When it comes to diversity of culture, London is a city unlike any other, and as the long-time home of English physician Richard Bright, deemed the 'father of nephrology', the city was an appropriate choice for the meeting of thousands of revered minds from across the globe.

The congress began with a CME programme offering 20 different courses arising from the work of several outstanding working groups. This was followed by a welcoming ceremony that featured opening speeches by Prof Andrzej Więcek and Prof David Goldsmith, ERA-EDTA President and Congress President, respectively. A special feature of this year's meeting was a collaboration with the UK's Renal Association, with the scientific programme reflecting the UK's contribution to the field of nephrology.

A record number of abstracts were submitted to the congress, with approximately 2,000 selected for presentation. There were over 270 national and international speakers, 32 free communication sessions,



ERA-EDTA ANNUAL CONGRESS 2015

150 exhibitors, over 20 mini-lectures, and 16 industry-sponsored sessions at the congress. "Overall we feel that a truly outstanding programme has been put together that will allow delegates to increase their knowledge through interaction during the congress with other participants and the many presenting experts," said Profs Więcek and Goldsmith in a joint address.

One of the highlights of the congress was the awards ceremony, which celebrated the exceptional achievements of dedicated individuals in the field. Dr Claudio Ponticelli received the 2015 ERA-EDTA Award for outstanding scientific achievements. One of the first to use new immunosuppressive drugs in renal transplantation, Dr Ponticelli's main contributions to nephrology are evident in the areas of primary glomerular diseases, lupus nephritis, and kidney transplantation. The recipient of the ERA-EDTA Award for outstanding contributions to ERA-EDTA was Dr Fernando Carrera, who has served as an exceptional Council Member, Secretary-Treasurer, and Congress President for ERA-EDTA. The Stanley Shaldon Award for Young Investigators was given to Dr Kate Stevens, a highly active contributor to ERA-EDTA and the Young Nephrologists' Platform.

"Overall we feel that a truly outstanding programme has been put together that will allow delegates to increase their knowledge through interaction during the congress with other participants and the many presenting experts."

Our summary of the 52nd ERA-EDTA Congress covers a range of cutting-edge presentations that showcased the abundance of international research on show. For example, a talk by Dr Julien Hogan explored the gender inequalities that exist in access to renal transplantation, with girls receiving slower access than boys, and emphasised the need for reform.

Ethnic disparities play a significant role in mortality in renal replacement therapy and access to transplantation in Europe, according to the ERA-EDTA Registry. A study presented by Dr Lidwien Tjaden underlined a worrying global trend, with outcomes poorest for black and Asian patients, supporting similar data obtained from previous studies in the USA, Canada, and Australia.

Dr Rosanna Coppo presented data from the VARIGA study, which showed how the identification and treatment of modifiable risk factors, including proteinuria, may limit the progression of IgA nephropathy. The amelioration of proteinuria and some forms of active renal lesion may benefit IgA nephropathy patients, while the emergence of biomarkers as predictors of prognosis may also open exciting routes to immune modulation.

We hope that our coverage of the 52nd ERA-EDTA congress will act as a refresher for those able to participate and encourage those who have not yet experienced the congress to attend in 2016. The accomplishments of this year's congress ensure that there is much to build on, and expectations are likely to be higher than ever for next year's meeting.

HIGHLIGHTS

Genetic Risk Factors Implicated in IgA Nephropathy Onset

MULTIPLE genetic risk factors influencing the onset of IgA nephropathy (IgAN), which results in kidney failure and subsequent transplantation in over 20% of patients, have been identified in a US-based study, the results of which were presented at the 52nd ERA-EDTA Congress.

Researchers from Columbia University Medical Center, New York City, New York, USA, in collaboration with Yale University, New Haven, Connecticut, USA and over 35 other international medical centres, explored the genomes of more than 20,600 individuals for genetic risk factors for IgAN. The team discovered 15 regions of the genome linked to the risk of disease. "Each one of these regions harbours a gene that is involved in the maintenance or protection of the mucosal lining of the intestine, or has been implicated in inflammatory bowel disease (IBD)," said principal investigator Dr Ali Gharavi, Chief of the Division of Nephrology, Columbia University Medical Center, in a recently written report published in ERA-EDTA's Daily Congress News, Issue 1, on the 28th May 2015. "The findings suggest that IgAN is an inflammatory disease involving, or perhaps initiated in the intestine." Therefore, current treatments for IBD may be adapted for the treatment of IgAN.

"The findings suggest that IgAN is an inflammatory disease involving, or perhaps initiated in the intestine."

The age of onset of IgAN was found to be significantly associated with a genetic risk score based on the 15 risk loci. In addition, the genetic risk factors were most common in Asian populations, who showed the highest incidence of IgAN, and were least common in Africans, who showed the lowest disease incidence. The researchers analysed these ethnic differences by comparing the distribution of various environmental factors with the prevalence of the genetic risk factors.

The team discovered that the strongest relationship was with the diversity of local pathogens,

and observed an especially strong connection with the diversity of local parasitic worms, known as helminthes, which frequently infest the intestine. "This strongly suggests that the genetic risk factors may have achieved high frequency in some populations because they provide protective adaptation against specific mucosal pathogens," added Dr Gharavi.

Risk Factors for Progression in IgA Nephropathy

PROGRESSION of IgA nephropathy (IgAN) may be mitigated through the identification and treatment of modifiable risk factors. Retrospective analysis of data from the VALIGA (Validation Study of the Oxford Classification of IgAN) trial was presented at the 52nd ERA-EDTA Congress by Dr Rosanna Coppo, City of the Health and the Science of Turin Health Agency, Regina Margherita Children's Hospital, Turin, Italy, and suggested that treatments capable of ameliorating proteinuria and some forms of active renal lesion may have beneficial effects in patients with IgAN.

Proteinuria is a modifiable risk factor as it was observed to respond to steroid/ immunosuppressive treatment, which also led to a protective effect in terms of preventing renal decline.

The VALIGA study, which was supported by ERA-EDTA, was conducted in 13 European countries and included 1,147 IgAN patients. After 10 years of follow-up, the presence of proteinuria <0.5 g/day was associated with significantly reduced risk of progression to a combined endpoint of 50% reduction in estimated glomerular filtration rate (eGFR) or end-stage renal disease, even compared with patients displaying proteinuria between 0.5 and 0.9 g/day, which has until recently been considered as benign. Proteinuria is a modifiable risk factor as it was observed to respond to steroid/immunosuppressive treatment, which also led to a protective effect in terms of preventing renal decline.

In IgAN, proteinuria is associated with active renal lesions, especially mesangial proliferation and endocapillary hypercellularity. In the VALIGA cohort, the presence of mesangial proliferation was a significant factor for prediction of IgAN progression, including in patients with either early diagnosis (proteinuria <0.5 g/day) or advanced disease (eGFR <30 ml/ min/1.73 m^2). However, this clinical variable lost its predictive power when patients receiving steroid/ immunosuppressive treatment were analysed separately, suggesting that this form of lesion may be amenable to this type of therapy. The presence of endocapillary hypercellularity and crescent formations was not shown to be a predictor of progression.

Prediction of prognosis in IgAN patients may be further enhanced by the characterisation of biomarkers that reflect variables influencing the increased production of IgA by mucosa-associated lymphoid tissue, and these may provide compelling new targets for immunomodulatory agents.

Combined Therapy Produces Promising Results for Amyloidosis Sufferers

INDUCTION therapy with bortezomib and dexamethasone (BD) prior to autologous stem cell transplantation (ASCT) has emerged as an effective and tolerable treatment for patients with systemic light chain (AL) amyloidosis.

The novel agent bortezomib is active in AL amyloidosis, but its exact role remains undefined. Dr Xianghua Huang, Research Institute of Nephrology, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China and colleagues presented their results at the 52nd ERA-EDTA Congress. They evaluated the efficacy and safety of bortezomib with BD in the treatment of patients with renal AL amyloidosis. Seventy-two patients who were newly diagnosed with AL amyloidosis received a median of two cycles of BD treatment.

A haematologic response was attained in 75% within a median time of 2 months, including 44.5% complete responses, while a renal response was attained in 50% of patients after 1 year and 60% after 2 years. The median time of progression-free survival was 45 months, and the estimated overall survival rates at 12 and 24 months were 83.0% and 75.8%, respectively.

To further improve the response rate in patients with AL amyloidosis, the team assembled a single-centre, prospective, randomised controlled trial to assess bortezomib in combination with BD for induction chemotherapy prior to ASCT. Fifty-six patients newly diagnosed with renal (100%), cardiac (57.1%), liver (7.1%), or nervous system (8.9%) AL amyloidosis were enrolled in the trial. An intention-to-treat analysis revealed a higher rate of complete remission in the BD + ASCT arm at both 12 and 24 months (67.9% and 70%, respectively) than with the ASCT-only therapy (35.7% and 35%, respectively).

After a median follow-up of 28 months, the survival rates at 24 months post-treatment were 95% in the BD + ASCT group and 69.4% in the ASCT-only group. "Our preliminary data suggest that the outcome of treating AL amyloidosis with BD induction and ASCT was superior to the outcome of the ASCT treatment alone," said Dr Huang, in a recently written report published in ERA-EDTA's Daily Congress News, Issue 3, on the 30th May 2015.

Over 270
national and international
invited
speakers

"Several AGT crystal structures have been obtained from mutated sequences, demonstrating how single amino acid changes affect the enzyme conformation and stability."

New Therapeutic Options to Replace Renal Transplantation in PH1

ISOLATED renal transplantation (RTx) is no longer recommended for the treatment of primary hyperoxaluria Type 1 (PH1), but a number of alternative approaches offer promising new therapeutic directions according to recent findings that were presented to the participants of the 52nd ERA-EDTA Congress.

An autosomal recessive disorder, PH1 is triggered by a defect in the liver-specific peroxisomal, pyridoxal-5'-phosphate-dependent enzyme alanine-glyoxylate aminotransferase (AGT), which results in oxalate overproduction. In tandem with a reduced rate of oxalate excretion by the kidneys, extended overproduction of oxalate by the liver causes plasma oxalate (Pox) levels to rise above critical saturation, which catalyses the deposition of oxalate in numerous organs.

RTx replenishes renal function and enables the removal of soluble Pox. However, oxalate overproduction and its resultant deposition in tissues continues, which leads to a high rate of urinary oxalate excretion and the subsequent build-up of oxalate within the graft.

Currently, the sole therapeutic option for PH1 is combined liver–renal transplantation, which confers substantial risks relating to the surgical procedure and long-term immunosuppression. In a recently written report published in ERA-EDTA's Daily Congress News, Issue 3, on the 30th May 2015, Dr Pierre Cochat, Professor of Pediatrics, Université Claude Bernard Lyon 1, Lyon, France, suggested that future studies should concentrate on molecular approaches addressing the fundamental metabolic defect. "Several AGT crystal structures have been obtained from mutated sequences, demonstrating how single amino acid changes affect the enzyme conformation and stability," explained Dr Cochat. "This may allow designing chemical chaperones to stabilise the AGT enzyme and restore its targeting to the correct cellular compartment for PH1 patients with missense mutations."

There are other promising alternatives to RTx also currently in development. For example, patient-specific induced pluripotent stem cells could provide an efficient approach to producing genetically-corrected cells, while approaches involving *in vitro*

synthesised interference RNA (RNAi) are encouraging.

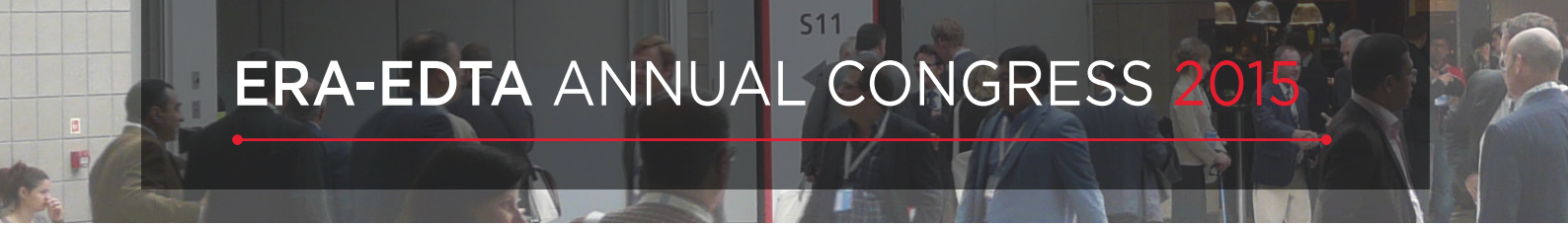
New Insights into European Treatment of Idiopathic Nephrotic Syndrome

COLLABORATION between the members of a new working group of the European Society of Pediatric Nephrology has begun to bear fruit with regard to understanding continental variations in the treatment of paediatric idiopathic nephrotic syndrome. The working group was established in 2013 and has already managed to enrol 94 members from 21 countries. The co-ordinator of the working group, Prof Georges Deschênes, Chief of Pediatric Nephrology, Hospital Robert-Debré, Paris, France, provided attendees of the 52nd ERA-EDTA Congress with an update on the group's activities.

Three Europe-wide surveys have already been completed, revealing wide variations in the treatment of idiopathic nephrotic syndrome. For example, a survey on the use of steroids at first manifestation was returned by 25 members and showed that the cumulative doses of prednisone (used by 13 members) or prednisolone (used by 12 members) ranged from 2,240-4,245 mg/m^2, with the duration of treatment ranging from 8-24 weeks. Furthermore, tapering of steroid therapy before withdrawal was included in 18/25 protocols; limitation of doses up to a maximum of 60 mg/day was present in 18/25 protocols, meaning that any patients with a surface area of >1 m^2 (30 kg body weight) are receiving less than the expected cumulative dose in mg/m^2; and 16/24 protocols are treating cases of steroid resistance with three intravenous infusions of methylprednisolone. Treatment of the first flare was shown to be uniform between Denmark, France, Germany, and the UK, albeit with three different protocols. The other two surveys addressed steroid resistance and the use of rituximab, and both reported wide differences in practice.

Three Europe-wide surveys have already been completed, revealing wide variations in the treatment of idiopathic nephrotic syndrome.

In addition to the surveys, the working group has also registered the various prospective trials that each member is co-ordinating and held annual meetings in order to update members with results from the trials and to develop new projects. Additional long-term goals include setting common definitions and minimal guidelines for standards of care and prompting greater co-ordination of research efforts.



Potential Bone Biomarkers May Aid in the Bone Health of Children with CKD

BONE and growth biomarkers are strongly associated with bone turnover osteocyte activity in paediatric CKD patients, a discovery that could enable the future development of targeted therapies. These promising results were presented to delegates at the 52nd ERA-EDTA Congress.

Mineral and bone disorder (MBD) is a frequent complication of CKD in children. CKD-MBD covers complex abnormalities of bone turnover and mineralisation, serum minerals, and regulatory hormones; it may also impact on linear growth, and through the promotion of vascular calcification is considered a prime cause of early cardiovascular morbidity in CKD.

Monitoring of CKD-MBD is difficult. Bone biopsy is considered the gold-standard procedure, but its invasiveness ensures that it is recommended only in exceptional clinical situations. Various bone biomarkers designed to assess the activity of different bone cell types have been proposed for use in paediatric patients.

In a recent study involving a large cohort of children with pre-dialysis CKD, newly established paediatric reference values for bone alkaline phosphatase, tartrate-resistant acid phosphatase 5b, sclerostin, and fibroblast growth factor 23 revealed important connections between serum bone biomarkers and patient characteristics, traditional indicators of bone metabolism, and linear growth. Overall, the observed values of the biomarkers suggested a high bone-turnover state in children with CKD, and growth hormone treatment in paediatric CKD patients resulted in osteoanabolic pattern and normalisation of osteocyte activity. Finally, osteocyte markers were linked to standardised height, and markers of bone turnover predicted height velocity.

"Although these results are promising, the value of these novel bone biomarkers in clinical practice remains to be established," said Prof Dieter Haffner, Director of the Department of Paediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School Children's Hospital, Hannover, Germany in a report published in ERA-EDTA's Daily Congress News, Issue 3, on the 30th May 2015.

Inconsistencies in Transplant Rates are Gender-Specific

INEQUALITIES in the access to renal transplantation (RTx) for girls and boys have been highlighted in a study led by Dr Julien Hogan, Department of Paediatric Nephrology, Armand Trousseau University Hospital and University Pierre and Marie Curie (UPMC), Paris, France, who presented the findings at the 52nd ERA-EDTA Congress.

"Although these results are promising, the value of these novel bone biomarkers in clinical practice remains to be established."

The theme for the Congress is the River Thames itself

In spite of the World Health Organization's guidelines regarding fair access to transplantation, adult studies have demonstrated significant inequalities between genders, with females experiencing lower access to transplantation in both Europe and the USA. Among children in France, a pattern of slower access to RTx for girls has been noted, albeit without proof of a statistically significant difference.

In a cohort of 6,454 children, researchers predictably found that girls had slower access than boys to RTx due to a 23% lower probability of receiving a preemptive transplantation. The team also found a longer follow-up time of almost 1 year before renal replacement therapy in boys (23.0 [IQR: 2.4-68.6] months) compared with girls (14.4 [IQR: 0.6-53.6] months).

The researchers theorised that the prominent nature of the gender difference among patients with congenital anomalies of the kidney and urinary tract (CAKUT) could result in earlier diagnoses. However, this was disproven by the lack of a significant gender difference in estimated glomerular filtration rate (eGFR) at first visit to a specialist when adjusting for age and cause of renal failure, while the lower rate of preemptive transplantation continued in girls.

"Our study should raise awareness for the management of girls with renal diseases and prompt all caregivers to avoid any undue delays in pre-transplant workup."

The team also tested the hypothesis that the gender difference could be explained by dissimilarity in time of progression towards end-stage renal disease, discovering a trend towards faster rate of eGFR decline in females. However, only 70% of the gender-specific difference in preemptive transplantation rates could be explained by medical factors; therefore non-medical determinants such as patient motivation must be studied in detail.

"Our study should raise awareness for the management of girls with renal diseases and prompt all caregivers to avoid any undue delays in pre-transplant workup," said Dr Hogan in a report published in ERA-EDTA's Daily Congress News, Issue 1, on the 30th May 2015.

Ethnic Disparities in Renal Transplantation

SURVIVAL on renal replacement therapy (RRT) and access to renal transplantation in Europe are affected by racial disparities, reflecting an emerging global concern.

Renal transplantation is widely recognised as the optimal renal replacement therapy (RRT) for patients with end-stage renal disease (ESRD). However, concern has emerged regarding racial disparities in access to transplantation, supported by studies conducted in the adult ESRD population.

"In conclusion we found important differences in mortality on RRT and access to transplantation, with less favourable outcomes for black and Asian paediatric ESRD patients in Europe."

Data from studies performed in the paediatric ESRD population in the USA, Canada, and Australia mirror those performed in adult patients, with black children experiencing reduced access to deceased donor wait-listing and lower rates of preemptive and living donor transplants compared with white children. As data of this type are still lacking in Europe, Dr Lidwien Tjaden, Department of Pediatric Nephrology, Emma Children's Hospital, Academic Medical Center, Amsterdam, Netherlands and colleagues, who presented their findings at the 52nd ERA-EDTA Congress, began a study with the aim of assessing the differences among racial groups in survival on RRT and access to renal transplantation in a large European paediatric ERSD population.

Using the ESPN/ERA-EDTA registry, the team enrolled 891 patients aged >19 years from eight medium-to-high-income countries, who began RRT between 2006 and 2012. Overall, 705 (79.1%) patients were white, 50 (5.6%) were black, 69 (7.7%) were Asian, and 67 (7.5%) were from other racial groups. After 3 years, 75% of white patients and 80% of other patients had received a first transplant compared with 66% and 63% of the black and Asian subsets, respectively.

"In conclusion we found important differences in mortality on RRT and access to transplantation, with less favourable outcomes for black and Asian paediatric ESRD patients in Europe," said Dr Tjaden in a recently written report published in ERA-EDTA's Daily Congress News, Issue 1, on the 28th May 2015. Alongside other global data, these results suggest that such disparities are a significant

global issue. The team therefore urges further research to address the restrictions to optimal treatment among ethnic minority populations.

Socioeconomic Factors Contribute to Chronic Kidney Disease in the Elderly

CHRONIC kidney disease (CKD) is more prevalent in the elderly population, and is affected by socioeconomic factors and a lack of awareness about the disease, according to the data analysis from a national survey, PolSenior, carried out in Poland. These observations were presented at the 52nd ERA-EDTA Congress by Prof Andrzej Więcek, Professor of Internal Medicine and Nephrology, Head of the Department of Nephrology, Endocrinology and Metabolic Diseases, Medical University of Silesia, Katowice, Poland.

The analysis included 3,797 elderly Polish individuals and it was reported that 29.4% of those over 65 years developed CKD, and this proportion increased with age up to a value of 65% in those aged over 90 years. The study also showed that CKD was more frequent among urban dwellers, those who undertook low levels of physical activity, and people with self-reported poverty. Other studies, such as NHANES in the USA and PREVEND in the Netherlands, have previously documented how factors such as income and education can affect the prevalence of CKD among the general population.

Another important finding from the PolSenior survey was the distinct lack of awareness among elderly individuals with CKD that they even had the disease. Indeed, just 3.2% of those with CKD were aware of their condition, which clearly must have a negative impact upon their clinical management.

"Results obtained by the PolSenior study clearly suggest that there is a need for improvement of nephrological care and better educational programmes in the elderly Polish population."

In a written-report featured in ERA-EDTA's Daily Congress News, Issue 1, on the 28th May 2015, Prof Więcek commented: "Results obtained by the PolSenior study clearly suggest that there is a need for improvement of nephrological care and better educational programmes in the elderly Polish population."

These observations highlight the need for a greater assessment of socioeconomic conditions by healthcare providers, as well as greater awareness of CKD among those at risk, in order to ensure better treatment of this condition.

CRP Levels May Help Treat Hidden Conditions in Dialysis Patients

OBSERVING levels of C-reactive protein (CRP) may be key in diagnosing and treating inflammation-associated illnesses in dialysis patients, offsetting the risk of hard events including cardiovascular (CV) events, according to findings presented at the 52nd ERA-EDTA 2015 Congress.

"Monitoring CRP levels might be useful to detect comorbid conditions that may be clinically silent..."

CRP is the most commonly used marker of inflammation due to its availability, cost, and reproducibility. Increased CRP levels may suggest an associated illness that must be ruled out, and monitoring these levels may uncover conditions including cancer and autoimmune and CV diseases.

Chronic inflammation in dialysis patients is associated with anaemia, malnutrition via increased catabolism, atherosclerosis, and arterial calcifications; these lead to increased mortality and a syndrome known as malnutrition inflammation atherosclerosis (MIA). Multiple studies have revealed a connection between the MIA syndrome and hard outcomes of dialysis patients, resulting in some countries recommending regular surveillance of inflammation in the biological follow-up.

Critics of regular dosing of CRP in dialysis patients say that therapeutic strategies for chronic inflammation are absent; clinical trials in non-CKD patients have proved that statins may reduce CRP levels and mortality. There is no documented therapeutic strategy to lower markers of inflammation and decrease the occurrence of hard events, especially CV events.

The usefulness of CRP monitoring has thus been questioned. In a recently written report published in ERA-EDTA's Daily Congress News, Issue 3, 30th May 2015, Prof Christian Combe, Professor of Nephrology, Bordeaux Segalen University, Bordeaux, France, said: "We believe first that monitoring CRP levels might be useful to detect comorbid conditions that may be clinically silent, which may lead to significant investigations and actions for the patient; second, in patients with the highest CRP levels, special attention will be given to CV assessment, and to nutritional assessment."

This may also lead clinicians to clinically relevant actions including CV interventions, or to initiation of nutritional support. However, further trials are required to validate these views, given the high frequency

and magnitude of inflammation in dialysis patients.

Vitamin D May Be a Heartfelt Problem for Renal Patients

VITAMIN D plays a greater role in the body's overall metabolism than has previously been recognised, with dysregulation of the vitamin potentially contributing to cardiovascular (CV) disease, an important cause of mortality in renal patients.

Data describing the activating enzymes, metabolites, transport proteins, specific receptor, and regulatory proteins involved in the 'vitamin D endocrine system' were presented at the 52nd ERA-EDTA congress by Prof Sandro Mazzaferro, Professor of Nephrology and Head of the Nephrologic Unit, "La Sapienza" University of Rome, Rome, Italy.

An important implication of vitamin D dysregulation relates to the strong link between vitamin D and the vascular system, with vitamin D exerting significant modulatory effects on cell types governing vascular function and involved in vascular disease. Research has shown how vitamin D receptors and vitamin D hydroxylases are consistently expressed by endothelial cells, vascular smooth muscle cells, and immune cells. It is therefore likely to be the case that the effect of vitamin D dysregulation in terms of its contribution to specific vascular diseases is complex, and may be especially relevant when trying to reduce the impact of these diseases in renal patients.

"The negative association with CV outcome, reported in several observational studies, warrants research efforts in particular in renal patients who are plagued with both vitamin D deficiency and CV mortality," said Prof Mazzaferro as reported in ERA-EDTA's Daily Congress News, Issue 1, on the 28th May 2015.

Although our knowledge of the impact of vitamin D on the cells that govern vascular function in both physiological and in pathological conditions has become greatly enhanced, there is still a need for further research on the effects of vitamin D dysregulation and how these may be addressed in order to positively impact CV mortality in renal patients.

"The negative association with CV outcome, reported in several observational studies, warrants research efforts in particular in renal patients who are plagued with both vitamin D deficiency and CV mortality."

"These data suggest that in AKI, more than in CKD, factors other than renal failure per se interfere with concentration of protein-bound uraemic toxins."

Uraemic Toxin Retention Could Influence Acute Kidney Injury

CORRELATION between indoxyl sulphate (IS) retention and occurrence of acute kidney injury (AKI) has been suggested by a series of studies in rat models, the outcomes of which, along with a wider scope of details, were presented at the 52nd ERA-EDTA Congress.

The extreme paucity of data in human AKI contrasts starkly with results from these animal trials, which indicate that the retention of protein-bound uraemic toxins such as IS in AKI causes tubular damage and dysfunction, as has previously been demonstrated in chronic kidney disease (CKD), as well as further functional kidney deterioration. Prof Raymond Vanholder, Department of Nephrology, Ghent University Hospital, Ghent, Belgium, and colleagues are currently conducting preliminary trials in patients with septic AKI.

Around 2000 abstracts have been selected for presentation, and 160 of these will be presented orally

AKI is a frequent cause of kidney failure, yet the vast majority of research on uraemic toxins in kidney disease has been focussed on CKD. In theory, similar degrees of kidney dysfunction should lead to similar retention patterns. However, in practice there may be numerous factors triggering an alternative evolution in AKI compared to CKD. The most noteworthy of these is the severity and suddenness of tubular dysfunction in AKI, disrupting a key mechanism for uraemic toxin removal called tubular clearance. In addition, differences in food intake pattern, patient immobilisation, and therapies such as antibiotics may interfere with the generation of protein-bound toxins.

In rat models, cisplatin caused retention of IS as well as inhibition of OAT function. Other models showed that ischaemia-reperfusion AKI and renal hypoperfusion induced by myocardial infarction in rats are accompanied by an increase in serum IS, while the drug meclofenamate was effective in preventing its rise in the ischaemic model.

"These data suggest that in AKI, more than in CKD, factors other than renal failure per se interfere with concentration of protein-bound uraemic toxins," said Prof Vanholder, in a recently written report published in ERA-EDTA's Daily Congress News, Issue 2, on the 29th May 2015.

BEST ABSTRACT AWARD WINNERS AT ERA-EDTA 2015

The recipients of the 11 Best Abstract prizes awarded at this year's ERA-EDTA congress addressed a wide variety of topics in the field of nephrology, and 6 of the 11 were also included in the list of 'Eight Best Abstracts presented by Young Authors'. The winners represented research teams from across the continent (and, in some cases, their collaborators from the USA), with four of the winning abstracts coming from Germany, three from the UK, and one each from the Netherlands, Norway, Sweden, and Spain. A special mention should go to researchers from the Saarland University Medical Center in Homburg, Germany, whose research on chronic kidney disease (CKD) was recognised with 2 of the 11 prizes.

The two prize-winning abstracts from Homburg addressed both basic and clinical aspects of CKD. Lisa Fell described how some of the various intravenous iron preparations used to treat anaemia in CKD patients can affect the *in vitro* differentiation of monocytes into macrophage and dendritic cell lineages. If these findings are replicated in subsequent *in vivo* studies then a more informed choice of which iron preparations to use may help to improve the immunocompetence of CKD patients and prevent infections in this vulnerable population. The second prize-winning abstract from Homburg was awarded to Kyrill Rogacev who identified growth differentiation factor 15 as a novel, strong, and independent plasma biomarker that correlates inversely with baseline glomerular filtration rate (GFR), and which is capable of predicting progression of CKD (the occurrence of a composite endpoint of either a halving of GFR or initiation of renal replacement therapy).

Patients with CKD were also the focus of Annette Bruchfeld's abstract that demonstrated the safety and efficacy of a combination of grazoprevir and elbasvir in the treatment of hepatitis C virus (HCV) infection in these patients. Patients with CKD and HCV infection have limited anti-HCV treatment options due to a lack of safety data in this setting, and this was the first Phase III study of an oral anti-HCV regimen in HCV-infected CKD patients. The study reported encouraging results, with the drug combination being generally well tolerated and highly efficacious at the fourth follow-up time point.

Another new, potential predictive biomarker for kidney disease was described by Ruth Pepper who reported the ability of serum calprotectin (S100A8/A9) measurements to predict the risk of relapse in anti-neutrophil cytoplasmic antibody-associated vasculitis. The study found that patients in whom calprotectin levels were suppressed between baseline and Month 6 displayed significantly greater relapse-free survival compared with those who did not display suppression, which suggests that this marker may be useful for identifying

patients who would benefit from alternative or more intensive therapy.

As well as improving our ability to predict the prognosis of patients with positively diagnosed diseases, developments in molecular diagnostic testing are also improving our diagnosis of conditions that have previously been difficult to assign a cause to. Albertien van Erde provided an example of how modern-omics technologies can be applied by describing how the genetic sequencing of 399 genes involved in renal disease or urinary tract development can help to provide a diagnosis in cases of end-stage renal disease (ESRD) in patients younger than 30 years. Approximately 25% of ESRD patients younger than 30 years do not have a primary renal disease diagnosis and this may hamper their likelihood of receiving a transplant and leave their genetic relatives at risk due to undetected disease. The researchers applied ultra-strict data filtering to the results obtained from 132 cases and were able to provide a molecular diagnosis in 15 cases (11.4%), which confirmed a registered diagnosis in 6 cases and led to an unexpected reclassification in 9 cases. The application of this type of genetic testing early in the management of young ESRD patients may help to improve the aetiological classification of disease, as well as provide opportunities for education and genetic counselling in affected families.

The power of modern analytical techniques was further underlined by the abstract of Ariadna Padullés who described the use of a Bayesian prediction model based on population pharmacokinetics to optimise the dosing of antiviral drug therapy for cytomegalovirus infection in kidney transplant recipients. The two-arm trial compared treatment with the manufacturers' recommended dose of either ganciclovir or valganciclovir with a regimen based on adjustment of doses in order to achieve desirable drug exposure targets based on Bayesian population analysis. Adjusted antiviral dosing resulted in 88.4% of patients achieving desirable area under the curve (AUC) therapeutic target values, whereas only 18.7% of patients in the group receiving an invariant dose achieved the AUC target. Furthermore, those patients receiving an invariant dose also took longer to achieve target AUC, and there were no differences in toxicity observed between the groups.

Recipients of renal transplants were also the focus of Julia Arnold's abstract describing the risk of fracture in transplant patients observed in England during the period 2001-2013. The study analysed 21,769 first renal transplant procedures and 112,512 patient-years of follow-up. The overall fracture rates following renal transplantation were lower than those reported by historical cohorts, which mainly describe older studies performed in the USA, and found that increasing age, female gender, Caucasian

ethnicity, and a history of pre-transplant diabetes mellitus or previous fracture were associated with all-fracture and hip fracture risks following renal transplantation, with hip fracture being independently associated with an increased risk of death.

As well as a greater risk of fracture, the increasing longevity of renal transplant recipients has also led to a growing need for second renal allografts in some patients, as the half-life of a renal allograft is 10-20 years. Many of those in need of a second transplant are elderly and many will have the comorbidity profile associated with long-term immunosuppressive therapy, which may affect graft outcome and patient survival. Kristian Heldal's abstract compared the outcomes of 720 Norwegian renal transplant recipients receiving either their first or second allograft after 65 years of age. Both the estimated 5-year graft survival rate and the risk of graft loss were similar between the two groups, showing that second renal transplants perform well in patients older than 65 years and that these patients are appropriate to receive a second transplant.

In addition to the increasing longevity of the general population, there is also a growing prevalence of cardiovascular disease. The abstract of Chris Laing described a large, multicentre, randomised controlled study investigating the effects of remote ischaemic preconditioning (RIPC, in which non-lethal ischaemia applied to an organ or tissue protects another organ or tissue as an adaptive response) as a promising renoprotective intervention in 1,612 patients at 28 UK sites. The study investigated the effect of RIPC on renal outcomes as part of the Effect of Remote Ischaemic preConditioning on clinical outcomes in patients undergoing Coronary Artery Bypass Graft surgery (ERICCA) study.

In addition to the clinical data described at the congress, fundamental studies investigating the pathophysiology of renal diseases and aiming to identify new molecular targets were also selected as prize winners. Beina Teng's abstract used a variety of *in vivo* and *in vitro* models to demonstrate that the CD2AP homologue CIN85 is involved in the endocytosis of nephrin in podocytes under diabetic conditions. Nephrin is a podocyte-specific protein that is crucial for an intact filtration barrier, and its loss has been observed in rodent models of experimental diabetes, as well as in human diabetic kidney disease. The results from the study suggest that CIN85 may be a novel target for the prevention of diabetic nephropathy. Another novel insight into disease pathophysiology was reported in the abstract of Shrikant Mulay who described an investigation into the various types of crystals that cause crystalline nephropathy and nephro-/urolithiasis. The study concluded that crystal-related cytotoxicity involves the TNFR1-RIPK1-RIPK3-MLKL signalling pathway of necroptosis and therefore the components of this pathway may represent novel targets for therapeutic interventions designed to limit crystalline nephropathy.

Vladimir Tesar

Professor of Medicine and Head of the Department of Nephrology, First Faculty of Medicine, Charles University and the General University Hospital, Prague, Czech Republic.

Q: As part of World Kidney Day (WKD) 2015, the steering committee of the event published an editorial leading with a quote from Dr Martin Luther King: "*Of all of the forms of inequality, injustice in health is the most shocking and inhumane.*" How do you see the status quo regarding healthcare inequality in general?

A: I agree that we cannot speak about human equality while tremendous differences in the access to healthcare and the availability of expensive but life-saving care still persist. On the other hand, improvements in hygiene, sanitation, vaccination, and effective treatment of infectious diseases must always precede the introduction of much more expensive interventions, because these fundamental improvements are usually most effective in terms of increasing an often still very low life expectancy.

Q: How did your team interpret the message of equality in healthcare expressed via WKD?

A: The main message of WKD to the public is that chronic kidney disease (CKD) is not rare and that it not only confers the relatively low risk of progression to end-stage renal disease (ESRD), but that it, much more importantly, dramatically increases cardiovascular (CV) morbidity and mortality. We should keep in mind that most patients with diabetic CKD 3 will die before they can progress to ESRD. Early identification of CKD patients (in Stages 1-3) may, and should, result in early implementation of various cardioprotective interventions, which may have a positive impact on the life expectancy of these patients.

Q: Does your department mark WKD in any special way?

A: In our department we regularly give those who are interested the chance to examine proteinuria and serum creatinine, and the attendance is usually around 300 patients. Similar activities are done in many other renal centres in the country, with thousands of patients examined in that way. Usually, there is also information partly related to our regular press conference on kidney disease presented on TV, on the radio, and in many newspapers.

Q: Do you have any plans for how you may continue to raise awareness of WKD, and kidney disease in general, within the Czech Republic?

A: We believe that we will be able to further expand our activities to other renal centres in the country and, based on our recent negotiations with the state authorities and insurance companies, we will be able to further advertise our prepared programme of CKD screening in high-risk populations.

Q: What do you hope WKD will achieve in the long term? Do you think it will pressure certain groups, be it the government or otherwise, to spread and implement these messages within their healthcare systems?

A: Before the long term, I believe that the medium-term task is to generate support for the active screening of CKD in high(er)-risk populations, e.g. in patients older than 50 years, especially those with diabetes and/or hypertension and/or CV disease. Effective care for the early stages of CKD (CKD 1-3) requires close co-operation with general practitioners and other specialists (e.g. diabetologists); CKD 4 patients should be referred to nephrologists.

Q: What first made you think that these issues needed to be addressed? Was there any particular experience that inspired you to take this point of view?

A: In most European countries we are still confronted with the late (and very late) referral of patients with CKD to nephrologists. In these late-referred patients there is limited opportunity for the diagnosis and treatment of primary renal disease (and the early treatment of the

complications of CKD), as well as a limited chance to choose the dialysis method and a limited chance of pre-emptive renal transplantation. All this triggers a greater need for unnecessary interventions (e.g. placement of intravenous catheters) and, most importantly, poorer outcomes in terms of mortality during the first year on renal replacement therapy (RRT). Therefore, the early identification of CKD and early referral to a nephrologist is of utmost importance.

Q: Which other conditions/diseases can lead to ESRD?

A: In developed countries, CKD clearly belongs among the 'diseases of affluence' and its prevalence is related to other metabolic (obesity, diabetes) and CV (hypertension, atherosclerosis) diseases. In developed countries, glomerulonephritides are still the cause of ESRD in about 20% of patients, and the most common inherited disease, autosomal dominant polycystic kidney disease (ADPKD), is responsible for about 8% of cases. In some ethnic minorities (e.g. African Americans) hypertensive kidney disease is more frequent than in their white compatriots. Renal disease related to infection still plays an important role in some developing countries, e.g. disease due to malaria in Africa.

Q: What changes would you like to see in the field of nephrology, either on a global scale or at a local level?

A: In general, the attention of nephrology is slowly shifting from improving the availability and quality of RRT to the early diagnosis and specific treatment of individual renal diseases and the prevention of ESRD. As an example, the biological treatment of some glomerular diseases (e.g. anti-neutrophil cytoplasmic antibody [ANCA]-associated vasculitis, lupus nephritis, membranous nephropathy, atypical haemolytic uraemic syndrome) and the putative treatment of ADPKD, such as with V2-receptor antagonists, is very expensive and this new barrier will further complicate patient access to this kind of treatment in developing countries, and potentially some ethnic minorities in developed countries.

Q: Are there any major differences in the way that healthcare is organised in the Czech Republic compared with other European countries?

A: I do not think so. RRT is available to all patients in the Czech Republic and traditionally there is a relatively high transplantation rate; what I appreciate very much is an increasing proportion of transplantation from living donors. There is a dense network of dialysis units and renal centres, and patients with glomerular disease and inherited kidney diseases are referred to special centres with access to the latest diagnostic and therapeutic facilities.

Q: With regards to organ transplantation, recent news in the UK has featured reports of an opting-out system in Wales, in which all individuals are registered as organ donors unless they apply not to be. How do you think such a system might impact upon the vast number of people on the donor waiting list?

A: I am not very familiar with transplantation medicine – we do not perform renal transplantation in my department as there is a large transplantation centre in another hospital in Prague. Of course, legislation has a great impact on the availability of organs from deceased donors. In countries with presumed consent, the availability is always much better compared with those countries where each individual must, in advance, express their consent for the use of his/her organs in transplantation.

Q: How can we encourage people to become donors, without making organ donation compulsory?

A: I believe that we should pay much greater attention to the dissemination of the necessary information, not only using mass media but also asking for help from general practitioners, nurses, and patient organisations, etc.

Q: Are there many things that can be done to sustain the lives of those waiting for a kidney?

A: The main aim is to shorten the waiting time by early identification of patients, and to increase the availability of living and deceased donors.

"CKD 4 patients should be referred to nephrologists."

To sustain the lives of patients waiting for renal transplantation means providing the patients with the highest quality of renal care available, including not only conservative and dialysis treatment, but also the treatment of complications and comorbidities.

Q: What is the next stage of your own research, and of kidney research in general?

A: My main area of interest has always been glomerular disease, especially ANCA-associated vasculitis, lupus nephritis, and IgA nephropathy. I am very happy that I have had the chance to take part in many areas of research in this particular field, including genome-wide association studies, registries, biomarker studies, and clinical trials. Tremendous progress in understanding the pathogenesis of these diseases has been translated into new, more specific, and better-tolerated modes of treatment and, fortunately, it is an ongoing process from which we can expect further exciting discoveries in forthcoming years.

Q: Do you have any advice for young doctors and practitioners who may already be in the field or are hoping to start out on a career in nephrology?

A: As I have been involved in pre-graduate, post-graduate, and continuous medical education for many years I have had a good chance to discuss this with many young physicians. The major drawback is that, in the minds of many physicians, nephrology is synonymous only with dialysis and this may not be very attractive for the graduates of medical schools. I try to persuade them that nephrology involves the diagnosis and treatment of many renal diseases and their complications, and that it is a very interesting medical discipline that also interfaces with genetics, immunology, rheumatology, osteology, cardiology, diabetology, and others.

David Game

Consultant Nephrologist, Department of Renal and Transplantation Medicine, Principal Investigator for Cell Therapy in Renal Transplantation, Guy's Hospital, London, UK.

Q: What do you cite as your main reasons for wanting to be a nephrologist?

A: There are many! Initially I was excited by the interesting diseases affecting the kidney and the dramatic benefit that transplantation can offer. While these still motivate me, I also enjoy the 'cradle-to-grave' healthcare that is nephrology in the UK, where you get to know your patients very well over many years and can usually foster a therapeutic partnership.

Q: What are the biggest advances you have seen in the field since you began your career in nephrology?

A: The expansion of transplantation and novel immunosuppressive/tolerance strategies – we are finally seeing the waiting list shrink in the UK. The option of compact home haemodialysis is revolutionary for some patients. The adoption of the knowledge that chronic kidney disease is a risk factor that needs to be taken seriously in primary care has been a huge step forward.

Q: How have renal transplantation procedures improved since you began working in this area?

A: Surgical advances in donor nephrectomy have made donation more attractive. Experience of higher-risk recipients (e.g. higher body mass index) has widened the pool of patients able to benefit.

Q: In a recent publication, you and your co-authors presented the case of a 33-year-old man who developed ketamine-associated cystitis and ureteritis and showed how this first case of autotransplantation for ketamine uropathy helps to demonstrate the potentially devastating effects of ketamine on the urinary tract. What impact do you think this presentation could have in the future?

"The option of compact home haemodialysis is revolutionary for some patients."

A: Hopefully this highlights the harm ketamine can do so that doctors seeing such patients can warn of these effects. In addition, we learned how we might manage these cases better in the future.

Q: Has there been a noticeable change in the prevalence and type of kidney conditions occurring in recent years?

A: Not really. The biggest burdens remain hypertension, diabetes, and vascular disease.

Q: In your opinion, what more could be done to encourage kidney donations? Would you be in favour of an 'opt-out' system of organ donation, for example?

A: I am not in favour of opt-out as I think this removes the idea of an altruistic gift and I am not convinced it will make much difference. One area we need to address is cultural and religious barriers to donation, which is challenging in London.

Q: Are there any new topics within nephrology that you would like to research in the future?

A: I am developing a tubular/stone clinic at our hospital with the help of colleagues from the Royal Free Hospital, London. I think that this is a neglected area in nephrology in the UK and deserves more energy.

Q: You work in the biggest transplant centre in the UK. Do you believe that there is a need for further growth of transplant centres, either at Guy's Hospital and/or in the UK in general?

A: In terms of the size or capacity of the UK transplant centres, I think it is fine as it is. There might be an argument for merging smaller units, but I am not convinced. We have made good progress in the tripartite agenda of clinical service, research, and teaching for transplantation but I do think this needs to be further advanced and is key for a large unit looking forward.

Q: Do you think that the public is sufficiently educated as to how to avoid developing kidney diseases?

A: Partly yes, partly no. There are important cultural challenges to this in London, which we are working on, but there is room for improvement.

Q: What is the main advice you would give to people for preventing onset of kidney problems?

A: Do not smoke, eat healthily, take exercise, know your blood pressure, and take your tablets!

Q: How important is the ERA-EDTA congress for helping nephrologists in their work?

A: This important meeting gets people together to enthuse about nephrology and share experiences and challenges – this can be very motivating.

"The biggest burdens remain hypertension, diabetes, and vascular disease."

William Herrington

Senior Clinical Research Fellow, Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), University of Oxford, and Honorary Consultant Nephrologist, Oxford Kidney Unit, Oxford University Hospitals, Oxford, UK.

Q: Who or what particularly inspired you in your choice of career?

A: During my second year as a junior doctor in 2004, I spent 6 months working in the renal unit at St Mary's Hospital, London. I witnessed the life-changing impact of renal replacement therapy (RRT) both in the acute and chronic setting. I started reading about nephrology and the rising tide of renal disease across the world. At the same time the seminal paper by Alan Go was published, which demonstrated the strong associations between chronic kidney disease (CKD) and cardiovascular risk. I had found the perfect career — a specialty where learning would be life-long, where patients' problems crossed multiple hospital specialities, there was a growing clinical need, and

the key therapy, RRT, had a 'number needed to save a life' of one!

Q: What are the biggest changes/developments that you have witnessed in the field of nephrology thus far?

A: In the last decade, large-scale, well-conducted, epidemiological research has been developed by the renal research community. Clear definitions of CKD provided by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI)™, combined with collaborative individual participant meta-analysis by the CKD Prognosis Consortium and large trials such as SHARP and TREAT have combined to (rightly) increase the profile of renal disease and provide a clear evidence-base for safe clinical practice. The renal community needs to continue to embrace this type of research so we as nephrologists can start to substantiate our (often strong) opinions with evidence!

Q: Has there been any particular piece of research that you have conducted that has especially surprised you with its results?

A: The Global Burden of Diseases project has recently identified that the large number of deaths attributed to diabetes in Mexico are, in large part, due to CKD. These vital statistics suggest kidney disease is the second leading cause of death in Mexico. Our recent prospective findings from Mexico City suggest that this genuinely is the case (more to follow shortly) and it appears that many Central and Southern American countries are following the same course. In order to prevent the diabetes epidemic spreading and overwhelming nephrology clinics worldwide, prevention and treatment of obesity and diabetes need even more urgent international attention.

Q: In the next 5 years, what do you foresee to be the biggest obstacles to overcome for nephrologists and other professionals in renal medicine?

A: In the next 5 years we will continue to see an increasing number of patients needing treatment for end-stage renal disease, many of whom will have more comorbidities than the historical cohorts of patients that have been cared for. The challenge will be to provide safe and effective integrated care to all these patients, both in the UK where I practise, and, importantly, in less privileged nations.

Q: What are the next stages of your own research, and of renal research in general?

A: Nephrology needs more large trials. One of the necessary components to successful trials is a culture of uncertainty about the safety and efficacy of untested treatments (both old and new), and a willingness of nephrologists to become trial investigators. To support willing clinician investigators, academic clinical trial units need to develop streamlined methods to make it easy for busy clinicians to give patients the opportunity to participate in large-scale trials addressing the key questions in nephrology. This is a key objective of mine over the next 5-10 years.

Q: To what extent does renal research differ between the UK and the rest of the world?

A: The proportion of patients from UK renal units in trials has fallen with time; this trend must reverse. The UK benefits from the NHS' joined-up provision of care to renal patients, routine healthcare data (in the form of national mortality, cancer, and hospital admission data), and a renal registry with full coverage. This makes the UK the ideal environment to foster extremely cost-effective, streamlined epidemiological cohorts and randomised trials. Industry and the UK government need to recognise this opportunity and ensure these resources are invested in, protected, and enhanced.

Q: What advice would you give to someone contemplating a career in nephrology, and what message or idea do you hope that this year's ERA-EDTA Congress will teach/instil in those attending?

A: Ask more questions, embrace uncertainty, and offer patients randomisation to a trial where the therapeutic choice is unclear.

"I witnessed the life-changing impact of RRT..."

Rosanna Coppo

Director of Nephrology, Dialysis, and Transplantation for Children,
Città della Salute e della Scienza di Torino, Regina Margherita Hospital, Turin, Italy.

Q: What drew you to nephrology and, more specifically, paediatric nephrology?

A: In my city, Turin, there was a need to improve paediatric nephrology from a scientific point of view, as well as a need to organise a transplantation programme, which the region lacked.

Q: How does the nephrological treatment of children, especially with regard to transplantation, differ from that of adults? Are procedures more challenging in younger patients?

A: It is a true challenge that attracts a huge amount of interest. It is impossible to think about a child in dialysis without the hope of renal transplantation. Transplantation in children is different to that in adults because there are additional considerations, such as their ongoing growth, but the lifespan of the grafted kidney is of paramount importance due to the long life expectancy of children.

Q: What are the most impactful changes that you have witnessed in the field since your career began? How has nephrology evolved in modern day practice?

A: The treatment of atypical haemolytic uraemic syndrome with eculizumab. Also, improved detection and treatment of chronic urinary tract infections and pyelonephritis in children, resulting in fewer referrals for dialysis.

Q: What are the biggest challenges facing nephrologists and paediatric nephrologists over the next 5 years and what can be done to overcome them?

> "Transplantation in children is different to that in adults because there are additional considerations..."

A: Maximising the survival of a grafted kidney after dialysis, as well as the treatment of focal segmental glomerulosclerosis and non-genetic, steroid-resistant nephrotic syndrome.

Q: What are the key factors in maintaining good renal health and what more can governing bodies and other healthcare providers do to raise awareness of risks and promote better lifestyles?

A: For individuals, the restriction of dietary salt intake is one way of reducing risk. For policy makers and healthcare providers, the early diagnosis of glomerular diseases with microscopic haematuria and media campaigns aimed at promoting public awareness of renal diseases are both important.

Q: What can be done to encourage more of the general population to become organ donors? Could an 'opt-out' system work?

A: In my opinion, the consent for organ donation should be automatic, without the need to ask for final permission from the family.

Q: What is the prevalence of paediatric kidney disorders and children in need of transplant in Italy, and how does it compare with the rest of the world? Is there any disparity? What are the factors (e.g. lifestyle, diet, etc.) that impact upon this?

A: Every year in Italy approximately 60-100 children enter dialysis therapy, an estimated 60 are put on the transplantation list, and around 60 receive a transplant. There is no disparity between Italy, France, or Northern Europe. Children from poorer families are at higher risk of chronic kidney disease, dialysis, and need for transplantation due to genetic factors, and are also at higher risk of less accurate diagnosis and follow-up. This is due to family reasons and not because of the healthcare system, which is very good.

Q: How do the standards of treatment compare and what can the rest of the world learn from Italy?

A: Standard treatments in Italy are the same as in the rest of the world; international protocols are used. However, Italian studies on post-transplant lymphoproliferative disorder and viral complications are very good.

Q: What, in your opinion, is the greatest accomplishment in your career thus far?

A: I am the General Secretary of the European Society of Pediatric Nephrology, which has been my greatest achievement. I was also the ERA-EDTA Chairperson of the Administrative Offices and Chairperson of the ERA-EDTA Working Group of Immunonephrology. All these positions have been great achievements in my career.

Q: What significance does the annual ERA-EDTA conference hold for you and how, if at all, does it differ from other meetings of its type?

A: The ERA-EDTA conference is the best congress in Europe for nephrology, dialysis, and transplantation: it cannot be missed.

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SUPPORTING CKD PATIENTS AT HOME

Summary of presentations from the Baxter Satellite Symposium held at the 52nd European Renal Association — European Dialysis and Transplant Association (ERA-EDTA) Congress, London, UK, on 31st May 2015

Chairperson

James Heaf[1]

Speakers

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MEETING SUMMARY

Dr Heaf opened the symposium by welcoming the attendees and introducing the speakers. Prof Cowie explained the concept of remote monitoring and outlined some of the tools available in cardiology, which include telephone monitoring, standalone equipment, and implanted devices. The challenges and usage of remote monitoring throughout 15 years of use in cardiology were explained, and emphasis was placed on the ability of remote monitoring devices to enable shared decision-making between the patient and healthcare professionals (HCPs) and their ability to align management strategies with patient needs. Prof Pestana then described the advantages and limitations of home-based peritoneal dialysis (PD). PD is an existing therapy that may benefit from additional patient and clinical support through telemonitoring and remote monitoring devices. Studies that assessed telemonitoring as a support for home-based PD versus centre-based haemodialysis were evaluated and the importance of shared decision-making was emphasised. The requirement for personalised decision-making tools in order to enhance medical supervision and provide more data for clinical decisions was discussed.

Learning From Others: The Benefits of Remote Monitoring in Cardiac Care

Professor Martin R. Cowie

The remote monitoring of patients with cardiac disease has been studied and used for around 15 years. Remote monitoring has received support from policymakers in order to move care from hospitals to the home environment, and the technology of remote monitoring is seen by politicians as a solution for sustainable healthcare. Remote monitoring has also been supported by patients; however, most patients who are involved in remote monitoring require reassurance through

some face-to-face contact with HCPs. Remote monitoring is unlikely to be required by every patient throughout the entire duration of their condition, but some technologies have demonstrated usefulness in detecting periods of sudden worsening and decompensation, which has resulted in earlier and more appropriate care and, in general, such technologies help to support self care and shared decision-making.

The current standard of care for patient management in cardiac disease is through a 10-minute physician appointment, with data collected during the appointment determining the management of the patient for the following 3 months. If the condition of a patient worsens then a long hospital admission may ensue, followed by discharge to the same follow-up methodologies of physician appointments. The simplest method of remote monitoring that builds upon patient—physician appointments is telephone communication, while standalone equipment can also be used to monitor clinical measures, patient activity, and symptoms. Implanted devices such as cardiac resynchronisation therapy (CRT) and implantable cardioverter defibrillators can provide an additional layer of information to healthcare providers, but also bring new challenges of how to manage the data provided, which data protection measures are required, and what legal protocols should be implemented.

Benefits of the remote monitoring devices include improvement in self-monitoring by patients and the earlier detection of deterioration. Patients adept in managing their own information can adjust their own therapy and become decision-makers. Furthermore, implementation of remote monitoring technologies requires the determination of responses and responsibilities by the patient for given situations. Depending on the requirements, remote monitoring devices can provide reminders about medication and lifestyle, and can help inform more focussed face-to-face follow-up, including the frequency, location, and content of such follow-up. For example, a remote monitoring device may allow patients to look at their data, set limits, enter symptoms, and access educational videos, as well as enable HCPs to monitor the data periodically. Implanted devices can provide detailed information of a patient's medical condition, including heart rhythm, fluid retention, pulmonary artery pressure, and also about their activity levels. Such information may aid decision-making by the patient and/or their healthcare team.

Publications describing the different types of remote monitoring devices have reported mixed results. A meta-analysis of small studies that evaluated the effect of telephone contact and standalone systems on patients with heart failure (HF) found that all-cause mortality was significantly reduced with telephone contact,[1] while reductions in hospitalisation related to chronic HF were reported for both the telephone and standalone system interventions. However, the large USA TELE-HF study that assessed the effect of an automated telephone service found that 15% of patients who were randomised never contacted the service, 50% of patients stopped using the service within 6 months, and there were no differences in measured clinical outcomes.[2] A German study of 710 randomised patients with a median follow-up of 26 months assessed the effect of telemonitoring and found no differences between groups regarding hospitalisation due to HF, cardiovascular (CV)-related death, and all-cause mortality.[3] However, it should be noted that the patients were relatively young and stable, with half exhibiting minimal symptoms and New York Heart Association (NYHA) Class II. Comparatively, the UK project 'Whole System Demonstrator' evaluated the effect of telehealth and telecare in 6,191 patients across 283 general practices, and found reductions of over 10% in emergency room visits, emergency admissions, elective admissions, bed days, and also an 8% reduction in tariff costs.[4] However, this initiative has not yet been rolled out at a national level, which could be due to the low value for money, with a reported quality-adjusted life year (QALY) cost of £92,000.[5]

Due to the cost, resource, and organisational implications of remote monitoring devices for all patients with chronic CV disease, the technology may be most effective if targeted at more unstable patients. Remote monitoring devices would enable closer surveillance of high-risk patients by the healthcare team for any deterioration in the patient's condition and facilitate earlier intervention with the aim of avoiding the need for hospitalisation. However, pattern recognition is required to monitor these patients and such skills take time to develop. Separating 'noise' from 'signal' is not always straightforward, and more data can sometimes result in more decision-making rather than a better outcome. In theory, indicators of worsening symptoms in HF can present around 2-3 weeks prior to HF decompensation.[6] A study that retrospectively analysed data from tens of

thousands of patients with HF and an implanted pacing device reported an algorithm that could stratify high and low-risk patients: patients who were at high risk were ten-times more likely to be admitted to hospital within the next 30 days due to HF compared with the low-risk patients, but even in the high-risk group the absolute risk of hospitalisation was still only 4% over 30 days.[7] Such a lack of a positive predictive value is off-putting to many clinicians.

One of the challenges of remote monitoring is to manage a potentially enormous data stream appropriately and make the correct decision with the large amount of data available, ensuring that support staff are trained in how to deal with any alerts. The controlled DOT-HF study assessed the effect of an audible alert when patients crossed preset thresholds of transthoracic impedance determined by an implanted cardiac device. It reported an increase of 79% in hospitalisations compared with devices without the preset thresholds (p=0.02). The increase in hospitalisations seen in association with preset thresholds may have been due to the pacemaker alarm that may have made patients anxious, and this anxiety was then transmitted to the HCPs who erred on the side of caution and admitted such patients to hospital for observation. This highlights the need for appropriate training and support for HCPs involved in remote monitoring programmes.[8] A more positive outcome was recently reported from the IN-TIME study,[9] conducted in Australia, Europe, and Israel, that compared the daily remote monitoring of cardiac implanted devices versus usual care. The study reported a >60% reduction in mortality in a total of 664 patients, as well as an 8.3% reduction in the composite all-cause score including all-cause death, overnight hospital admission for HF, change in NYHA class, and change in patient global assessment (p=0.013).[9] The ALTITUDE study also demonstrated improved survival of patients who were given heart monitoring devices that were networked to transmit remote data versus non-networked devices, albeit in an observational setting. Further results are imminent as one of the world's largest remote monitoring studies, REM-HF, is near completion. The REM-HF study has randomised 1,650 patients with implanted cardiac devices from 9 English hospitals, and has a follow-up of at least 2 years.[10]

Another aspect of remote monitoring is the allowance of greater involvement of the patient in managing their own care. Patients with diabetes can now monitor their blood glucose levels and adjust the insulin accordingly, while a mid-level team member can monitor the data and determine if and when input from the physician is required.[11] This provides the patient with greater confidence, an improved ability to self care, and a deeper understanding of their signs and symptoms. It also better utilises the time of the physician.[12]

In conclusion, the technology of remote monitoring lends itself towards shared decision making between the patient, mid-level team members, and physicians. Remote monitoring supports self care and involvement of the patient and a more tailored approach towards their needs.[11]

Remote Monitoring to Support CKD Patients: What Are the Needs?

Professor Manuel Pestana

Dialysis currently represents the most expensive chronic therapy available: the treatment is 6-7 times more expensive than treating a patient with acquired immune deficiency syndrome, and 30-40 times more costly than the management of chronic obstructive pulmonary disease. Within the dialysis modalities, studies into home-based PD have shown various benefits compared with haemodialysis, with a cost saving of >€25,000 per year and >€45,000 per QALY reported in Spain,[13] and economic benefits reported globally.[14] A breakdown of the main areas where home-based PD cost savings have been reported compared with haemodialysis is provided in Table 1.[15] Furthermore, home-based PD has certain clinical and psychological advantages over haemodialysis. These include improved short-term patient survival, similar long-term survival, and greater independence due to flexibility around how, when, and where the dialysis is performed. It also allows for a more liberal diet.

Requirements of home-based PD include a medical support system as there is greater patient responsibility to manage their therapy and clinical characteristics including weight, blood pressure, and fluid balance, as well as how to handle complications and any difficulties. In this respect, a well-structured home visit programme may be beneficial in areas such as improved knowledge coupled with continuous training and better compliance. Studies have reported an increase

in patients who choose PD upon availability of the home-visit programme[16] and also improved technique survival (p=0.018) over 60 weeks.[17,18] Retrospective cumulative survival was also significantly improved over 400 days in incident patients managed with home-based PD (p<0.001) versus patients given haemodialysis with an arteriovenous fistula or central venous catheter.[17] However, the majority of patients worldwide are still treated with in-centre haemodialysis due to structural and social factors, poor training, and a lack of interest from nephrologists.[19] As the sustainability of healthcare systems requires reflection upon the costs and efficiencies of the services, PD represents an under-used modality.

Although PD offers many benefits, there are still some challenges in optimising the modality. As well as support provided to the patient for any difficulties or complications, improved communication between the patient and centre is required so that clinical decisions are not delayed and the patient does not require a visit to the emergency department or nephrology centre. If these challenges are not addressed, the patient may perceive the nephrology centre as being remote. Therefore, there is a need to improve the prediction and detection of any complications that may occur. Additionally, supportive tools to empower the self-management of the patient, shared decision-making with the physician, and improved feedback and evaluation of actions taken by the patient to HCPs at the treatment centre, may improve home-based PD.

Remote monitoring, or telemedicine, is a tool that may help improve the communication between patients and HCPs and reduce the perceived remoteness of PD.[20] As most patients own the necessary equipment and internet connection for telemedicine,[21] the technique may serve to improve the detection of complications, thereby reducing the need for unscheduled visits to the nephrology centre or emergency department. A study evaluated the efficacy of telemedicine through websites for PD in urban and rural areas of India and found that rural patients had significantly improved survival compared with urban patients.[22] Gallar et al.[23] also found a reduction in hospitalisation rates from 5.7 days to 2.2 days per year through the use of videoconferences and teleconferences where patients were at home, with cost savings also reported.

Table 1: Cost analysis of HD and PD access in incident dialysis patients.[14]

	Mean cost in euros (€ [95% CI])			
Intervention	With AVF (n=65)	With TCC (n=45)	PD (n=42)	p value
Access surgery	401.7 [343.8-459.6]	252.9 [190.5-315.4]	540.7 [526.8-584.7]	<0.001
HD catheter interventions	141.2 [57.7-234.6]	718.7 [576.0-861.5]	72.8 [26.9-118.8]	<0.001
Diagnostic imaging	344.7 [187.8-501.7]	151.3 [52.9-249.8]	0	<0.001
Hospitalisation	469.2 [57.9-996.3]	2746.2 [494.8-4997.5]	516.7 [67.5-965.9]	0.010
Transportation	193.4 [128.3-258.5]	339.1 [236.0-442.2]	41.4 [28.1-54.6]	<0.001
Total	1555.2 [974.0-2136.2]	4208.2 [2050.7-6365.9]	1171.6 [737.6-1526.0]	<0.001

From Manuel Pestana, presentation at the 52nd European Renal Association — European Dialysis and Transplant Association (ERA-EDTA), London, UK, on 31st May 2015.
AVF: arteriovenous fistula; CI: confidence interval; HD: haemodialysis; PD: peritoneal dialysis; TCC: tunnelled cuffed catheter.

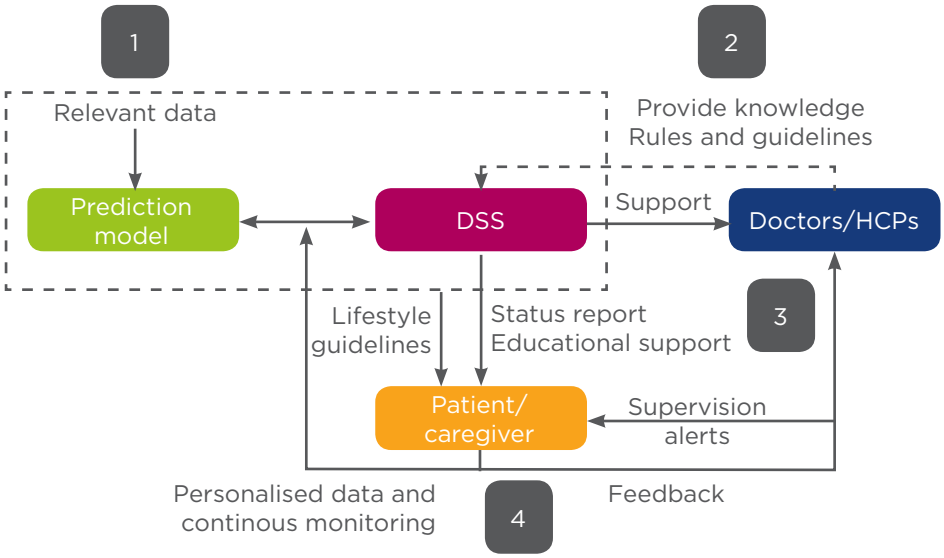

Figure 1: Illustration of a personalised decision-support system, which is based upon predictive models, established clinical guidelines, and the health and lifestyle monitoring strategies of the patient.
From Manuel Pestana, presentation at the 52nd European Renal Association — European Dialysis and Transplant Association (ERA-EDTA), London, UK, on 31st May 2015.
DSS: decision-support system; HCP: healthcare professional.

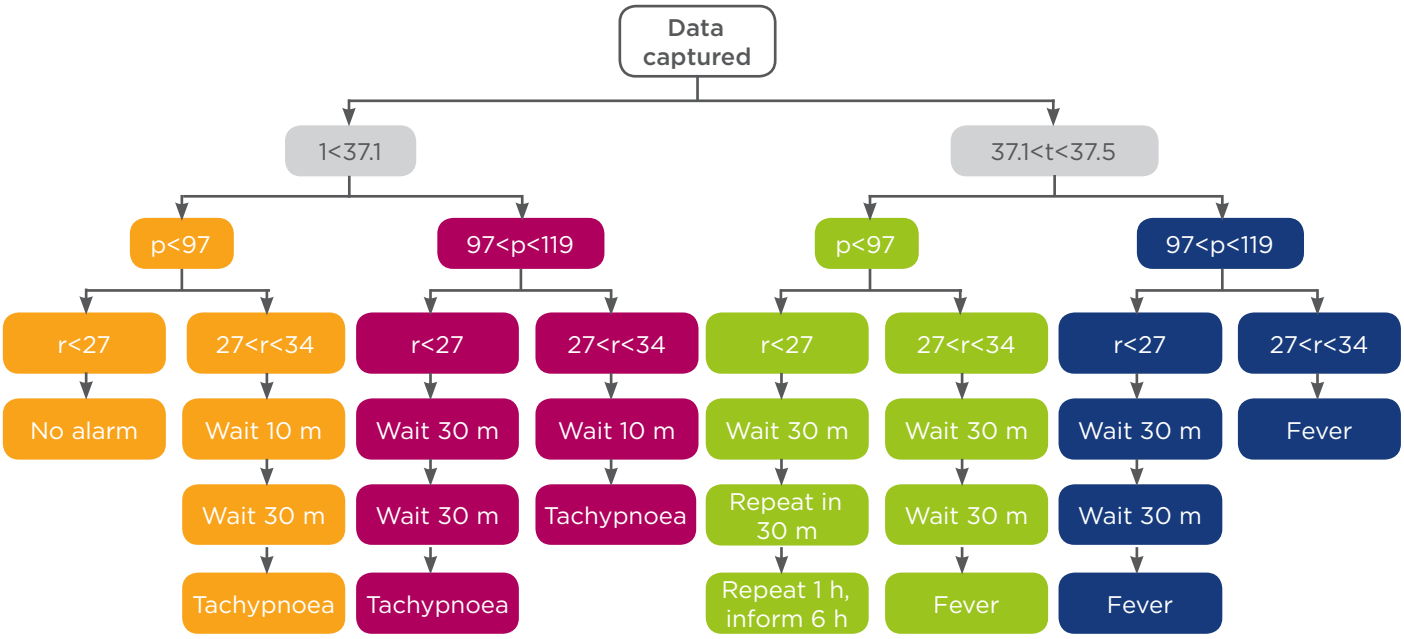

Figure 2: Flowchart of a medical decision protocol using temperature, pulse, and respiratory rate.
From Manuel Pestana, presentation at the 52nd European Renal Association — European Dialysis and Transplant Association (ERA-EDTA), London, UK, on 31st May 2015.
p: pulse; r: respiratory rate; t: temperature; h: hour; m: minute.

Although studies of remote monitoring have shown some positive results, unmet needs include the improvement of shared decision-making between patients and HCPs through personalised decision support tools, clinical guidelines, health and lifestyle monitoring, and improved risk prediction. Shared decision-making between the patient and HCPs involves the exchange of information, deliberation of options, deciding on the priority for taking action, and then making a decision.[24] Shared decision-making can be facilitated by the requirement for explicit decisions to be made

within the remote monitoring tool by the patient and HCP. Through the provision of balanced information on the benefits and risks of certain options to the patient as well as knowledge and understanding of their needs and goals to provide context, support from the remote monitoring tool as well as complementary information from an HCP can provide context to decisions that are required of the patient.[25] Barriers to shared decision-making include time constraints and a lack of applicability to certain patients or clinical situations.[26] Within the field of diabetes, a power imbalance between the patient and provider, lack of health literacy, and denial of the situation by a patient were also found to be obstacles in shared decision-making. Facilitators of the shared decision-making process were improved HCP motivation and training of the patient as well as patient-mediated interventions.[26]

Data collection regarding the lifestyle of the patient by the remote monitoring tool can be helpful to make more informed clinical decisions. The accumulation of demographic, clinical, and social data from the patient may influence certain clinical outcomes and support the development of personalised decision-support systems (DSS), as shown in Figure 1. The development of an effective DSS tool involves the development of a prototype and then increasing the fidelity of the prototype through the observation of prospective users' interactions with the prototype. Through understanding the needs, goals, strengths, limitations, and context of the user, more intuitive processes can be put in place and the prototype refined through facillitating the tool towards the user.[25] Patient decisions and certain system alerts can also be tailored and supported through a greater knowledge of the patient's clinical situation, enabling patient empowerment, remote monitoring of the parameters of the patient, and improved compliance.

Accumulation of patients' clinical and demographic data can also allow for more accurate prediction and detection of risks, as well as the earlier identification and knowledge-based handling of complications. Alert messages can include the probability of the complication occurring, with a warning message and explanation of the factors underlying the decision, again enabling a co-decision by the patient and allowing for communication between the patient and HCP on a more timely basis. A medical decision protocol, as shown in Figure 2, provides an example of a decision flow chart of the remote monitoring tool, with certain observations requiring confirmation through repeated measurements prior to the issue of an alert, explanation, and plan of action to the patient and HCP. As an example, the diagnosis of volume overload or depletion will be determined from certain clinical, patient-related, and prescription-related parameters that include blood pressure, weight, impedance, ultrafiltration volume, PD modality, dwell time, residual renal function, and body mass index.

In summary, improved integration of home and personalised healthcare monitoring systems with secure and effective communication between patients and HCPs, as well as appropriate tools for shared decision-making with HCPs, may result in enhanced medical supervision and improved clinical outcomes. The use of predictive systems based on computer modelling will provide a sound rationale for clinical decisions. Personalised decision-making tools will also refine the communication between patients and HCPs, and ameliorate clinical supervision through better monitoring and management of the care process.

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THE ONGOING MANAGEMENT OF HYPERKALAEMIA IN CHRONIC KIDNEY DISEASE PATIENTS: CASES FOR CLINICAL DECISIONS

This symposium took place on 30th May 2015 as part of the 52nd European Renal Association — European Dialysis and Transplant Association (ERA-EDTA) Congress in London, UK

Chairperson

David C. Wheeler[1]

Speakers

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MEETING SUMMARY

This educational symposium provided an insight into the most current clinical evidence of the efficacy and safety of renin—angiotensin—aldosterone system inhibitors (RAASis) for patients with chronic kidney disease (CKD). The programme provided an opportunity to discuss ways to optimise and maintain RAASis in this population by introducing CKD patient cases and the dilemmas of their clinical presentation, and novel treatment options, including benefits, harms, and potential consequences.

Prof David C. Wheeler introduced the debate about the use of RAASis and the associated risk of hyperkalaemia in CKD patients. Prof Francesco Locatelli discussed the management of blood pressure (BP) in CKD and reviewed the most current guidelines for the prevention of hyperkalaemia in this population. Prof Adrian Covic presented the controversies around the use of RAASis in specific group populations. Survival, cardiovascular events (CVEs), and progression of CKD were the main points of his presentation. Finally, Prof David C. Wheeler discussed the latest research on novel therapies for the management of hyperkalaemia.

Welcome and Introductions

Professor David C. Wheeler

Treatment with agents that block the renin—angiotensin—aldosterone system, the so-called RAASis, are considered to be the standard of care for patients with CKD.[1] However, their use has been associated with an increased risk of hyperkalaemia. Hyperkalaemia, a condition defined by an abnormally high concentration of potassium (K^+) in the blood (>5 mmol/l according to the Kidney Disease Outcomes Quality Initiative [KDOQI] guidelines)[2] is of special concern to health providers treating patients with CKD. Whether acute or chronic, hyperkalaemia may increase the risk of adverse CVEs in this population.[1,3,4] The current

practice is to discontinue or reduce the use of RAASis and/or other drugs associated with the development of hyperkalaemia.[5]

Current guidelines recommend the use of RAASis to control BP in patients with CKD, proteinuria and heart failure.[2,6] However, the risk of hyperkalaemia limits the titration of these drugs and leads to variation in practice as clinician attempt to avoid harm.[7,8] Several trials have assessed combinations of RAASis in various populations with different medications and doses, but such combination therapies are also limited by the high risk of hyperkalaemia (and acute kidney injury [AKI]).[9] The use of RAASis may become more problematic as kidney disease advances, with an increased risk of hyperkalaemia in those with more severely impaired kidney functions. Strategies for the management of hyperkalaemia in the acute setting include: intravenous insulin and dextrose, oral polystyrene sulfonate resins, and inhaled beta-adrenergic agonists.[10] These agents have side-effects, some of which are potentially harmful, and are not suitable for use in the longer term. In this symposium the potential of two new therapeutic agents for the management of hyperkalaemia in a chronic setting was discussed.

The learning objectives of the symposium were: 1) to explain why RAASi doses should be optimised and maintained, especially aldosterone blockade in late-stage CKD; 2) to identify why RAASi medications delay CKD progression; 3) to evaluate current Kidney Disease: Improving Clinical Outcomes (KDIGO) and KDOQI guideline recommendations for BP treatment in CKD patients and subsequent management of hyperkalaemia; and 4) to contrast the mechanism of action of organic polymer resins and new therapies for hyperkalaemia.

Chronic Kidney Disease Patients at Risk for Hyperkalaemia: Review of Current Guidelines

Professor Francesco Locatelli

The distribution of electrolytes in our bodies determines the chemical and physical reactions that occur within the fluids. Changes in K^+ concentration are of paramount importance in determining its effects on the heart,[11] and while K^+ equilibrates freely and rapidly within the extracellular fluid, its stable concentration and balance needs to be maintained in order to help the heart and other muscles to work properly.

In addition to angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), and aldosterone antagonists, hyperkalaemia can be caused by other mechanisms including dietary ingestion, acidosis, hyperglycaemia (diabetes), hyporeninaemic hypoaldosteronism, oliguria, and certain drugs.[2] Foods with high K^+ content (>250 mg/100 g) include fruits, vegetables, and meats, among others (e.g. nuts, brand cereals, chocolate, tea, mussels).[2] Drugs that impair renin—aldosterone function (e.g. ACEis, ARBs, aldosterone antagonists, β-blockers) or alter K^+ distribution (e.g. insulin agonists, hypertonic solutions, K^+ and herbal supplements, K^+-sparing diuretics, cyclosporine, tacrolimus, trimethoprim, and lithium) can cause hyperkalaemia in CKD.[2] Errors in the sampling (e.g. haemolysed red blood cells, inappropriate sample handling, erroneous reporting, equipment malfunction) should also be taken into consideration when determining clinical factors influencing the presence of hyperkalaemia.[2]

Management of blood pressure in chronic kidney disease — what do the current guidelines recommend?

For adult non-diabetic CKD patients, the 2012 KDIGO guideline recommends the use of BP-lowering drugs (ACEis or ARBs) where indicated, if urine albumin excretion is 30-300 mg (Level 2D) or >300 mg (Level 1B) over a 24-hour period.[2] CKD patients often have reduced capacity for K^+ excretion, which occurs when the glomerular filtration rate (GFR) falls. While ACEis and ARBs are valuable BP-reducing agents in CKD,[2] they can increase the risk of hyperkalaemia and paradoxically reduce the level of GFR; in this context, their role in slowing the progression of CKD needs to be evaluated, in particular in patients with renal artery stenosis, increased renal artery resistance, or reduced intravascular volume in general.[2] If hyperkalaemia occurs in CKD patients under ACEi medication, possible interventions include dietary advice, dosing reduction, or adding a K^+-losing diuretic. Current evidence does not support discontinuing ACEis and ARBs in patients with advanced CKD in an effort to preserve residual kidney function; discontinuation may be recommended due to the risk of hyperkalaemia

and in cases of undercurrent clinical problems (e.g. fever, diarrhoea, vomiting, hypotension, etc.).[2]

Popular and widely recommended weight-loss diets are commonly high in K^+ and protein, and may therefore increase the risk of hyperkalaemia and favour CKD. Moreover, as their potential benefits and harms have not been specifically addressed in the CKD population, the use of these diets in these patients is not recommended.[6] Aldosterone antagonists such as spironolactone have proven to be beneficial in non-CKD patients with HF, including HF after myocardial infarction. However, because of the risk of hyperkalaemia and reduction in GFR in CKD patients, aldosterone antagonist therapy should be considered with caution in this population.[6] In 2004, following the results of the Randomized Aldactone Evaluation Study (RALES)[12] that showed significant improvements in outcomes following treatment with spironolactone in patients with severe HF, there was a dramatic increase in the prescription rate of this drug. The increased use of spironolactone was, however, associated with an increased rate in hospital admissions and deaths due to the hyperkalaemia—spironolactone—ACEi-related interaction.[12] These results highlight the importance of close monitoring and judicious use of these agents in patients with CKD, especially with concomitant ACEi or ARB medication.

The risk of hyperkalaemia in CKD populations highlights the need not only to take into consideration their diet, but also to put into place other measures aiming to reduce the risk of hyperkalaemia. As mentioned, these measures include reducing ACEi intake or adding a K^+-losing diuretic. In general, the use of ACEi, ARB, and aldosterone antagonists should be carefully evaluated in patients using concomitant medications (painkillers, non-steroidal anti-inflammatory drugs, K^+-sparing diuretics) or patients with underlying conditions (non-dialysis patients, transplant patients) that can increase the risk of hyperkalaemia. While thiazides are known to potentiate the effect of other antihypertensive agents, particularly ACEis and ARBs, they also reduce the risk of hyperkalaemia.[6]

The KDOQI guidelines[2] detail measures to lower serum K^+ for prevention and management of hyperkalaemia due to ACEis or ARBs in CKD and/or according to baseline serum K^+. Acute interventions with the use of Ca^{2+} salts are recommended by the National Institute for Health and Care Excellence (NICE)-accredited collaboration between the Renal Association and the Resuscitation Council (UK).[13] These guidelines highlight the need to implement K^+ and BP monitoring for the prevention and identification of hyperkalaemia and, overall, the need to be prepared to treat severe complications in CKD patients.[13,14]

Controlling serum K^+ is an important goal in the maintenance of haemodialysis.[15] Hyperkalaemic patients who achieve K^+ balance through haemodialysis have better survival rates.[15] Studies have concluded on the association of certain modifiable dialysis practices with mortality.[15,16] A high dialytic removal of K^+ does not necessarily prevent a rapid post-dialysis rebound of plasma K^+, and therefore patients with marked hyperkalaemia should be monitored closely post-dialysis.[17] High dialysate bicarbonate levels have also been shown to be associated with a faster decrease in serum K^+.[18] This finding could have an impact on patients with life-threatening pre-conventional haemodialysis hyperkalaemia.[18]

In summary, there is compelling evidence on the importance of maintaining a good concentration and balance of K^+, not only for controlling the risks related to hyperkalaemia but also for controlling the risks related to hypokalaemia. It should be noted that: 1) the use of dialysate K^+ <3 mmol/l is very common and leads to low post-haemodialysis K^+ levels; 2) the risk of sudden death is higher for patients in haemodialysis units where more patients have dialysate K^+ below 3 mmol/l; 3) higher risk with low dialysate K^+ is especially clear for patients with pre-haemodialysis serum K^+ <5 mmol/L; and 4) use of profiled K^+ dialysate concentration reduces arrhythmogenic risk.

RAASi Use in Chronic Kidney Disease

Professor Adrian Covic

Angiotensin II has been implicated in a number of pathophysiological processes leading to hypertension, end-organ damage, HF, and death.[19] To date, there is compelling evidence for the end-organ benefit when using RAASis, including in non-diabetic CKD patients, patients with diabetes, and patients who are undergoing dialysis or kidney transplantation (KTx).[20-23]

Diabetic patients

In patients with diabetic nephropathy, RAASis are the cornerstone of treatment, and their beneficial effects have been demonstrated across each stage of disease progression.[24] The KDIGO guidelines recommend ACEis or ARBs as primary prevention of CKD in diabetic nephropathy patients to reduce GFR, and in normotensive patients with albuminuria levels >30 mg of albumin per g of creatinine per 24 hours to reduce microalbuminuria.[6] However, no benefit has been confirmed in normotensive patients with normoalbuminuria.[6]

In a recent meta-analysis of 35 clinical trials and involving up to 32,827 patients with diabetes mellitus (DM), treatment with ACEis reduced all-cause mortality, cardiovascular (CV) mortality, and major CVEs, but not stroke.[25] ARBs had no beneficial effect on these outcomes.[25] In a systematic review and Bayesian network meta-analysis of 63 randomised clinical trials (RCTs) involving 36,917 participants, ACEis showed superior ranking positions in all outcomes (mortality, requirement for dialysis, and doubling of serum creatinine [SCr] levels) versus ARBs.[26] The study showed that the combination therapy of ACEi plus Ca^{2+} channel blocker was the best treatment for reducing mortality, followed by ACEi plus a diuretic, ACEis, Ca^{2+} channel blockers, ARBs, and β-blockers. Compared with placebo, only ACEis significantly reduced the doubling of SCr levels.

In a systematic review and meta-analysis study of 9 clinical trials with 9,797 participants, the effect of RAASis on all-cause mortality and CV mortality in DM patients with advanced CKD was not significantly different compared with control groups (placebo or other antihypertensive drugs).[27] However, patients treated with ACEis experienced a mild 10% reduction in the risk of developing non-fatal CVEs and a 19% risk reduction in the need for renal replacement and doubling of the SCr.[27] These results indicate a small but beneficial effect of ACEis on the survival of patients with more advanced CKD. Combination therapy with ACEis and ARBs has no beneficial effect on survival or CV symptoms in patients with diabetes nephropathy.[28] Moreover, the combination therapy has been associated with an increased risk of AKI, hyperkalaemia, and hypotension, highlighting the potential concern related to the use of double blockade in this population.[28-30]

Non-diabetic chronic kidney disease patients

In a recent analysis conducted with non-dialysis-dependent patients with CKD, ACEi—ARB administration was associated with greater survival over a 6-year period compared with an untreated group.[31] The study involved 141,413 USA veterans with a mean estimated GFR (eGFR) of 50±13 ml/min/1.73 m^2 who had been previously unexposed to the double blockade.[31]

Do patients with early CKD benefit from RAASis? In people with Stage 3 CKD, ACEi use has been shown to impact the all-cause mortality or CVEs in a meta-analysis of 4 RCTs involving 2,177 participants.[32] The results of this study did not confirm the effectiveness of ACEis or ARBs in patients with early (Stage 1-3) CKD who do not have DM.[32]

Do patients with advanced CKD benefit from RAASis? In a prospective study involving 28,497 hypertensive adult patients with advanced CKD (Cr >6 mg/dl), ACEi—ARB therapy reduced the risk for initiating long-term dialysis or death by 6% in a median follow-up of 7 months.[33] The renal benefit of ACEi—ARB use was consistent across most patient subgroups, as was that of ACEi or ARB monotherapy.[33] Compared with non-users, the ACEi—ARB users had a higher hyperkalaemia-associated hospitalisation rate, but the risk of pre-dialysis mortality caused by hyperkalaemia was not significantly increased.[33]

In a small study (n=68) conducted with hypertensive elderly patients with advanced CKD (Stage 4 and 5, not on dialysis), there was an improvement in eGFR 24 months after stopping ACEis or ARBs.[34]

Patients on dialysis

In a meta-analysis involving 1,679 dialysis patients, antihypertensive medications (primarily ACEis or ARBs) were associated with lower risk of all-cause mortality and CV mortality than control regimens.[35] The effect of ACEis and ARBs on haemodialysis was evaluated in an analysis of 8 RCTs involving 837 patients on dialysis.[36] Although ACEi or ARB use was associated with reduced left ventricular mass, it was not associated with a lower risk of CVEs.[36] However, the analysis included very small studies and were of limited duration and so may have been underpowered to detect these differences.[37]

Patients with kidney transplantation

According to some studies, the use of ACEis and ARBs may help to reduce the high incidence of death and/or renal allograft failure in patients undergoing transplantation.[38,39] In a retrospective open cohort study involving 2,031 kidney transplant recipients, the use of ACEi—ARB combination has been associated with a prolonged patient and graft survival 10 years after KTx.[39] In a longitudinal study of 990 single-renal recipients, the use of ACEi—ARB was also associated with a reduction of the mortality risk in a median 14-month period after transplantation, but no significant improvements in graft survival were observed.[38] In a more recent large-scale retrospective study of prospectively collected data involving 29,251 kidney transplant recipients, the use of ACEi—ARB resulted in similar CVE rates to those observed in non ACEi—ARB users.[40] Therefore, despite the wide use of RAASis after KTx, the evidence for an improvement remains mixed.[40]

Table 1: Patient cases at a glance.

Current history	Discussion	Message
An everyday clinical case, by Francesco Locatelli (Case 1)		

- A patient with CKD treated with an ACEi who develops hyperkalaemia and metabolic acidosis
- High-to-normal BP
	- What to do first: correct metabolic acidosis or directly hyperkalaemia?
	- If you correct acidosis (e.g. sodium bicarbonate), then hyperkalaemia may persist – *then what?*
	  - Use diuretic as first step (e.g. furosemide; thiazides or chlorthalidone could be added in some situations)
	  - Then, control hyperkalaemia with a resin and withdraw the ACEi if hyperkalaemia persists
		- In case of complications (e.g. fever, diarrhoea, vomiting), treatment with diuretics and ACEis, ARBs, and aldosterone antagonists should be stopped to avoid hypotension, hyperkalaemia, and further deterioration of renal function

An emergency case, by Adrian Covic (Case 2)		
Male, 56-years-old, came to the emergency room - 'Some diarrhoea' in the past 3 days; back pain treated with over-the-counter non-steroidal anti-inflammatory drugs in the past week - In 2003 (43-year-old): diagnosed with Type 2 diabetes mellitus, treated with insulin - In 2014 (55-year-old): diabetic kidney disease; proteinuria 0.78 g/day; eGFR 58 ml/min; medication included ACEis, β-blockers, and insulin - Upon clinical evaluation: dehydrated; biochemistry: eGFR 40 ml/min; normal K^+ level; proteinuria 0.8 g/day Treatment • Fluids • ACEis were stopped temporarily, eGFR recovered	**After 6 months** - Periodical evaluation; euvolaemic; BP 145/95 mmHg; proteinuria 2.1 g/day; eGFR 45 ml/min; K^+ 5.2 mmol/l; no back pain; compliant Treatment • Spironolactone 12.5 mg/day was added to his medication regimen	**A month later** - Euvolaemic; BP 135/85 mmHg; proteinuria 1.2 g/day; stationary eGFR 40 ml/min; hyperkalaemia K^+ 6.0 mmol/l - Cardiologist: stop ACEi + magnetic resonance imaging, switch to Ca^{2+} channel blockers and β-blockers

CKD: chronic kidney disease; ACEi: angiotensin-converting enzyme inhibitor; BP: blood pressure; ARB: angiotensin receptor blocker; eGFR: estimated glomerular filtration rate.

How about novel strategies?

Aldosterone antagonists can be added to prevent further progression of CKD.[41] In a systematic review of 27 RCTs, the use of aldosterone antagonists alone or in combination with an ACEi or ARB (or both) reduced proteinuria and BP in adults with mild-to-moderate CKD.[41] However, because aldosterone antagonists can cause or exacerbate hyperkalaemia, only one-third of those patients hospitalised for HF are being recommended.[42,43]

In summary, there is compelling evidence demonstrating that RAASis, in particular ACEis, increase survival and slow CKD progression at an early stage. Evidence also indicates that non-fatal CVEs and CKD progression are prevented in advanced-stage CKD, but there is uncertainty regarding the benefits of RAASis in patients undergoing dialysis and transplantation. Dual blockade with ACEis and ARBs does not necessarily correlate with improved morbidity and mortality in CKD patients. Finally, some short-term clinical studies have shown renoprotective effects of aldosterone blockade. By discussing two different clinical cases of CKD the speakers discussed practical steps for improving the management of hyperkalemia in such patients (Table 1).

New Strategies in the Management of Hyperkalaemia

Professor David C. Wheeler

Do we have therapies to control K^+ levels and allow the continuing/increasing use of RAASis?

Prof Wheeler introduced his presentation by contrasting two patients with hyperkalaemia, one in an acute setting and the other in a chronic setting (Table 2).

Patiromer sorbitex calcium (RLY5016S; cross-linked polymer of calcium 2-fluoroprop-2-enoate with diethenylbenzene and octa-1,7-diene, combination with D-glucitol) and sodium zirconium cyclosilicate (ZS-9; silicic acid [H_2SiO_3], sodium zirconium [4+] salt [3:2:1], hydrate) are two novel compounds for the treatment of hyperkalaemia.[44,45] Patiromer is a non-absorbable polymer that enhances K^+ excretion by the exchange of Ca^{2+}, predominantly in the distal colon. ZS-9 is a non-absorbable cation trap that selectively binds K^+ in exchange for H^+ and Na^+; it binds K^+ immediately upon ingestion. New research indicates that both compounds are promising drugs in the treatment of hyperkalaemia.

In a two-part, single-blind, Phase III study (the OPAL-HK study) patiromer decreased the serum K^+ levels and reduced the risk of hyperkalaemia recurrence compared with placebo in patients with CKD.[44] The approximate sorbitol content of the drug product at starting doses of 4.2 g and 8.4 g patiromer (each given BID) used in the current study were 2 g and 4 g per dose (i.e. 4 g and 8 g daily), respectively. During the first 4 weeks, if a first recurrent hyperkalaemic event occurred, an up-titration of patiromer in the patiromer group and a dose reduction of RAASi medication for the placebo group was required. In either group, if a subsequent elevation in serum potassium occurred (≥5.1 mmol/l), discontinuation of RAASi medication was required. During the second 4 weeks, an up-titration of patiromer in the patiromer group and a dose reduction of RAASi medication in the placebo group was required. The study comprised 237 CKD patients with hyperkalaemia (K^+ 5.1-<6.5 mmol/l) who received at least one dose of patiromer and had at least one post-dose K^+ measurement, and who were on RAASis. Patients with baseline K^+ of 5.1-<6.5 mEq/l received patiromer (4.2 or 8.4 g twice daily initially) for 4 weeks. Doses were adjusted in order to reach and maintain a target K^+ level according to a prespecified algorithm. At the end of the 4 weeks, 76% of patients reached the predefined K^+ target range of 3.8-<5.1 mmol/l; the mean change in serum K^+ from baseline to Week 4 was statistically significant, indicating the effectiveness of patiromer. At the end of this 4-week period, patients with a baseline K^+ level of 5.5-<6.5 mmol/l in whom the level decreased to 3.8-<5.1 mmol/l entered an 8-week randomised withdrawal phase (follow-up phase). Throughout the 8-week period, the recurrence of hyperkalaemia occurred in a significantly lower proportion of patients in the patiromer group (15%) compared with the placebo group (60%; $p<0.001$).[44] Constipation was the most frequent adverse event (AE) (11% of patients across both groups) during the initial phase (Table 3). No serious gastrointestinal (GI) events were reported during this phase. Mild-to-moderate constipation, diarrhoea, and nausea were the most common GI events reported with patiromer (each in 4% of patients) during the follow-up period. Overall, rates of AEs in the patiromer groups were similar to those in the placebo group.

Table 2: An acute versus chronic case of hyperkalaemia.

A case of acute hyperkalaemia (Case 3)	A case of chronic hyperkalaemia (Case 4)
• Young patient brought into the emergency room with acute kidney injury; K^+ 8.5 mmol/l; electrocardiographic changes of hyperkalaemia Treatment options • Insulin 10 units + 50 ml 50% glucose (intravenous) • Polystyrene sulfonate resins (e.g. resonium; oral or rectal) • β-adrenergic agonists (e.g. salbutamol; inhaled)	• 56-year-old male, with known CKD; Type 2 diabetes mellitus for 8 years • Previous non-ST segment elevation myocardial infarction; heart failure (New York Heart Association Stage 2) • eGFR 32 ml/min/1.73 m^2 • Dipstick protein +++, albumin: creatinine ratio 124 mg/mmol • HbA_{1c} 77 mmol/mol on metformin 500 mg • Cholesterol 6.3 mmol/l on simvastatin 20 mg • BP 165/95 mmHg on bendroflumethiazide 2.5 mg and irbesartan 150 mg; serum K^+ 6.5 mmol/l

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; BP: blood pressure; HbA_{1c}: glycated haemoglobin.

Table 3: Patients with adverse events in the OPAL-HK study, number of patients (%).[44]

Adverse event	Initial treatment phase and through the safety follow-up period for that phase*	
≥1 Adverse event†	114 (47)	
Constipation	26 (11)	
Diarrhoea	8 (3)	
Hypomagnesaemia	8 (3)	
Nausea	8 (3)	
Anaemia	7 (3)	
Chronic renal failure	7 (3)	
≥1 Serious adverse event‡	3 (1)	
	Randomised withdrawal phase and through the safety follow-up period for that phase*	
	Placebo (n=52)	**Patiromer (n=55)**
≥1 Adverse event	26 (50)†	26 (47)
Headache	4 (8)	2 (4)
Supraventricular extrasystoles	1 (2)	2 (4)
Constipation	0	2 (4)
Diarrhoea	0	2 (4)
Nausea	0	2 (4)
≥1 Serious adverse event	1 (2)	0

*The safety follow-up period was 1 to 2 weeks after discontinuation of the study drug. Events are listed in the initial/safety phase if they occurred in at least 3% of the 243 patients overall; and in the randomised withdrawal phase if they occurred in at least 4% of patients in the patiromer group.

†During the initial treatment phase (i.e. excluding the safety follow-up period), one or more adverse events were reported in 107 patients (44%), and one or more serious adverse events were reported in 2 patients (1%). During the randomised withdrawal phase (i.e. excluding the safety follow-up period), one or more adverse events were reported in 24 patients (46%) in the placebo group.

‡The serious adverse events included atrial fibrillation (in 1 patient), enterococcal endocarditis (in 1), escherichia bacteraemia (in 1), urinary tract infection (in 1), sub therapeutic anticoagulant blood levels (in 1), and chronic renal failure (in 1).

The results showed that patiromer is effective in decreasing serum K^+ levels, and also in reducing the risk of hyperkalaemia in patients with CKD who are receiving RAASis and who develop hyperkalaemia.

In a multicentre, two-stage, double-blind, placebo-controlled Phase III study (the ZS-003 study), ZS-9 was effective in reducing hyperkalaemia among patients with comorbidities such as HF, CKD, DM, and on concurrent medications for management of their disease.[46] The study involved 753 patients with hyperkalaemia (K^+ 5.0-6.5 mmol/l), most of whom were on RAASis (75%) and/or had eGFR <60 ml/min/1.73 m^2 (67%).[46] Initially, patients were randomised to receive ZS-9 (1.25, 2.5, 5, or 10 g) or placebo three times daily for 48 hours (acute phase); then patients with normokalaemia at 48 hours were randomised to receive ZS-9 or placebo once daily on Days 3-14 (maintenance phase).[46] Compared with placebo, the reduction in serum K^+ was significant as early as 1 hour after administration of 10 g ZS-9, and maintained after 24 hours (89% of patients) and 48 hours (98%) (Figure 1); both the 5 g and 10 g daily doses of ZS-9 were significantly superior to placebo in maintaining normokalaemia during the maintenance period (p=0.008 and p<0.001, respectively). Patients on placebo returned to hyperkalaemic range. Overall the safety profile of ZS-9 was similar to that of placebo where the rates of AEs observed were similar between groups (25% for both groups). The incidence of GI and systemic AEs was low in both groups. The most common AE at all doses and during both study phases was diarrhoea, with a frequency of 1.8% with ZS-9 versus 2.5% with placebo during the initial phase, and 1.7% versus 2.2% during the maintenance phase, respectively.

The efficacy and safety of ZS-9 has also been evaluated in a more recent Phase III study (the HARMONIZE study).[47] The study involved 258 outpatients with hyperkalaemia (K^+ ≥5.1 mmol/l) who received ZS-9 initially three times daily during the first 48-hour open-label phase.[47] Forty-eight hours after treatment, ZS-9 reduced serum K^+ to within normal levels in 98% of patients. The median time to normalisation was 2.2 hours. First statistical efficacy was at 1 hour, 84% normal within 24 hours. Patients achieving normokalaemia (n=237; 3.5-5 mmol/l) were then randomised to receive ZS-9 (5, 10, or 15 g) or placebo for 28 days. Compared with placebo, all doses of the drug resulted in the continued maintenance of normokalaemia (80% of patients with 5 g, 90% with 10 g, and 94% with 15 g) over a period of 28 days (Figure 2).[47]

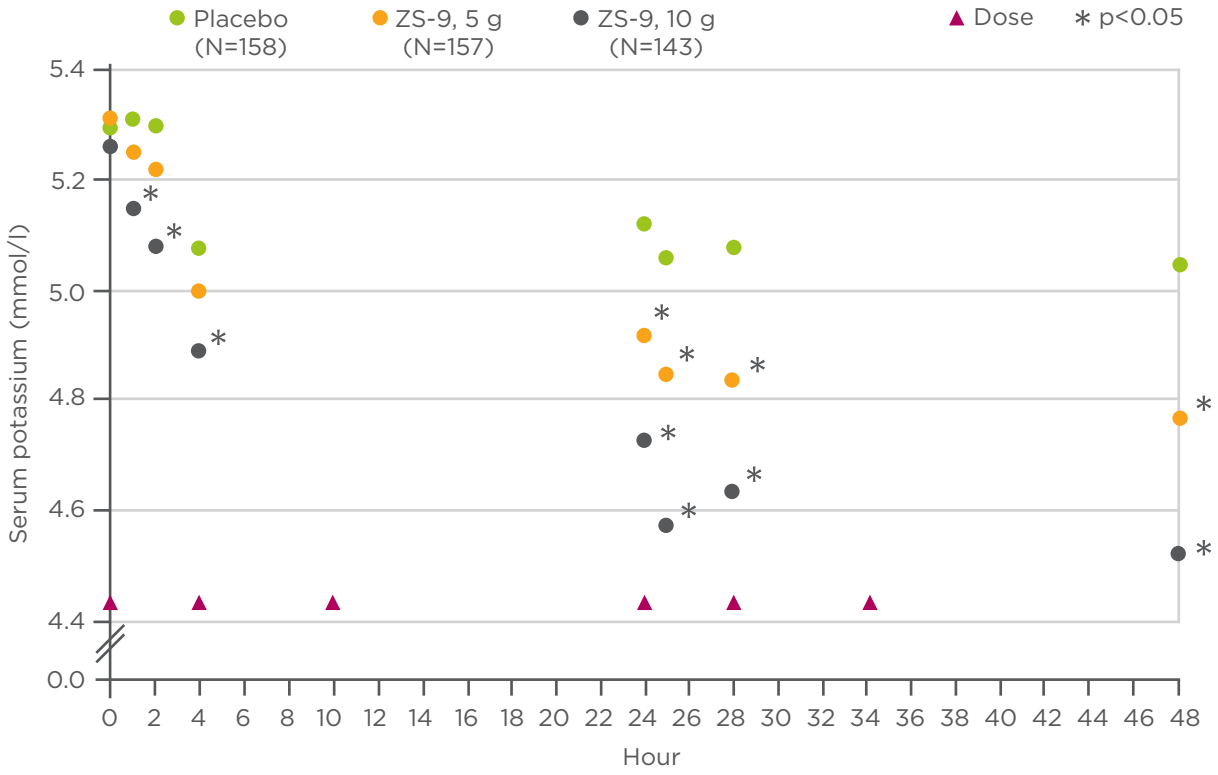
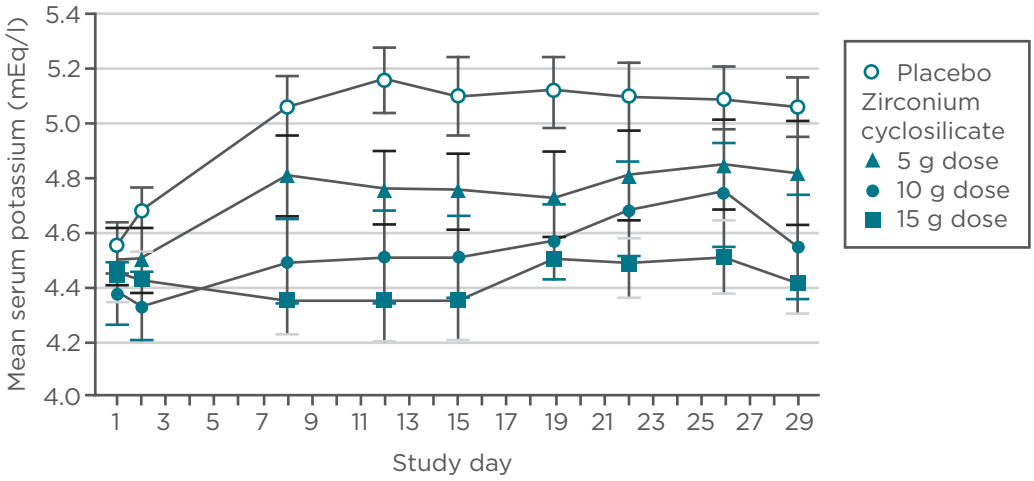


Figure 1: ZS-9 is associated with significantly lower serum K^+ levels than placebo during the acute phase.[46]



No. of patients

Placebo	82	81	81	80	80	78	77	74	73
5 g dose	45	45	45	44	44	43	43	42	39
10 g dose	50	49	50	47	47	47	45	45	38
15 g dose	54	54	54	53	52	51	51	51	43

Figure 2: All doses of ZS-9 maintained normokalaemia during the randomised phase of the HARMONIZE study.[47]

Adapted with permission from Kosiborod M et al.[47] Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. JAMA. 2014;312(21):2223-33.

ZS-9 and patiromer sorbitex calcium are two promising advanced therapies for the treatment of hyperkalaemia. The studies conducted with patiromer and ZS-003 excluded patients with K^+ levels >6.5 mmol/l, whereas the HARMONIZE study had no upper limit of serum potassium level for patient inclusion. The study included patients with K^+ levels up to 7.2 mmol/l. However, all studies described excluded patients who were hospitalised and/or on dialysis.[47] Further studies to determine the long-term efficacy and safety of these new therapies for the treatment of hyperkalaemia in CKD and HF are currently ongoing.

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RENAL TRANSPLANTATION IN AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

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ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) affects approximately 1 in 1,000 people in the general population. The natural history of ADPKD includes the progression of chronic kidney disease to end-stage renal disease (ESRD) in a large proportion of patients. Renal transplantation is the treatment modality of choice in these patients. However, there are some specific issues that should be addressed in ADPKD, and the aim of the current review is to describe the issues that need to be considered in the pre and post-transplant management of ADPKD patients, excluding routine procedures.

Keywords: Autosomal dominant polycystic kidney disease, intracranial aneurysms, native nephrectomy, renal transplantation.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is considered one of the most common genetic disorders. It affects approximately 1 in 1,000 people in the general population and, therefore, the number of patients is substantial, with more than 500,000 cases estimated for the whole of the European Union. The disease is due to a mutation in one of two genes: *PKD1* in Type 1 ADPKD and *PKD2* in Type 2 ADPKD. Mutation of *PKD1* is more prevalent and causes 85% of cases of the disease. The natural history of ADPKD includes the progression of chronic kidney disease to end-stage renal disease (ESRD) in a large proportion of patients.[1] Effectively, ADPKD is the fourth most common renal disease requiring renal replacement therapy (RRT), with a prevalence of 91.1 cases per 1 million individuals.[2] The average age of patients with ESRD depends on the type of the disease and amounts to 58.1 years in Type 1 ADPKD, and 79.7 years in Type 2 ADPKD.[3] Due to the extrarenal distribution of polycystins, encoded by *PKD1* and *PKD2* genes, ADPKD is a systemic disease with multiple extrarenal manifestations, including arterial hypertension, aneurysms, and cysts in solid organs such as the liver, pancreas, and spleen.[1]

Similar to other causes of ESRD, renal transplantation (RTx) is the treatment modality of choice in ADPKD patients who require RRT. However, there are some specific issues that should be addressed in these patients. The aim of the current review is to describe the issues that should be considered in the pre and post-transplant management of ADPKD patients, excluding routine procedures.

PRE-TRANSPLANT PROCEDURES

Native Nephrectomy

The first issue that should be addressed is whether the patient requires a native nephrectomy (NN); ADPKD is not an indication for this procedure per se. The indications for NN are: renal cyst infection, pain, suspicion of tumour, recurrent haematuria, and a lack of space for the

implantation of the transplant. In effect, only 20% of ADPKD patients require NN.[4] The volume of a native kidney decreases after transplantation.[5] Therefore, if the space for the renal graft is available at the moment of transplantation there is no need for NN due to the aforementioned indication. Maximal kidney length >21.5 cm was proposed as an optimal criterion in making decisions concerning NN in ADPKD patients.[6] The timing and the method of NN remain controversial. In general, nephrectomy may be performed before or at the moment of transplantation. Simultaneous nephrectomy and transplantation is considered a safe approach in experienced centres. It is associated with acceptable morbidity and does not affect patient and graft survival.[7-11] Additionally, some clinicians prefer post-transplant nephrectomy as the safest option.[12] The next question that should be raised is whether the patient requires unilateral or bilateral nephrectomy. Some clinicians report bilateral nephrectomy as a safe method,[9-11] but others prefer a unilateral procedure due to the perioperative complication rate.[7] Finally, a choice between conventional and laparoscopic nephrectomy is to be made; the latter is considered a safe option.[7,9] To reduce postoperative pain and the risk of incisional hernias, as well as to improve the cosmetic result of laparoscopy, laparoscopic nephrectomy with morcellation of the specimen was proposed.[13] Alternatively, embolisation of enlarged polycystic kidneys may be considered.[14]

Cardiovascular System

The involvement of the cardiovascular system is common in ADPKD. Vascular manifestations of the disease are due to the fact that both polycystins are expressed within arterial smooth muscle cells,[15-17] and a systemic vascular defect has been observed in the oligosymptomatic stage of the disease.[18,19] Arterial hypertension (AH) in ADPKD is common and has complex pathogenesis, with three main pathological mechanisms: i) activation of the renin-angiotensin-aldosterone system secondary to intrarenal ischaemia caused by growing cysts; ii) activation of the sympathetic nervous system; and iii) ciliopathy-related endothelial dysfunction.[20] Therefore, careful cardiovascular assessment, including AH and its complications, is of special value in ADPKD.

Additionally, intracranial aneurysms (ICANs) are attributable to complications specifically associated with ADPKD. Aneurysm formation is due to primary cilia dysfunction in a mechanism dependent on downregulation of survivin expression.[21] In effect, the frequency of ICANs is increased in ADPKD compared with the general population[22] and is estimated at 4-22.5%.[23,24] Additionally, ADPKD has been proven to be associated with increased risk of intracranial haemorrhage among ESRD patients.[25] To avoid complications associated with ICAN rupture, screening for ICANs is recommended: i) in those with family or past personal history of ICAN or its rupture; ii) in case of symptoms suggesting ICAN; iii) in patients with a job or hobby in which loss of consciousness may be lethal; iv) before major elective surgery; and v) when a patient is extremely afraid of possible ICAN.[26] Additionally, the risk of ICAN increases with the patient's age[27] and in Caucasians the prevalence is substantially increased after 45 years of age.[28] Irrespective of the type of ADPKD, the average age of ESRD patients is greater than 45 years. Therefore, most ADPKD patients should be considered as candidates for screening for ICANs during their preparation for RTx. Indeed, screening for vasculocerebral malformations in ADPKD patients is performed in numerous centres.[29] In some centres up to 91% of patients undergo such screening.[30]

The optimal method of screening for ICANs is magnetic resonance angiography (MRA) of the brain, due to the lack of X-ray exposure and no need for contrast media administration.[28] In patients with contraindications for MRA, the most important being implanted electronic devices or ferromagnetic foreign bodies, computed tomography angiography should be implemented as an alternative method. However, in such cases the risk of contrast-induced acute kidney injury, especially in patients with impaired renal function, must always be kept in mind and preventive measures must be implemented.

A patient with an ICAN detected on imaging should be referred to a specialist in neurosurgery in order to decide whether treatment is required, and when and how (endovascularly or surgically) it should be done. Due to the relatively low rate of progression and rupture of ICANs in ADPKD, only those at high risk of rupture require treatment. The decision is made on the basis of ICAN size and location, its morphology, the patient's age, and comorbidities. If the treatment is not conducted, the method and timing of follow-up must be determined.[31]

Liver

Polycystic liver disease (PLD) is observed in 75-90% of ADPKD patients.[32] ADPKD does not impact liver function and in most cases PLD is benign and asymptomatic.[33] However, in rare cases the condition may be complicated with massive hepatomegaly leading to mass effect with compression of the surrounding organs, or acute complications including torsion of the cyst, intraluminal haemorrhage, or infection.[32] Management of acute complications has been discussed previously.[34] In mass effect, when there is a lack of space for a renal graft, NN should be considered as a first-line treatment. When a reduction in liver volume is required, the treatment options include: i) interventional radiology with arterial embolisation or percutaneous sclerotherapy, and ii) surgical intervention with fenestration or hepatic resection. Liver transplantation (LTx), including combined LTx and RTx, should be reserved for the most severe cases, especially those with liver failure.[26,32]

In ADPKD patients with PLD, serum carbohydrate antigen 19-9 (CA19-9) may be increased due to its secretion by the biliary epithelium lining the liver cysts.[35] As exclusion of neoplastic disease is a part of pre-transplant assessment, levels of tumour markers are often examined in potential transplant recipients. Thus, in ADPKD patients a modest increase in serum CA19-9 need not be connected to cancer or inflammation.

Diverticular Disease

Due to the fact that RTx recipients with ADPKD are at risk of colonic diverticulosis and its complications, elective colonic resection should be considered before transplantation in patients with medical therapy for acute diverticulitis in their medical history.[36]

Living Related Kidney Donor

Living kidney donation should always be considered in candidates for RTx. However, exclusion of ADPKD is required in the potential living related kidney donor. Imaging studies may be insufficient for certain exclusion of ADPKD in a potential donor, especially if he or she is below 40 years of age. In such cases genetic testing is useful.[37]

POST-TRANSPLANT MANAGEMENT

Results

Graft and patient survival rates are at least not inferior in patients with ADPKD compared with those who underwent RTx for other reasons. One-year graft survival reaches 100%,[30] and 5-year graft survival exceeds 80%, which according to some is better when compared with other causes of ESRD.[29] Long-term graft survival is similar to other nephropathies.[38] Additionally, improved patient survival has been noted in recent years, which is connected with a decrease in cardiovascular mortality.[2] In effect, 1 and 5-year patient survival may exceed 90% and is not inferior compared with other causes of ESRD.[8,29,38] Similarly, no difference exists between ADPKD and non-ADPKD groups in patient survival at 10 and 15-year follow-up. Jacquet et al.[39] suggest that graft survival is even better in the ADPKD group, despite a higher risk of graft failure due to usually older donors and longer cold ischaemia times. According to most clinicians, ADPKD RTx recipients are older and their body mass index (BMI) is usually higher compared with non-ADPKD patients,[39,40] which may impact upon the long-term complications rate. In a study conducted by Jacquet et al.[39] ADPKD and non-ADPKD RTx recipient groups did not differ in terms of the incidence of biopsy-proven acute rejection, although the occurrence of metabolic disorders such as post-transplant diabetes, hyperlipidaemia, hypertension, and stroke was higher in ADPKD patients. Infections, cardiovascular disorders, and neoplasia are the main causes of mortality in patients with ADPKD after RTx.[40,41] There are no known examples of disease recurrence in the transplanted kidney.

Native Kidneys

The volume of the native kidneys after transplantation tends to decrease;[5] however, vigilance is required due to cases of recurrent cyst infections and mechanical compression of the transplanted kidney and ureter by an enlarged native kidney,[42] recurrent lumbar pain,[43] and possibility of carcinogenesis.[44] Native kidneys produce erythropoietin that induces higher haemoglobin levels at Month 3 post-transplant in ADPKD compared with other nephropathies.[45,46] On the other hand, excessive secretion of erythropoietin may lead to erythrocytosis, which is defined as an increase in haematocrit above 51%.[40]

Cardiovascular System

Research results contradict the idea that hypertension is more frequent in transplant recipients with ADPKD compared with patients with other nephropathies,[40] and some studies indicate improved arterial pressure control after transplantation in ADPKD.[41] Although cardiovascular events are the second biggest cause of death in patients with ADPKD after transplantation,[40] they do not occur more frequently in this group compared with the control,[29] and according to some researchers myocardial infarction and heart failure are even less frequent in patients with ADPKD who reached ESRD compared with non-diabetic controls with ESRD.[46] Valvular abnormalities (mitral valve [MV] prolapse and MV regurgitation), however, are characteristic in ADPKD transplant recipients.[47] Also, pericardial effusion incidents occur more frequently in these patients.[48]

ICANs are more common in patients with ADPKD than in the general population[23] and ADPKD is a well-documented risk factor for intracranial haemorrhage among patients undergoing dialysis and after transplantation.[25,49] The potential for aneurysm formation in other arteries should not be forgotten, including aortic aneurysms. Thus, ADPKD RTx recipients should undergo periodic screening for abdominal aortic aneurysms. In the case of rupture, emergency endovascular repair is suggested to be superior compared with open surgery.[50,51] Among the vascular complications present in ADPKD patients after transplantation, thromboembolic disease (venous thrombosis and pulmonary embolism) should not be neglected due to its more frequent occurrence compared with other RTx recipients, which applies to patients with increased BMI in particular.[39]

Liver

Hepatic cysts are frequent but rarely symptomatic in ADPKD transplant recipients.[39] In contrast to native kidneys, the volume of a polycystic liver increases after RTx.[5] In the case of massive liver enlargement, therapeutic options include somatostatin analogues or surgical treatment, such as aspiration combined with sclerotherapy, laparoscopic or laparotomic fenestration, liver resection, or even LTx.[52] Additionally, hepatic cyst infection, enlargement, or rupture should be considered in the differential diagnosis of abdominal or chest pain in this group of patients.[53]

Diverticular Disease

The incidence of diverticulitis and colon diverticulum perforation is increased in RTx recipients with ADPKD when compared with patients after RTx for other reasons.[54,55] In RTx recipients these complications of diverticular disease are associated with higher mortality rates than in the general population, reaching up to 100% of patients hospitalised for this reason.[56] Early symptoms of inflammation and perforation of the diverticulum may be less tangible due to the patient receiving immunosuppressive therapy.[57] Therefore, we must remain vigilant in cases of abdominal pain in this group of patients, especially in the lower abdomen quadrants, and appropriate imaging must be carried out, with abdominal computed tomography as the method of choice. In the case of a positive diagnosis, some researchers recommend early surgical treatment.[36]

New Onset Diabetes after Transplantation

New onset diabetes after transplantation (NODAT), previously referred to as 'post-transplantation diabetes mellitus', is a frequent post-transplant complication that diminishes recipients' quality of life and has an adverse impact on graft and patient survival. In a large prospective study, 12-year graft survival was 48% in patients that developed NODAT compared with 70% in patients who were not affected by diabetes after RTx.[58] A case-control study from the Cleveland Clinic showed an increased rate of graft rejection in patients with NODAT (47%) compared with control patients (23%).[59]

According to some researchers ADPKD may be a predictor of NODAT, yet available data are controversial. A study conducted by de Mattos et al.[60] demonstrates a significant association between ADPKD and development of NODAT within the first year following RTx (17% versus 7.4%). Similar conclusions can be drawn from a Portuguese study where NODAT occurred in 33.3% of patients with ADPKD compared with 17.1% of the non-ADPKD control group.[40] In addition, a UK retrospective study showed that 13.4% of patients with ADPKD developed diabetes, whereas NODAT occurred in only 5.2% of the patients with other nephropathies. Moreover, twice as many patients with ADPKD and NODAT required treatment with insulin compared with the non-ADPKD diabetic group.[61] Additionally, according to the analysis

of Caillard et al.,[62] ADPKD is associated with risk factors for NODAT.

However, other studies do not support the concept that ADPKD is associated with a higher incidence of NODAT. In a retrospective cohort study conducted in 505 transplant recipients, there was no significant difference in NODAT incidence between ADPKD and non-ADPKD groups,[63] and several other studies yielded similar results.[64-66] Irene et al.[67] examined the incidence of NODAT and impaired glucose tolerance (IGT) in 65 renal allograft recipients with ADPKD compared with a gender and year of transplantation-matched control group and found no differences between groups. There was also no difference in the number of acute rejections between groups. Interestingly, a higher risk of NODAT development in RTx recipients with ADPKD may be associated with the HLA-B27 antigen.[65] Nevertheless, periodical assessment for NODAT should be performed in RTx recipients with ADPKD, especially when additional risk factors for NODAT exist, including BMI exceeding 25 kg/m^2, pre-transplant IGT, and acute rejection.[62]

Infections

Infections are an important class of complications arising in kidney recipients with ADPKD, and for most clinicians are considered as one of the main causes of death in this population. However, except for urinary tract infections (UTIs), they do not occur in this group with higher prevalence than in RTx recipients with other nephropathies.[29,68] Immunosuppression favours the spread of infections, including into the graft. Ascending UTIs and cyst infections occur mainly in patients who have not undergone a pre-transplant nephrectomy.[43] Due to immunosuppressive therapy, opportunistic pathogens should be included in the differential diagnosis of native kidney infection, including *Mycobacterium tuberculosis*.[69] Interestingly, renal graft recipients with ADPKD were suggested to be less prone to BK virus infection due to a lower cellular permissivity of the renal tubular epithelial cells in this disease.[70]

Neoplastic Diseases

Neoplastic lesions occur with increased frequency in patients receiving immunosuppressive therapy after transplantation, regardless of its cause, and cancer is one of the major causes of death in this group.[71,72] ADPKD appears to be a risk factor for renal tumours in the pre-transplant period, although the available studies do not provide consistent data.[44,73,74] In this context it is important to keep in mind the possibility of kidney tumours in patients who have not undergone nephrectomy. The increased risk of cancer in organ-transplant recipients with ADPKD has not been the subject of many studies. Recently, Wetmore et al.[75] compared the incidence of cancer in 10,166 RTx recipients with ADPKD and 107,339 without polycystic disease. Although the overall incidence of cancer was higher in patients with ADPKD, it was shown to be lower after adjustment for the higher age of recipients in this group. In a study by Vega et al.[38] the rate of cancer was similar in ADPKD and non-ADPKD RTx recipients. Other studies show no difference between the incidence of kidney cancer in recipients with ADPKD and control patients.[39,76] However, ADPKD may be a risk factor for non-melanoma skin cancer (NMSC) in patients after RTx. In a study conducted in 1,019 patients, a significantly higher risk of NMSC (both basal and squamous cell cancer) was demonstrated in RTx recipients with ADPKD compared with other nephropathies, regardless of age, sex, phenotype of the skin, or immunosuppression. In the same study, no relationship between ADPKD and solid tumours after transplantation was reported.[77]

Immunosuppressive Treatment

Although potential benefits of proliferation signal inhibitors in post-transplant immunosuppressive regimens in ADPKD patients have been suggested,[78] to date there are no data supporting their routine use. Despite results from experimental studies, sirolimus does not impact the growth of hepatic cysts after RTx.[79] Its benefits were only proven in casuistic reports, for example in the rare association of ADPKD with tuberous sclerosis.[80] Therefore, there are no special recommendations concerning immunosuppressive therapy after RTx in ADPKD patients, and they should be treated according to the general rules.

CONCLUSION

RTx in ADPKD is currently associated with excellent results. However, to obtain satisfactory outcomes several specific issues should be addressed in pre-transplant assessment and post-transplant management. Native kidneys, the cardiovascular system, and the gastrointestinal system require special attention in these patients. Immunosuppression should be administered according to the general rules.

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COMPLEMENT INVOLVEMENT IN RENAL TRANSPLANTATION

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ABSTRACT

The complement system is involved in several renal diseases and in renal transplantation (RTx). The authors review the complement cascade and its involvement in innate and adaptive immunity in the field of RTx. The complement cascade is involved in several steps of RTx: ischaemia—reperfusion injury (IRI), T cell-mediated acute rejection (TMR), antibody-mediated rejection (ABMR), and progressive kidney injury and fibrosis. The high frequency of complement involvement in RTx is the subject of several studies because complement could be a relevant target in treating the aforementioned conditions. There is an increasing number of ongoing clinical trials aimed at verifying the efficacy and safety of many drug candidates. The anti-C5 monoclonal antibody is already approved to prevent and treat ABMR and is the subject of trials investigating the treatment of other conditions such as IRI, TMR, and progressive fibrosis. Other molecular targets, such as C1, C3, C5a, and C5a receptor, are the subject of international trials and could prove to be effective in the near future.

Keywords: Renal transplantation, complement cascade, ischaemia—reperfusion injury, acute and chronic rejection, renal fibrosis, therapies targetting complement.

INTRODUCTION

The complement system is an essential component of the innate immune system and plays an indispensable role in the elimination of invading microorganisms as a first line of defence.[1,2] The complement system bridges innate and adaptive immunity. In addition, another key component of the immune system, the cross-talk between Toll-like receptors and the complement system, has been a key area of research.[3]

Complement Cascade

Complement activation occurs through three major pathways: the classical pathway (CP), the alternative pathway (AP), and the mannose-binding lectin pathway (LP), all of which generate the C3 convertase enzyme complex that cleaves C3 into C3a and C3b, thus leading to the complement cascade with activation of C5 convertase and terminal pathway activity.[4] The AP is constantly activated at low levels in healthy subjects. The activation and progression of the cascade are strictly controlled by complement-regulating proteins (Figure 1).[5] A number of soluble regulators are involved in the control of complement activation. C1 inhibitor (C1-INH) prevents auto-activation of the initial complex formed in the CP. C4b-binding protein is a decay-accelerating factor (DAF, CD55) for C3 convertase in the CP and a co-factor for cleavage of C4b opsonin by complement factor I (CFI). Similar activity in the AP is provided by complement factor H, which is involved in the decay of convertase and C3b inactivation by CFI. Clusterin and vitronectin both act on terminal complexes and prevent their insertion into cell membranes. Also, carboxypeptidase N is a part of fluid-phase regulatory activity of the three pathways, acting as an anaphylatoxin inhibitor. Finally, cell surface-bound regulatory proteins such as complement receptor 1 (CR1), membrane co-factor protein (MCP, CD46), and DAF shorten the half-life of cell surface-assembled C3 and C5 convertase.

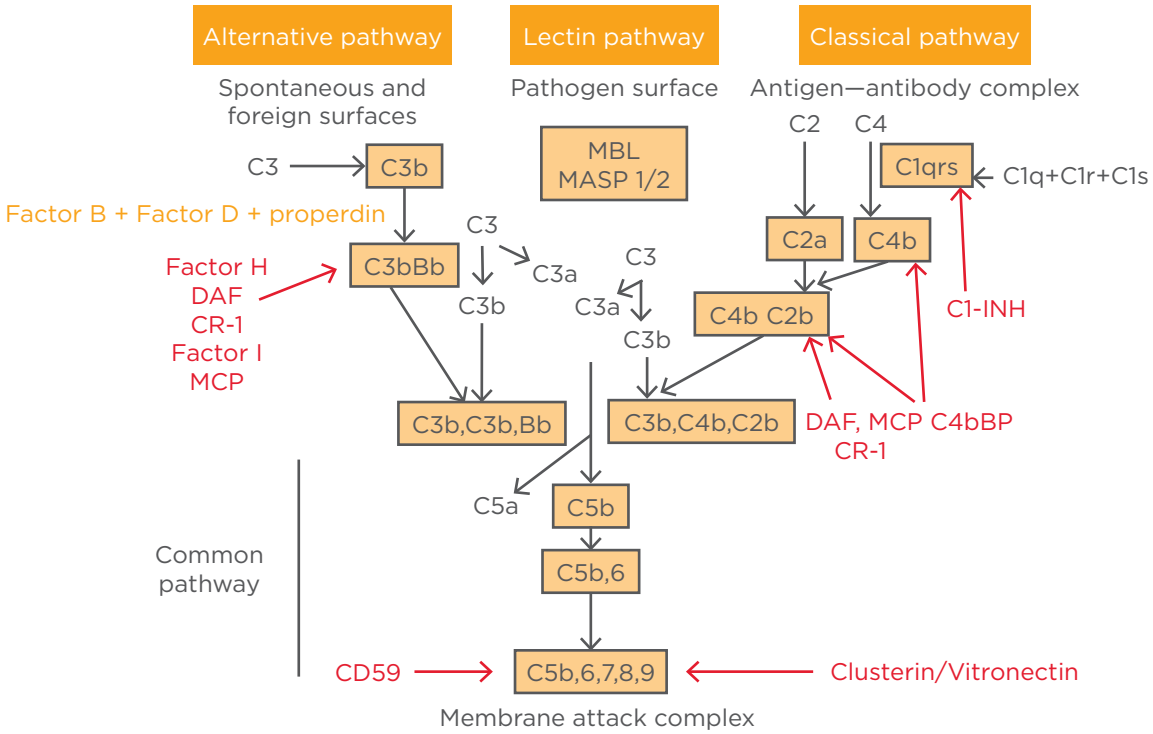

Figure 1: Representation of the classical, lectin, and alternative pathways of complement activation, including regulatory molecules (red).

MBL: mannose-binding lectin; MASP 1/2: mannan-binding lectin-associated serine protease 1/2; C1-INH: C1 inhibitor; DAF: decay-accelerating factor; CR-1: complement receptor 1; MCP: membrane co-factor protein.

Complement-mediated injury will proceed if the triggered activation of any complement cascade outweighs the inhibitory potential of the pathway regulators.[6,7]

Evidence emerging over the past 15 years supports the concept that the complement cascade, which has been traditionally considered a component of innate immunity, also regulates kidney ischaemia—reperfusion injury (IRI), acute T cell-mediated rejection and humoral alloimmunity that underlie transplant rejection, as well as post-transplant recurrence of glomerular diseases such as complement-mediated and progressive kidney injury that result in late graft failure. All these data support the need for further studies testing the efficacy of targetting complement and its receptors for the improvement of RTx outcomes.[8]

COMPLEMENT AND ISCHAEMIA—REPERFUSION INJURY

Early evidence from *in vivo* models indicated that IRI following transplantation is related to donor kidney-derived C3 and not to systemic recipient C3.[9] Further studies using *in vivo* models support the conclusion that IRI upregulates production of complement components by kidney endothelial and tubular cells, as well as by infiltrating immune cells. Local activation through the AP yields C3a and C5a, which amplify local inflammation and injury through autocrine and paracrine interaction with their receptors expressed by cells within the graft.[10,11] It should be highlighted that the majority of kidneys transplanted in humans are retrieved from cadaveric donors. Damman et al.[12] found higher gene expression of C3 and increased deposition of C3d in kidney biopsies obtained from deceased-donor grafts. de Vries et al.[13] detected soluble C5b-9 following reperfusion of kidneys from deceased donors, but not from living-donor kidneys. Whole-genome expression profiling of human renal allograft protocol biopsies at implantation confirmed significantly higher expression levels of complement genes in deceased-donor kidneys.[14] Van Werkhoven et al.[15] found that brain death initiates systemic complement activation, upregulates C5a receptor (C5aR) expression by tubular cells, and is associated with induction of intrarenal cytokines.

Table 1: Anti-complement agents in clinical trials for ischaemia—reperfusion injury.

Complement inhibitor	Target	Major mechanism of action
Eculizumab	C5	Inhibition of C5b-9 and C5a formation
rhC1-INH	C1r, C1s, plasmin, C3b, kallikrein, XIa, XIIa, MASP1, MASP2	• Regulatory effect on coagulation • Inhibition of the alternative pathway • Control of the release of bradykinin
sCR-1	C3b, C4b	Inactivation of C3 and C5 convertase

rhC1-INH: recombinant C1 inhibitor; MASP 1/2: mannan-binding lectin-associated serine protease 1/2; sCR-1: soluble complement receptor 1.

Moreover, the complement component C5a, which is generated by the donor brain death, may act directly on the C5aR expressed by tubular cells and infiltrating cells.

C3 is implicated in the activation of the renin—angiotensin system and in the epithelial—mesenchymal transition.[16,17] This observation also supports the concept that synthesis of complement components by renal epithelial cells is a mediator of tubular damage in proteinuria-associated renal diseases and transplantation. Indeed, several studies document that intragraft complement activation contributes to chronic dysfunction. Accordingly, C3—/— kidney isografts transplanted into wild-type recipients were protected from progressive renal failure.[18]

Going into molecular details, Simone et al.[19] documented that complement activates reduced nicotinamide adenine dinucleotide phosphate enzymes in renal IRI. In addition, complement has a critical role in the induction of the endothelial—mesenchymal transition (EndMT) during renal IRI and these data shed light on the pathogenic factors that regulate this particular form of endothelial dysfunction, which has an important role in the regulation of renal fibrosis.[20] Castellano et al.[21] documented that activation of the CP and LP of the complement system occurs primarily at the level of the endothelial cells during IRI. As EndMT contributes to the development of tissue fibrosis, the same authors investigated the possible role of complement in the induction of EndMT in a swine model of renal IRI by using recombinant C1-INH *in vivo*. They observed that the activation of the Akt pathway was pivotal for C3a and C5a-induced EndMT *in vitro*. In accordance, the inhibition of complement *in vivo* led to the abrogation of Akt signalling with hampered EndMT and tissue fibrosis.[22]

Several drug candidates are currently undergoing evaluation in clinical trials investigating the prevention of IRI through the inhibition of complement (Table 1). Eculizumab, a humanised monoclonal antibody (mAb) directed against the C5 component of the complement cascade, is already used to treat atypical haemolytic uraemic syndrome (aHUS) and antibody-mediated rejection (ABMR) and may be capable of preventing IRI. Studies evaluating the role of eculizumab in the prevention and treatment of IRI and delayed graft function (DGF) in kidney allograft are currently ongoing.[23-25]

The beneficial effect of recombinant C1-INH on IRI has been widely studied by Castellano et al.[21] Purified or recombinant C1-INH is a serine protease inhibitor first recognised for its ability to regulate the activity of the C1 complex, but it also acts at the level of mannose-binding lectin (MBL) and thereby inhibits complement activation via the CP and LP.[26] To date, one trial (NCT02134314) with C1-INH has been initiated to investigate the prevention of DGF in patients receiving a deceased-donor RTx. Soluble CR1 (sCR1) is another protein that regulates C3 convertase. CR1 itself is a cell-surface glycoprotein expressed by erythrocytes, monocytes, neutrophils, B cells, some T cell subsets, dendritic cells (DCs), and podocytes, and it modulates the complement cascade at multiple levels.[27] The effect of Mirococept (APT070, a form of sCR1) has been widely described by

Sacks et al.[28] and is currently the subject of a large-scale study evaluating its use in the prevention of IRI in cadaveric RTx.[29]

The aforementioned findings indicating that brain death is associated with complement activation in the donor kidney prior to organ removal raise the intriguing possibility that complement inhibition in the donor could be an effective prophylactic therapy to prevent IRI in the new host. Innovative study design will need to be developed to test this possibility.[8]

COMPLEMENT, ALLOREACTIVE T CELLS, AND T CELL-MEDIATED REJECTION

Pratt et al.[30] documented that C3 produced by an allograft and the recruited immune cells is a trigger that not only induces post-perfusion injury, but also late rejection-associated allograft injury. Indeed, a recent study[31] documented that intragraft-generated complement may affect the systemic immune response to antigens requiring a functional AP of complement activation. The C3 cleavage products C3b and C3d deposited on antigen-presenting cells (APCs) may increase antigen uptake and presentation to T cells, which aids the generation of alloreactive clones. Indeed, C3-positive APCs have been shown to potentiate the T cell response *in vitro*.[30] T cell activation by the complement system enhances expansion of effector T cell clones by limiting antigen-induced apoptosis.[32] Moreover, data published in 2013 indicate that complement also modulates regulatory T cell (Treg) induction, function, and stability.[33,34] According to a recent study,[35] peripheral murine natural Tregs express C3aR and C5aR, and signalling through these receptors inhibits Treg function.

Important confirmatory studies in humans were published in 2013 and documented that C3a and C5a are generated in *in vitro* cultures of human T cells responding to allogeneic DCs.[36] To summarise, complement activation through any pathway generates C3a and C5a. These anaphylatoxins bind to both APCs and T cells to stimulate T cell proliferation and activation.[37] Li et al.[38] documented that a deficiency of C5aR limited the adaptive response of recipient T cells to alloantigens. C1q appears to have a regulatory role in the threshold for T cell activation by DCs.[39] It should be highlighted that all resident renal cells may contribute to generate complement components. Also, endothelial cells have been documented to be able to generate C3 when stimulated with tumour necrosis factor alpha *in vitro*.[40,41] Moreover, C5aR expression was increased in renal tissue and in cells infiltrating the tubular interstitium in human kidney transplants undergoing acute rejection.[42] The same authors documented that the infiltration of monocytes/macrophages was significantly attenuated in transplanted mice treated with a C5aR antagonist, perhaps as a result of levels of monocyte chemoattractant protein 1 and intercellular adhesion molecule 1. However, a murine model of RTx with C4 deficiency demonstrated that a cell-mediated rejection may occur in the absence of CP or LP activation.[43] This suggests that the AP may play a key role in cell-mediated rejection. However, more recent studies documented that renal injury may also be mediated via activation of MBL-associated serine protease 2. These studies also documented that LP activation does not require C4.[44]

Whether complement antagonists may be therapeutically useful in controlling T cell alloreactivity while simultaneously promoting Treg induction, function, and stability in transplant patients remains to be determined.[8] Anti-C5 mAb and C5aR antagonists are currently being tested in humans for other indications, providing opportunities to assess their effects on human alloreactive T cells *in vivo* (NCT01363388).

COMPLEMENT AND ANTIBODY-MEDIATED REJECTION

ABMR involves donor-specific antibodies (DSAs) and the CP of complement activation. C1 complex is activated after binding to DSAs. Once activated, C3 is cleaved into C3a and C3b. C3b amplifies the AP, while C3a and C5a recruit macrophages and neutrophils, which cause additional endothelial injury. The overall result is that arteries and basement membranes are remodelled, leading to fixed and irreversible anatomical lesions that permanently compromise graft function.[45,46] C4d, a degradation product of C4, binds at the site of complement activation and remains covalently attached and detectable by immunochemistry.[47] As a consequence, C4d staining has become a valuable tool for diagnosing ABMR. Importantly, diagnostic sensitivity depends on staining methodology and cases of C4d-negative ABMR have been reported.[48] Indeed, high endothelial-specific gene expression in RTx biopsy samples

with DSAs but without C4d have been reported.[49] C4d-negative ABMR is characterised by the high intragraft endothelial gene expression of alloantibodies, by histology typical of chronic or acute ABMR, and by poor outcomes. Lack of complement deposition may have various explanations: i) low sensitivity to C4d[50,51] due to a technical issue; ii) some DSAs, although showing poor complement-fixing ability, may nonetheless activate endothelial cells;[52] iii) the various prophylactic strategies used to prevent ABMR may decrease the burden of complement activation within capillaries.[53]

Eculizumab has been successfully used to reduce the level of antibodies in highly sensitised patients with positive cross-matches prior to transplantation.[54-56] In a larger case—control study, the patients with DSAs were treated with eculizumab plus plasmapheresis before and after transplantation, and then compared with historical controls.[57] Eculizumab treatment proved successful in significantly reducing ABMR and decreasing the 1-year transplant glomerulopathy incidence rate. Anti-C5 mAb also successfully reversed established ABMR.[58] In addition, recent data also document complement involvement in antibody-mediated chronic rejection where the 'bad' activity of antibodies may also be involved in previously considered 'chronic lesions' (e.g. transplant glomerulopathy).[59,60] Finally, in light of the association between anti-human leukocyte antigen antibodies and chronic ABMR, ongoing studies are testing the efficacy of eculizumab in preventing graft loss in RTx recipients with DSAs (NCT01327573).

COMPLEMENT INVOLVEMENT IN THE RECURRENCE OF GLOMERULAR DISEASES AFTER TRANSPLANTATION

Some glomerular diseases are clearly mediated by complement activation. These diseases may recur after transplantation and may be treated by anti-complement drugs. aHUS is associated with a high rate of recurrence and poor outcomes after RTx. Recurrent thrombotic microangiopathy is very rare in patients who develop end-stage renal failure following HUS caused by Shiga-toxin-producing *Escherichia coli*, whereas disease recurrence is common in patients with aHUS.[61] The recurrence rate[62] of C3 glomerulopathy after RTx is estimated at approximately 60%, as derived from the small case series of Servais et al.[63] and Little et al.,[64] and confirmed in the recent article by Zand et al.[65] In such conditions anti-complement therapy with eculizumab could be useful.[66] In the case where C3 dysregulation prevails (some dense-deposit diseases and C3 glomerulonephritis) an anti-C3 therapy might be useful.[67]

COMPLEMENT, PROGRESSIVE KIDNEY INJURY, AND FIBROSIS

Alterations in complement activation within the kidney have been implicated in multiple diseases leading to renal fibrosis, among which is renal allograft rejection.[68] The role of complement activation in the modulation of immunity and pathogenesis of renal fibrosis in the context of IRI is a field of several avenues of research. IRI of the kidney is a well-established cause of renal fibrosis. Factors such as sustained innate immune activation, endothelial cell dysfunction, hypoxia, and chronic microvascular injury have all been implicated in the promotion of fibrosis.[69] As mentioned above, several studies[70,71] point to the EndoMT and highlight a central role for the endothelium in progression to fibrosis, and a novel role for complement in the modulation of endothelial cell activation and EndMT. In further support of the concept that intragraft complement production modulates progressive kidney injury, proteomic studies of kidney allograft tissue by the Salomon group demonstrated a strong association between interstitial fibrosis/tubular atrophy (IF/TA) and the AP.[72] An ongoing study of chronic anti-C5 mAb therapy in RTx recipients (NCT01327573) could provide further insight into the role of complement as a mediator of progressive graft dysfunction and IF/TA.

CONCLUSION

Emerging evidence has recently suggested that the complement cascade is a common pathogenetic mechanism in many kidney diseases and in RTx rejection. The complement system is now recognised as a pervasive, multifaceted mediator of transplant injury in animal models and in human transplant recipients. The development of pharmacological agents that block human complement components and receptors in the setting of RTx now represents the basis of the concept that targetting the complement system in RTx recipients will improve graft and patient survival rates.

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RETROGRADE INTRARENAL SURGERY FOR COMPLEX STONES IN A TODDLER WITH CONGENITAL RENAL ANOMALIES: TECHNICAL DETAILS

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ABSTRACT

We report herein the management of a challenging case due to anatomic and stone-related complications in a 37-month-old Caucasian toddler with megacalycosis and complex stone in the left kidney and duplicated ureter on the right side.

Keywords: Retrograde intrarenal surgery, flexible ureteroscopy, micropercutaneous nephrolithotomy (microperc), percutaneous nephrolithotomy, kidney, complex stone.

INTRODUCTION

Since a surgeon's first experience with many complex endourological techniques is generally in adults and then later implemented in children, knowledge and expertise in paediatric complex renal stone treatment falls behind that for adults. Percutaneous nephrolithotomy (PCNL) is considered as the first-line treatment option in complex renal stones, either alone or in combination with shock wave lithotripsy (SWL).[1] Departments specialised in endourological stone treatment are able to employ the most up-to-date treatment modalities in paediatric stone cases. In addition to PCNL, retrograde intrarenal surgery (RIRS) and micropercutaneous nephrolithotomy (microperc) may also be used for the treatment of complex renal stones.[2] Limited data are available regarding percutaneous treatment and/or retrograde intrarenal management of kidney stones in children with congenital anomalies. We report herein the management of a challenging case due to anatomic and stone-related complications in a 37-month-old Caucasian toddler with megacalycosis and complex stone in the left kidney and duplicated ureter on the right side.

CASE

A 37-month-old Caucasian female was referred to our department with left kidney stone and recurrent urinary tract infection complaints over the previous 2 years. The patient had been diagnosed with left renal stone in an outpatient clinic 2 years before. She had an 8 mm renal stone in the left lower pole, and 2 mm and 3 mm renal stones in the middle pole. As the renal stones were observed to have grown at follow-up she was referred to our centre. Her examination revealed several stones filling two calyces in the left lower pole (with the largest being 35 mm in diameter), one in the middle pole filling one calyx and extending towards the pelvis, and several in the upper pole calyces (Figure 1). A duplicated collecting system on the right and rotation anomalies on the left were also diagnosed (Figure 2). There was no growth in the urine culture and blood values were within normal limits. The patient's weight and height were 13 kg and 85 cm, respectively. Removal of the renal stones using endoscopic techniques was decided. Despite the greater experience available with PCNL, RIRS was considered due to the presence of stones in many calyces and concern that a stone-free status could not be achieved with monotherapy and

limited fluoroscopy time. Regardless of the technique employed, it was decided that SWL would be applied for any residual stones. The patient's family was informed about the relevant treatment options and related risks. RIRS was considered as the first-line treatment modality to access the renal stones. If the ureteral access sheath (UAS) could not be placed due to the ureteral anatomy, the surgical team was also prepared for percutaneous intervention.

OPERATION THEATRE

The patient underwent RIRS under general anaesthesia in the standard lithotomy position. Two lead collars were used in the present case, as these were considered to be better shaped for positioning during cystogram and intervention to the kidney stones. The cystogram obtained prior to RIRS was unremarkable. Cystoscopic evaluation was performed by 7.5 Fr paediatric semi-rigid ureteroscope (STORZ, Tuttlingen, Germany), and two ureter orifices were observed on the right and one on the left. A hybrid guide wire was introduced from the left ureteral orifice and advanced until the upper calyx. Another guidewire used as a safety guidewire and a 9.5 Fr 28 cm UAS were also placed in the proximal ureter over the first guidewire under fluoroscopy. The retrograde pyelogram revealed high-insertion ureteropelvic junction (UPJ), narrow infundibulopelvic angle, megacalycosis, and a small renal pelvis (Figure 3). Access of the flexible ureteroscope (Flex-X2, STORZ, Tuttlingen, Germany) to the stone was difficult due to the small pelvis and high insertion of the UPJ. The pelvic stone could be partially fragmented by holmium: YAG laser, whereas calyceal stones in the lower and middle poles were fragmented with either 272-micron (0.6 J and 10 Hz) or 200-micron (0.6 J and 8 Hz) laser probes (Sphinx, LISA, Katlenburg-Lindau, Germany). All the stones were fragmented until they were considered small enough to pass spontaneously.

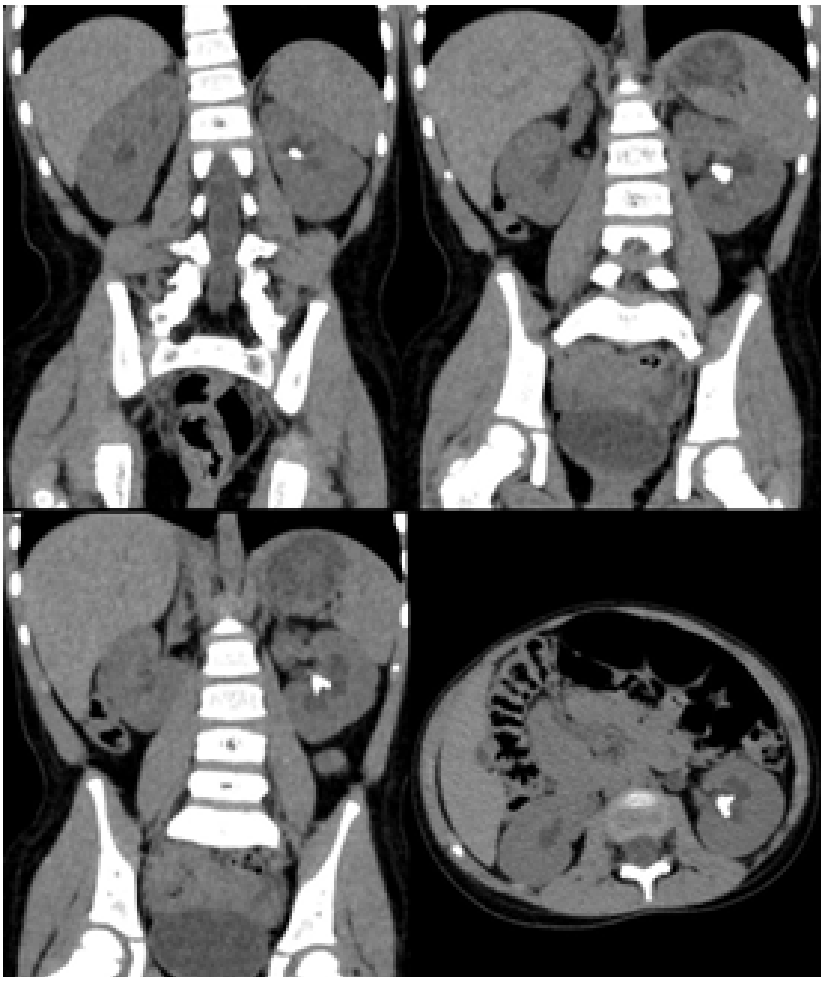

Figure 1: Stones filling two calyces in the left lower pole, one in the middle pole filling one calyx and extending towards the pelvis, and several in the upper pole calyces.

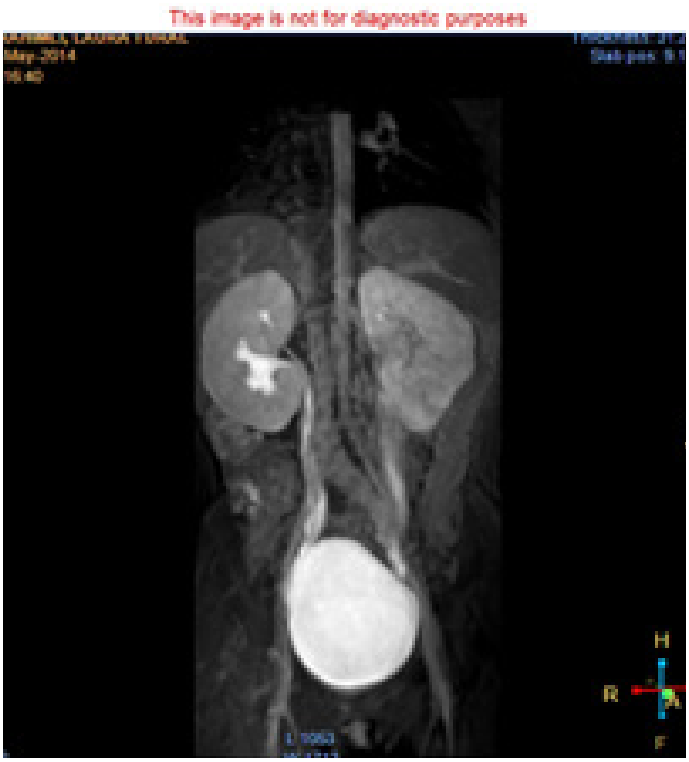

Figure 2: A duplicated collecting system on the right and rotation anomalies on the left.

A manual irrigation pump was used during the procedure. Sufficient samples for stone analysis were taken by using a basket catheter. After the placement of a 16 cm double J catheter and a 10 Fr Foley catheter the intervention was completed with a total fluoroscopy time (including diagnostic imaging) of 70 seconds. The postoperative follow-up was uneventful. The patient was discharged on the third postoperative day. As the patient was from abroad, she was hospitalised for an additional day.

DISCUSSION

Although SWL is a good option in children with renal stones up to 20 mm in diameter, miniperc is considered the best choice for stones larger than 20 mm.[1,3,4] On the other hand, RIRS is an effective and well-tolerated option that can be used to manage renal stones in toddlers.[5] In the present case, the stones were settled in different calyces and thus RIRS alone or combined with miniperc or microperc was preferred over direct miniperc.[6] In paediatric renal stone cases, contrast-enhanced computed tomography (CT) or intravenous urogram imaging are not considered in the routine initial radiologic evaluation due to the inherent side-effects.[7] In line with the paediatric protocol, urinary CT without contrast material was utilised. Consequently, duplicated ureter on the right kidney and megacalycosis in the left kidney were seen in the retrograde pyelography performed during the intervention. Both megacalycosis and duplex collecting systems are congenital anomalies. The latter is seen in 0.7% of the normal adult population and in 2-4% of patients investigated for urinary tract symptoms. Similarly, megacalycosis is also a rare congenital developmental anomaly of the kidney characterised by nonobstructive dilatation of the renal calyces with symptoms such as urinary tract infection and stone formation due to stagnant urine. As there was no vesicoureteral reflux or hydronephrosis, the present anomalies were decided to be followed after stone management.

UAS usage differs according to the preference of the surgeon: there are reports of UAS usage in all patients[8-10] as well as in none.[11] In our centre, we prefer to use UAS in all patients. In paediatric cases, we use 13, 20, or 28 cm 9.5 Fr UAS depending on the length of ureter. However, we prefer to avoid using UAS in boys to prevent urethral stricture. In some cases, ureteral balloon dilatation is required. In the present case, although the UAS could not be placed in the ureter on the first attempt, it was placed easily after passage of the internal sheath with slight dilatation. On the other hand, due to the left kidney anomaly and UPJ anatomy, the technical use of the flexible ureteroscope was difficult. Multiple calyceal stones and narrow infundibulopelvic angle made access to the lower pole difficult. Use of a 200-micron laser probe for access to the lower pole facilitated the procedure. Percutaneous access was not necessary since RIRS was feasible despite the difficulties. According to the post-ureteroscopic lesion scale,[12] damage to the ureter after the intervention was Grade 1.

One of our main concerns in complex renal stone treatment in children is sepsis. Minimising the laser stone fragmentation time and maintaining low intrapelvic and intrarenal pressure take on greater importance in the growing toddler's kidney. UAS usage is known to lower intrapelvic pressure up to 57-75%.[13] Moreover, using UAS may help in removing the stone fragments more easily. The stone fragmentation time was minimised to the greatest extent possible. Fragmentation was preferred over dusting. The manual irrigation pump was only used during the procedure if absolutely necessary.

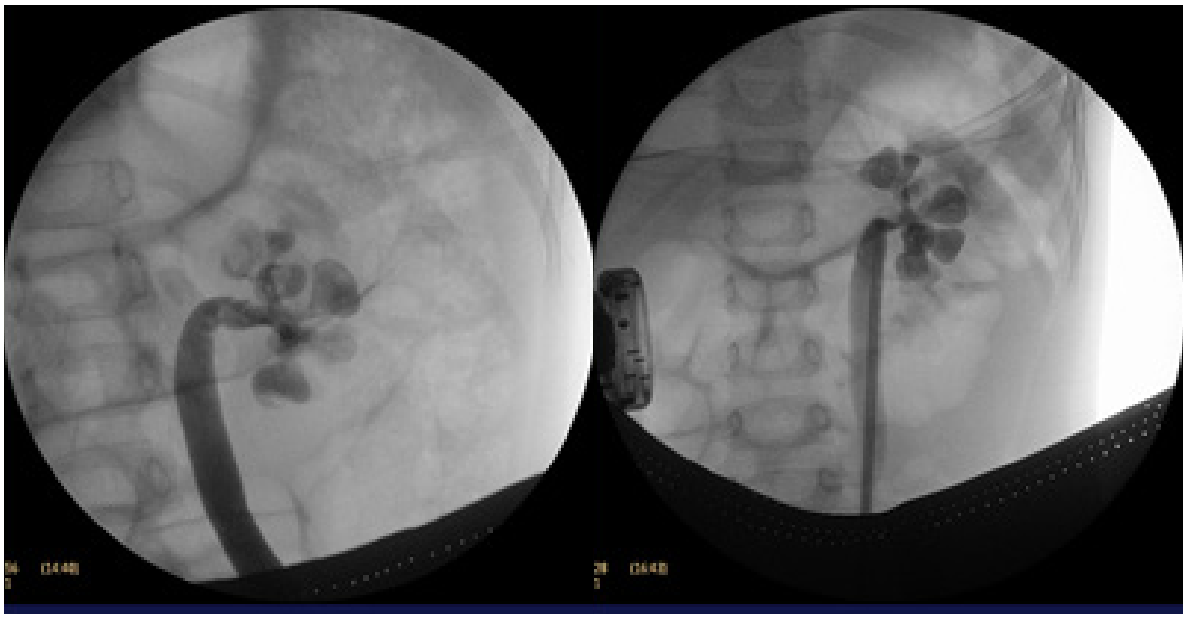

Figure 3: The retrograde pyelogram revealed high-insertion ureteropelvic junction, narrow infundibulopelvic angle, megacalycosis, and a smaller pelvis.

In paediatric PCNL, miniperc, RIRS, and microperc are the treatment modalities that can yield high stone-free rates with monotherapy compared with SWL. Our approaches to adult kidney stones have changed with technological developments and increase in expertise. Our experiences in adults enable us to transfer these developments to children. With the changing paradigms in paediatric renal stones, reports of application of RIRS in children have begun to accumulate in the literature. However, RIRS series in paediatric renal stones include school-aged children up to 17 years of age, and ureteral stones. Detailed reports about toddlers and preschool children are limited. Moreover, approaches to paediatric renal stones in the presence of congenital anomalies are of particular importance, and our knowledge about the use of RIRS in these patients is limited.

In this case study, we provide details about a challenging case with complex stones and congenital anomalies in an era of multiple endourological intervention alternatives by reviewing the technical details of RIRS. RIRS was applied in this patient. In Turkey, where stone disease is endemic, urologists should gain expertise in all endourological treatment modalities for recurrent stone disease, especially for use in high-risk patients.

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ACUTE KIDNEY INJURY - AN UPDATE

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ABSTRACT

The syndrome of acute kidney injury (AKI) occurs frequently in hospitalised patients, leading to increased morbidity, mortality, and healthcare expenditure. In the context of a precipitating insult, disturbances in both global and microcirculatory renal blood flow, tubular cell damage, and activation of pro-inflammatory pathways lead to impairment of numerous elements of renal function. Classification systems, including the recent 'Kidney Disease: Improving Global Outcomes' (KDIGO) classification, typically define and stage AKI in terms of the magnitude of rise in serum creatinine (SCr) and the presence of oliguria. At present there is no cure for AKI and the key principles of its management include early recognition, haemodynamic optimisation, correction of hypovolaemia, ceasing and avoidance of nephrotoxic medications, and treatment of the underlying cause. Recent data show that the type and volume of fluid therapy can affect renal function and that further guidance is required. In the future it is hoped that novel technologies, including biomarkers and real-time measurement of glomerular filtration rate will allow the earlier identification of patients with AKI, whilst a greater understanding of the pathogenesis of AKI will lead to the identification of new therapeutic targets. Despite SCr usually recovering after an episode of AKI, there is growing recognition that survivors of AKI are at an increased risk of subsequent chronic kidney disease, including end-stage renal failure and premature death.

Keywords: Acute kidney injury (AKI), fluid therapy, AKI biomarkers, AKI e-alert.

INTRODUCTION

Acute kidney injury (AKI) is a frequent complication in hospitalised patients. It is associated with serious short and long-term morbidities, an increased risk of dying, and significant healthcare costs. Even small rises in serum creatinine (SCr) independently predict poor outcome.[1] This review focuses on recent developments in AKI that are of interest to the general physician.

DEFINITION

AKI is a syndrome encompassing many different aetiologies and is characterised by an acute deterioration of renal function. The most common causes are sepsis, volume depletion, haemodynamic instability, and nephrotoxic injury. AKI comprises simultaneous impairment of nitrogenous waste excretion, fluid balance and electrolyte regulation, and acid-base homeostasis, which occur to varying degrees and reversibility according to the magnitude and nature of the insult. Traditional diagnostic tools to diagnose AKI include SCr, blood urea nitrogen, urine output, urine chemistry, urine microscopy, and histology. The need for a standardised definition culminated in the 'Kidney Disease: Improving Global Outcomes' (KDIGO) AKI classification,[2] which evolved from the 'Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease' (RIFLE) and AKI Network criteria (Table 1).[3,4]

Although SCr is readily available in clinical practice, it is affected by muscle mass and fluid status, can change in response to certain drugs without change in renal function, is not reliable in patients with liver disease, and may take 24–36 hours to rise after a definite renal insult. Conversely, patients with advanced chronic kidney disease (CKD) may have a SCr rise as part of natural progression or a relatively small decrease in glomerular filtration rate (GFR), which may bias them towards a diagnosis of AKI. Epidemiological studies have

also shown that some patients have a slow but persistent (creeping) rise in SCr but do not fulfil the criteria for AKI. The term 'acute kidney disease' has been suggested to describe this scenario.[2]

Accurate measurement of urine output is challenging in patients without a urinary catheter and oliguria may be missed, especially outside of critical care areas. Urine output can be manipulated by diuretics and may persist until renal function almost ceases. Importantly, oliguria may be an appropriate response in the setting of hypovolaemia reflecting under-resuscitation rather than kidney injury. The use of weight-based urine output criteria for AKI may be misleading in obesity and result in the overdiagnosis of AKI. The European Renal Best Practice Guidelines (2012) recommend using the ideal weight rather than the true weight when calculating urine output in ml/min/kg to avoid a misdiagnosis of AKI.[5]

There remains debate about the definition of baseline SCr.[2,6] Extending the baseline assessment period to 3, 6, and 12 months prior to hospital admission results in progressively more patients being classified as having AKI, but with decreasing in-hospital mortality.[6] Despite these limitations and potential pitfalls it is recommended to use the KDIGO classification of AKI in clinical practice and research until more specific and sensitive tests are routinely available. The use of formulae to calculate an estimated GFR cannot be recommended in AKI.[2]

EPIDEMIOLOGY

The incidence of AKI is increasing with time[7-9] due to population changes (ageing/comorbidity), changing healthcare behaviours (increasing use of potentially nephrotoxic drugs, contrast media, high-risk interventions), and increased recognition. AKI affects 7-22% of hospital inpatients. Older and critically ill patients are at particular risk. A large, multi-national meta-analysis identified 154 cohorts published between 2004 and 2012, including 3.4 million hospitalised adults that allowed classification according to KDIGO criteria.[10] The pooled incidence of AKI was 22%. The odds of death in the 2.2 million patients for whom data was available was five-times greater for those with AKI than without. The annual incidence in the community may be as high as 1%.[11] The financial burden of AKI is huge as it greatly increases length of stay in the intensive care unit (ICU) and in the hospital, and both in-hospital[12] and post-discharge patient-care costs. The cost of AKI-related inpatient care in England consumes 1% of the entire healthcare budget, and is estimated to be higherthan that of the four most common cancers combined.[13]

EARLY RECOGNITION

The best chance of ameliorating the severity of AKI is through early recognition and intervention. The majority of AKI develops in the context of an acute medical or surgical illness outside renal or critical care units. The UK National Confidential Enquiry into Patient Outcomes and Death (NCEPOD) report in 2009 – 'AKI - adding insult to injury' – was a retrospective case analysis of patients who had died and been coded as having AKI.[14] In only 50% of cases was care considered to be 'good'. In 30% of cases, AKI was deemed to have been both predictable and avoidable. Failures of care included the non-institution of basic measures such as stopping nephrotoxins, prescribing supplemental fluids, and unacceptable delays in recognition. Electronic alert systems use changes in SCr to identify AKI and alert the clinical team with the aim of instituting a review and management plan. A number of studies have suggested that electronic alerts can positively influence physician behaviour and improve outcomes.[15-19] However, a recent randomised controlled trial (RCT) showed no difference in mortality or need for dialysis.[20]

PATHOPHYSIOLOGY

The kidneys receive around 20% of the cardiac output, and renal oxygen extraction is low (approximately 10-15%), yet they are very susceptible to tissue hypoxia, especially during an acute illness. In recent years, the previously held belief that AKI develops due to a global decrease in renal perfusion associated with a state of shock has been called into question.[21,22] For instance, AKI does not necessarily occur in survivors of cardiac arrest despite prolonged periods of hypotension.[23] In sepsis, animal models demonstrated that renal blood flow (RBF) may be reduced, increased, or unchanged, which implies that factors other than RBF play an important role.

Current evidence suggests that the origin of most cases of AKI is multifaceted rather than the result of an individual insult. Several concurrent mechanisms contribute, including regional

variations in perfusion and oxygen consumption, impaired autoregulation, distortion of peritubular and glomerular microcirculation, tubular cell injury, endothelial injury, microvascular thrombosis, and arteriovenous shunting, resulting in the activation of inflammatory processes.[24] AKI is now considered a pro-inflammatory condition. Numerous pro and anti-inflammatory mediators and pathways have been identified, which account for some of the clinical sequelae of AKI and may also serve as therapeutic targets in the future.[25-27]

TREATMENT

The management of AKI is supportive with focus on the optimisation of fluid and haemodynamic status, treatment of the underlying illness, avoidance of further nephrotoxic insults, and renal replacement therapy (RRT) if necessary. There is no cure for AKI. Many pharmacological treatments have been tried with disappointing results. The recent KDIGO expert group appraised and summarised current evidence-based management (Table 2).[2] In cases where the necessary evidence was missing, recommendations were made based on expert opinion.

Avoidance of Nephrotoxic Agents

Nephrotoxic drugs often contribute to the development of AKI during an acute illness. For example, in the UK, angiotensin-converting enzyme (ACE)-inhibitors and angiotensin II receptor blockers are the second most commonly prescribed class of drug and increased prescribing may be responsible for 15% of the increase in admissions for AKI.[28] Non-steroidal anti-inflammatory drugs are easily available and commonly implicated too. Although evidence-based data from RCTs is missing, it makes sense to recommend that during an episode of AKI, drugs with potential for nephrotoxic injury should be avoided or dose adjusted if possible.

Haemodynamic Optimisation

Haemodynamic optimisation uses fluid therapy and vasoactive drugs to achieve cardiac output and perfusion pressures that will restore/maintain adequate oxygen delivery to tissues including the kidneys. Optimisation has three main components:

i) Pre-load optimisation aims to maximise stroke volume (and therefore cardiac output) by augmenting left ventricular end-diastolic volume with intravascular filling. The use of central venous pressure to guide volume expansion is not recommended.[29]

ii) Afterload optimisation aims to ensure adequate perfusion of the kidneys and is especially important in the management of distributive shock, where vasopressors can improve renal haemodynamics.[30]

iii) Contractility optimisation aims to improve oxygen delivery if shock persists, despite pre-load and afterload optimisation. The most commonly used drugs are inotropes.

Table 1: KDIGO definition and classification of acute kidney injury.[2]

Definition	AKI is diagnosed if SCr increases by at least 0.3 mg/dl (26.5 µmol/l) in 48 hours or rises to at least 1.5-fold from baseline within 7 days.	
Stage	SCr rise	Urine output
1	1.5–1.9 × baseline OR ≥0.3 mg/dl (≥26.5 µmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 × baseline	<0.5 ml/kg/h for ≥12 hours
3	3.0 × baseline OR increase in SCr to ≥4.0 mg/dl (≥353.6 µmol/l) OR initiation of renal replacement therapy	<0.3 ml/kg/h for ≥24 hours OR anuria for ≥12 hours

SCr: serum creatinine; KDIGO: Kidney Disease: Improving Global Outcomes; AKI: acute kidney injury.

Table 2: Summary of guidelines for treatment of acute kidney injury from KDIGO.[2]

Do	Do not
Discontinue all nephrotoxic drugs if possible.	Restrict protein intake with the aim of preventing or delaying initiation of RRT.
In the absence of haemorrhagic shock, use isotonic crystalloids rather than colloids as initial management for expansion of intravascular volume.	Use diuretics to prevent or treat AKI, except in the management of volume overload.
Use vasopressors in conjunction with fluids in patients with vasomotor shock with or at risk of AKI.	Use low-dose dopamine, fenoldopam, ANP, or rIGF-1 to prevent or treat AKI.
Consider protocol-based management of haemodynamic and oxygenation parameters in high-risk patients in the perioperative setting or in patients with septic shock.	Use aminoglycosides if a non-nephrotoxic alternative is available (close monitoring of trough levels if unavoidable).
Consider alternatives to radiocontrast procedures.	Use oral fluids, theophylline, fenoldopam, or RRT for prophylaxis of CIN.
In critically ill patients, use insulin therapy targeting plasma glucose 110-149 mg/dl (6.1-8.3 mmol/l).	Use conventional formulations of amphotericin B (lipid preparations are less nephrotoxic).
Achieve a total energy intake of 20-30 kcal/kg/day.	
Provide nutrition preferentially via the enteral route.	
Use lipid formulations of amphotericin B rather than conventional.	
Use intravenous 0.9% saline or isotonic sodium bicarbonate and oral NAC in patients at high risk of CIN.	
Initiate RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist.	
When considering RRT, consider the presence of conditions that can be modified with RRT, and trends of laboratory tests, rather than single urea and creatinine thresholds.	

AKI: acute kidney injury; ANP: atrial natriuretic peptide; CIN: contrast induced nephropathy; rIGF: recombinant insulin growth factor; RRT: renal replacement therapy; NAC: N-acetylcysteine; KDIGO: Kidney Disease: Improving Global Outcomes.

Fluid Therapy

i) Type of fluid: The optimal type of fluid for prevention and management of AKI is not known. However, there is increasing evidence that starch-based colloids can cause or worsen AKI if given in large volumes and should be avoided in critically ill patients.[31-33] Use of chloride-rich solutions like 0.9% saline is associated with hyperchloraemic metabolic acidosis and an increased risk of AKI.[34] There is some evidence that balanced crystalloid solutions such as Ringer's Lactate, Hartmann's solution, or Plasma-Lyte may have benefits over saline.

Analysis of a large US database of patients undergoing major abdominal surgery showed that patients who received 0.9% saline had a higher unadjusted in-hospital mortality (5.6% versus 2.9%) and need for RRT compared to patients treated with Plasma-Lyte.[35] After correction for confounders, the increased rate of RRT remained significant. Based on animal models the underlying mechanism is believed to be chloride-induced renal vasoconstriction and decrease of renal artery blood flow and GFR.[36-38] It is important to note that all data suggesting that balanced solutions may be superior to 0.9% saline are based on observational studies. An RCT is still awaited.

ii) Volume of fluid: Classically, in volume-depleted patients with intact tubular function, avid retention of sodium is reversible with fluid therapy and oliguria improves. Prolonged volume depletion is harmful to kidney function; fluid administration beyond the resuscitation phase in patients with AKI is not only ineffective but also harmful and associated with reduced chances of renal

recovery and an increased mortality.[39] Fluid overload results in tissue oedema, obstruction of capillary blood flow and lymphatic drainage, impaired diffusion of oxygen, and disturbed cell–cell interactions.[40] Progressive organ dysfunction may result. The effects are pronounced in encapsulated organs such as the kidneys, which cannot accommodate extra volume without an increase in interstitial pressure and compromised organ blood flow. Although both inadequate and overzealous fluid resuscitation are harmful in AKI, there are currently no reliable tools to diagnose euvolaemia. The decision of when to stop fluid therapy is mainly based on the regular clinical assessment of the patient.

Blood Pressure Management

Hypotension and low cardiac output are deleterious for kidney function but the optimal haemodynamic targets for patients with early AKI are unknown. Data in the literature are conflicting. A large Finnish study showed that septic patients who developed AKI within 5 days of ICU admission had a significantly lower mean arterial pressure (MAP) (74 mmHg) compared to septic patients without AKI (MAP: 79mmHg).[41] In contrast, Bourgoin et al.[42] reported that raising MAP to >85 mmHg in patients with shock did not result in an improvement of urine output or SCr. Similarly, an RCT comparing a target MAP of 80-85 mmHg versus 65-70 mmHg in patients with septic shock showed no difference in mortality (although both groups achieved MAPs greater than their target resulting in a less pronounced difference between both groups).[43] Interestingly, patients with chronic hypertension randomised to the high MAP group needed RRT less often. The current recommendation is to tailor MAP targets to the individual. It is reasonable to aim for a higher MAP in patients with chronic hypertension with persistent oliguria or rising SCr.

Exclusion of Obstruction

Ultrasound imaging of the urinary tract is recommended in patients at high risk of obstruction or where there is no obvious cause of AKI.[44] It will also identify important pre-existing anatomical variations, like a single kidney or small kidneys in the case of CKD.

AKI Care Bundles

There has been a trend in critical care towards the use of care 'bundles', which are a structured way of improving the processes of care and patient outcomes through a small set of evidence-based practices that, when performed collectively, improve patient outcomes.[45] Care bundles have been successfully integrated into the management of potentially life-threatening conditions like sepsis or ventilator associated pneumonia. The initial treatment of AKI may benefit from a similar approach but evidence from RCTs is lacking.[46]

Prevention of Contrast-Induced Nephropathy

Iodinated contrast media can cause AKI by several mechanisms including direct tubular toxicity and renal vasoconstriction. It is uncommon in stable patients without risk factors[44] but frequently contributes to AKI in patients with an acute illness or pre-existing CKD, especially if procedures which necessitate high contrast volumes are necessary. Other risk factors are advanced age, diabetes with CKD, heart failure, and concurrent use of nephrotoxic drugs. The only proven effective preventative strategy is to optimise volume status with saline or isotonic sodium bicarbonate before the procedure whilst addressing any treatable components of the acute illness (Table 2).[47] The use of oral N-acetylcysteine is a weak KDIGO recommendation[2] that has been dropped from the recent guideline by the National Institute for Health and Care Excellence UK.[44]

Renal Replacement Therapy

RRT should be considered when the benefits outweigh any potential risks, independent of specific urea and creatinine results, but before the development of any uraemic emergencies.[2] Continuous RRT is recommended for patients who are haemodynamically unstable or have conditions associated with increased intracranial pressure.[2] Peritoneal dialysis is an option but is rarely used in adults in developed countries.[48]

LONG-TERM PROGNOSIS

Several large epidemiological studies have shown that the prognosis of AKI (even with good recovery of SCr) is not entirely benign. Survivors of AKI are at an increased risk of death and CKD including progression to end-stage renal failure, which has a major impact on the patient's life expectancy and contributes to healthcare costs.[49-51] Patients with diabetes, chronic vascular disease, and CKD are particularly at risk. There are several reasons for this, including common comorbidities as well as factors directly related

to repair processes following AKI. A single-centre observational study in Pennsylvania, USA found that patients with AKI were 50% more likely to die and nearly twice as likely to develop CKD following hospital discharge compared with matched controls without AKI.[51] Proteinuria has recently been identified as more common in AKI survivors than controls and is associated with CKD progression.[52] Other studies have found an association between AKI and subsequent risk of coronary events,[53] strokes,[54] fractures,[55] and reduced quality of life.[56] There have been calls for regular follow-ups for patients who survive a hospital admission complicated by AKI in order to improve their long-term prognosis, but the most effective strategy has not yet been identified.[57]

The assessment of residual renal function after an acute illness is challenging. SCr results may be misleading due to changes in muscle mass and metabolism, clearance of excess tissue water, and temporary discontinuation of drugs that affect GFR, such as ACE-inhibitors.[58] This 'pseudo-normalisation' may become apparent only if a repeat SCr is measured after recovery from critical illness. AKI and CKD are complex, interconnected syndromes (Figure 1). Prospective longitudinal studies in AKI survivors are in progress and will be valuable to guide decision making.[59,60]

Self-Management

It is recommended that patients at risk of AKI are informed of the conditions that may cause AKI (i.e. diarrhoea and vomiting) and the drugs to avoid during sick days.[44] This is particularly relevant for patients with CKD.

FUTURE DEVELOPMENTS

There is an ongoing search for more sensitive tests to diagnose AKI before elevations in SCr occur, which may also facilitate the discovery of potential therapies.

Novel Biomarkers

Novel biomarkers of AKI vary in their origin, function, distribution, and time of release following renal injury.[61,62] They can be divided into:

i) Markers of glomerular function: Small molecular weight molecules that are present in the systemic circulation and undergo glomerular filtration (i.e. cystatin C). In the case of reduced GFR their plasma concentration rises.

ii) Markers of tubular function: Molecules that are filtered and undergo tubular reabsorption (i.e. retinol-binding protein) and may appear in the urine in the case of tubular injury.

iii) Markers of tubular injury, damage, or repair: Molecules that are released into urine or plasma as a result of direct renal cell damage, inflammatory activation, or following gene upregulation, i.e. kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), tissue metalloproteinase-2, and insulin-like growth factor-binding protein 7.

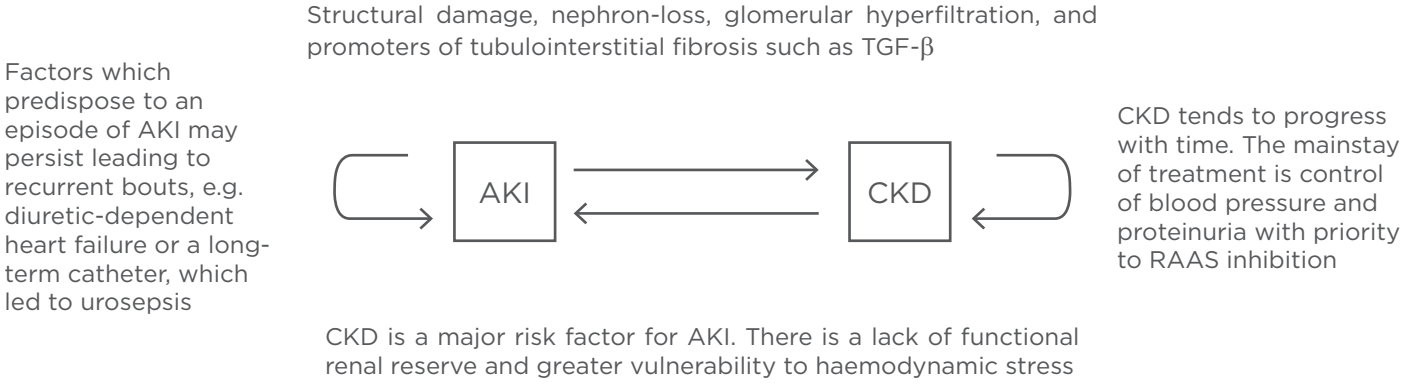

Figure 1: Relationships between acute kidney injury and chronic kidney disease.
Underpinning all these relationships are a large number of potential factors that increase risk for both AKI and CKD e.g. advanced age, hypertension, coronary artery disease, diabetes, heart failure, proteinuria, etc.
AKI: acute kidney injury; CKD: chronic kidney disease; TGF-β: transforming growth factor β; RAAS: rennin angiotensin aldosterone system.

The most-studied biomarkers are neutrophil gelatinase-associated lipocalin, cystatin C, KIM-1, and IL-18. Studies have shown that the use of novel biomarkers in certain situations may indicate the onset of AKI earlier than SCr or urine output, correlate with severity of AKI, and/or prognosticate the need for RRT. However, the results are variable and depend on the case-mix, cause of AKI, clinical setting, associated comorbidities, and timing of biomarker measurements.[63] To date, novel AKI biomarkers have not been integrated into routine clinical practice.

Real-Time GFR Measurement

Knowing the actual GFR would not only define and stage AKI earlier and more accurately, it may also improve clinical management, for instance facilitating correct drug dosing.[62] Some investigators have made progress in real-time GFR techniques. For instance, external whole-tissue radioactivity measured after intravenous injection of Tc-labelled diethylenetriaminepentaacetic acid allowed an accurate, fast, and convenient way to measure total and individual kidney GFR.[64] Several commercial companies are in the process of developing rapid, sensitive, reproducible, and affordable techniques to measure real-time GFR.

Curative Therapies

Novel strategies including mesenchymal stem cell therapy, anti-inflammatory agents, and treatment with alkaline phosphatase are currently being investigated and the results of these studies are awaited.

CONCLUSION

The mainstay of AKI management remains prompt recognition followed by early optimisation of haemodynamics, correction of volume depletion, avoidance of nephrotoxins, and treatment of the underlying cause. The development of new diagnostic tools, including biomarkers and techniques to measure GFR in real time, offers new opportunities and the prospect of diagnosing AKI earlier and more accurately. Until then, strategies to improve AKI care are likely to include a co-ordinated approach to education, electronic alerts, and care bundles. Increasing recognition of the long-term complications confirms that AKI is no longer just an acute illness and deserves long-term follow-up.

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MANAGEMENT OF REFRACTORY LUPUS NEPHRITIS

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ABSTRACT

Despite the significant advances in the field, up to one-third of lupus nephritis (LN) patients still do not respond adequately to initial immunosuppressive treatment. This group of patients is heterogeneous in terms of clinical presentation (deterioration of glomerular filtration rate, variable degrees of persistent proteinuria, active urine sediment) and the potential for reversion (ongoing kidney inflammation versus irreversible damage due to scarring and fibrosis). A repeat kidney biopsy can be highly informative in this regard and should be strongly considered. High-quality evidence regarding the treatment of refractory LN is lacking, and management is largely based on observational studies and expert opinion. Options include switching between mycophenolate mofetil (MMF) and cyclophosphamide (CYC), using rituximab as monotherapy or add-on therapy, or combining MMF with a calcineurin inhibitor in cases of persistent proteinuria. Renal response can be maintained with MMF or prolonged pulses of intravenous CYC administered bimonthly or quarterly. The efficacy of novel biological agents and those under development in refractory forms of LN remains to be determined. Tight control of cardiovascular risk factors, use of hydroxychloroquine, immunisations, and osteoporosis prophylaxis are important adjunctive measures. For the future, we anticipate that research efforts for the identification of accurate biomarkers together with accumulating data from observational and controlled studies will assist therapeutic decisions and improve outcomes in patients with refractory LN.

Keywords: Autoimmune diseases, immunosuppressives, biologics, biopsy, biomarkers.

INTRODUCTION

Renal involvement constitutes one of the most severe manifestations of systemic lupus erythematosus (SLE) and is a major determinant of the overall morbidity and mortality associated with the disease.[1] In a recent single-centre study, life expectancy of SLE patients with renal disease and those with irreversible renal damage was reduced by an average of 15.1 years and 23.7 years, respectively, compared with the general population.[2] The current 'treatment paradigm' in lupus nephritis (LN) includes an initial induction phase, which aims to halt ongoing immunological injury and ideally put the disease into remission, followed by a maintenance phase, with the ultimate goal being to consolidate the response and prevent damage accrual.[3] The choice of therapeutic agents is based on risk stratification, according to renal pathology and patient demographic, and clinical and laboratory features.

The fundamental goal of treatment in LN is long-term preservation of renal function and improved survival. To this end, prevention of flares and avoidance of treatment-related harm is crucial. According to the recently published joint recommendations by the European League Against Rheumatism (EULAR) and the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA),[4] treatment should ideally aim at complete renal response (CRR), defined as a urine protein loss <0.5 g/24 h (urine protein:creatinine ratio [UPr] <50 mg/mmol) and at least near-normal glomerular

filtration rate (GFR) (i.e. within 10% of normal GFR if previously abnormal).[4] This is based on evidence that patients with proliferative or membranous LN who achieve CRR display favourable long-term renal outcome with low risk of developing end-stage renal disease.[5,6] Partial renal response (PRR), defined as ≥50% reduction in proteinuria to subnephrotic levels and normal or near-normal GFR, may be acceptable in certain circumstances; this should nevertheless preferably be achieved by 6 months and no later than 12 months following treatment initiation.

Given these widely accepted treatment goals, a considerable proportion of patients fail to achieve the target. This subset of patients has 'refractory LN', which represents a particularly challenging population for the treating physician and typically requires a multidisciplinary approach. In this review, we deal with the different definitions of this heterogeneous group of patients, scrutinise available data on therapeutic choices, and reflect on unmet needs and the future agenda in the field.

DEFINITIONS OF REFRACTORY LUPUS NEPHRITIS AND THE DIAGNOSTIC VALUE OF REPEAT KIDNEY BIOPSY AND BIOMARKERS

How is 'Refractory' Lupus Nephritis Defined?

A universally accepted definition of refractory LN is lacking.[5,7] The EULAR/ERA-EDTA recommendations consider refractory LN for the following groups of patients: i) those who fail to improve within 3-4 months (i.e. no reduction in UPr or deterioration of GFR), ii) those who do not achieve PRR after 6-12 months, and finally iii) those who do not reach CRR after 2 years of treatment. The respective guidelines from the American College of Rheumatology have adopted a more lenient definition; refractory disease is defined as a worsening of nephritis (i.e. >50% increase in UPr or serum creatinine [SCr]) by 3 months or generally, 'treatment failure' (judged by the treating physician) by 6 months.[8] It should be noted, however, that the aforementioned definitions have not been validated as treatment strategies in the context of controlled trials and therefore should not be treated as 'strict rules'. Nevertheless, they intend to guide physicians towards the optimisation of treatment. Using different definitions, the prevalence of LN patients not responding to conventional immunosuppressive therapy ranges between 14% and 33%.[5,9,10]

How Long Should We Wait Before Diagnosing Refractory Lupus Nephritis?

A critical question faced by physicians caring for patients with LN is when to label a patient as 'refractory'. The 'tempo' of response to immunosuppressive treatment in terms of proteinuria is helpful in this regard. The 'Euro-Lupus' trial showed that a good long-term renal outcome (SCr <1.4 mg/dl at 10 years) is predicted by an early (3-6 months) drop in proteinuria by at least 50% or to <1 g/24 h,[11,12] a finding that has been validated by subsequent studies.[13] Therefore, the 6-month timepoint from the initiation of induction therapy represents a critical checkpoint for determining the response to treatment. Nevertheless, complete resolution of proteinuria (UPr <0.5 g/24 h) may take longer, especially in patients with higher baseline UPr levels. In a recent retrospective study, the proportion of LN patients who achieved UPr <0.5 g/24 h increased from 28% in the first year to 74% at 5 years.[14] Taken together, these findings justify a 'hurry up and wait' approach, whereby intensified induction therapy should aim ideally for at least PRR at 6 months, followed by a watchful monitoring period of up to 2 years, when the highest rates of CRR are usually observed.

Is a Repeat Kidney Biopsy Necessary in Refractory Lupus Nephritis?

Its importance in LN notwithstanding, renal biopsy is an invasive procedure with potential, although uncommon, complications. Thus, a rational selection of patients that would benefit from repeat biopsy is desirable. Re-evaluation of renal histology will be considered valuable when it leads to optimisation of the therapeutic approach, to avoid both over and undertreatment of patients. Although no consensus currently exists, repeat biopsy may be considered in cases of inadequate renal response (PRR or no response) i.e. with residual proteinuria >1 g/24 h or GFR deterioration. In a significant proportion of these cases (up to 40% in partial responders and 60% in non-responders) histological transformation to more severe LN forms may be revealed, therefore justifying modification/intensification of immunosuppressive therapy.[15] However, at least one-third of patients with PR (and approximately 15% of non-responders) show an absence of active lesions on repeat biopsy[16] but an

increase in chronic, irreversible glomerular or tubulointerstitial lesions. In such cases, persistence of proteinuria does not justify more intense immunosuppression.

Repeat kidney biopsy may also be considered in severe nephritic or nephrotic renal flares.[17] Biopsy results will most often lead to a change in immunosuppressive treatment, especially in flares with nephrotic-range proteinuria, persistent deterioration of GFR, or in patients who were in remission for longer periods before they flared. Class switching to a proliferative LN type is most likely in patients who had no proliferative lesions in their original histology,[18] while scarring also tends to accrue over time.

Biomarkers for Monitoring Lupus Nephritis

The quest to identify reliable biomarkers as surrogate markers of renal histology is ongoing.[19] A wide array of urine-excreted proteins have been evaluated for their potential association with histologic findings of LN, including neutrophil gelatinase-associated lipocalin, vascular cell adhesion molecule-1, and tumour necrosis factor-like weak inducer of apoptosis (TWEAK).[20-22] Although some of these molecules have shown promising results, they still lack firm validation and standardisation. Serological tests such as antibodies against C1q (anti-C1q Ab) are closer to clinical implementation. A recent meta-analysis of observational studies calculated an anti-C1q Ab sensitivity and specificity of 76% and 80%, respectively, to discriminate between active and inactive LN.[23]

THERAPEUTIC OPTIONS IN REFRACTORY LUPUS NEPHRITIS

Well-designed, randomised controlled trials (RCTs) are lacking in patients with refractory LN. Most data originate from observational studies performed in centres with expertise in the disease, and therapy is often individualised and based on expert opinion. Irrespective of the immunosuppressive or biological agent used, concomitant use of steroids is recommended, especially in the presence of significant histological activity in kidney biopsy. Although there are no data to support the use of high-dose steroids in refractory LN, we often advocate for three pulses of intravenous (IV) methylprednisolone (MP) followed by oral prednisolone 0.5-0.75 mg/kg/day with gradual tapering. Supplementing monthly IV cyclophosphamide (CYC) pulses with IV MP pulses is also an option.[24]

Switching from Mycophenolate Mofetil to Cyclophosphamide and Vice Versa

CYC and mycophenolate mofetil (MMF) are the two therapeutic agents most commonly used as induction therapy in LN. Consequently, it seems reasonable that failing to respond to one could justify switching to the other.[25] Rivera et al.[26] examined 85 patients with relapsing (n=50, who had experienced at least one relapse after having responded) or refractory (n=35, who had not responded after 6 months) LN (mean UPr: 2.5-3.1 g/24 h, 38% with GFR <60 ml/min), 86% of whom had previously received IV CYC.[26] All patients received MMF and at 24 months 87% of patients had responded (the majority within the first 6 months). Accordingly, both the EULAR/ERA-EDTA and the American College of Radiology (ACR) guidelines recommend switching from CYC to MMF in cases of LN not responding to the former.[4,8] The opposite approach (switch from MMF to CYC) is also proposed based on the good long-term efficacy data of CYC in LN, although this has not been formally tested.

Calcineurin Inhibitors and 'Multitarget Therapy'

Calcineurin inhibitors (cyclosporine A, tacrolimus) exert potent antiproteinuric effects and have been employed in difficult LN cases. Open-label studies have shown that both tacrolimus and cyclosporine, used as monotherapy, can be effective in reducing proteinuria in cases resistant to CYC with residual UPr >1 g/24 h. These data, although encouraging, should be cautiously interpreted due to the low numbers of patients included, the open-label, uncontrolled design of the studies, and the short follow-up period (12 months maximum).[27-29]

Both calcineurin inhibitors have been used in combination with MMF as part of a 'multitarget' approach. In a recent large RCT (n=362) in China, the combination of tacrolimus (4 mg/day) with MMF (1 g/day) was superior to monthly IV CYC (0.75 g/m^2) at 6 months (rates of CR: 45.9% versus 25.6%) as induction therapy.[30] Another observational study in 70 patients with proliferative LN not responding to MMF showed that the addition of tacrolimus led to an additional 70% of patients (12 out of 17) achieving clinical response after 24 months.[10] The combination has also shown better efficacy than IV CYC in an observational study of 40 patients with mixed Class V+III/IV LN

(UPr: 4.0-4.4 g/24 h, preserved renal function), 65% of whom had previously been treated with MMF or CYC.[31] These promising results should nevertheless be viewed with the limitation of short follow-up. Moreover, caution is needed when using calcineurin inhibitors in cases of reduced GFR (<60 ml/min), advanced chronic damage (fibrosis) in renal histology, or in the presence of arterial hypertension.[32] Diligent monitoring of SCr and blood pressure is mandatory.

Rituximab

Both the EULAR/ERA-EDTA and the ACR guidelines recommend the use of rituximab (RTX) either as add-on treatment or as monotherapy in cases of refractory LN.[4,8] This is despite the fact that the LUNAR trial failed to meet its primary endpoint in demonstrating the superiority of RTX over placebo in active Class III-IV LN.[33] However, this trial has received criticism for two main reasons: i) the use of high background immunosuppressive treatment (i.e. both arms received high-dose glucocorticoids and MMF 3 g/day) that might have diluted any effect attributable to RTX, and ii) the lack of adequate power to detect statistically significant differences in response rates (RR) between RTX and placebo. As a result, the 16% difference (31% versus 15%) in PRR favouring RTX over placebo did not reach statistical significance. To put this in perspective, a similar difference in RR (approximately 15%) between active drug and placebo arms in the larger BLISS trials led to the approval of belimumab in extrarenal SLE.[34]

Notwithstanding the above, advocacy for the use of RTX in LN is based primarily on positive experience with this agent, as well as a wealth of observational evidence, especially in cases with inadequate response to initial immuno suppression.[35-37] Pooled data from two different countries reported CRR or PRR in approximately two-thirds (67%) of 164 patients with LN treated with RTX, used mainly as a second-line option in refractory or flaring disease;[38] 76% of these patients received concomitant CYC or MMF. The presence of nephrotic syndrome or renal failure at the time of RTX administration was a predictor of poor prognosis and non-response. These predictors were confirmed in another systematic literature review of 300 patients treated with B cell depletion for variably defined refractory LN, who had previously received various immunosuppressive agents.[39] Similar to the previous study, RR reached a total of 74% (40% CRR and 34% PRR), reinforcing the notion that RTX is indeed efficacious in 'difficult' LN. Conversely, mixed forms of nephritis (Class V+III/IV) may respond less favourably to B cell depletion (CRR: 24%)[39] and a recent small observational study reported no efficacy of RTX in cases of rapidly progressive, crescentic glomerulonephritis.[40]

Plasma Exchange Therapy

Plasma exchange (plasmapheresis) has been successfully used in severe, life-threatening, or recalcitrant-to-immunosuppressive-agents SLE. In an open-label, non-randomised study in patients with steroid-resistant LN (mainly Class IV), plasma exchange (double filtration or immunoadsorption plasmapheresis) synchronised with monthly pulses of IV CYC was superior to either modality alone in inducing renal response and preventing flares.[41,42] Stummvoll et al.[42] have also reported favourable long-term (average 6.4 years) results with prolonged cycles of immunoadsorption combined with azathioprine or MMF in 11 patients with LN refractory to CYC. Notwithstanding these findings, immunoadsorption should be reserved for LN patients who have failed with multiple immunosuppressive and/or biologic agents, or in the presence of severe antiphospholipid antibody-associated nephropathy, and should be performed at experienced clinical centres.

Other Biologics and Novel Agents

Patients with severe LN were specifically excluded from the large RCTs that led to the approval of belimumab, an anti-B lymphocyte stimulating monoclonal antibody, for the treatment of SLE. This fact precludes any firm conclusions regarding the use of this agent in LN, including refractory forms of the disease. Nevertheless, a pooled post-hoc analysis of the BLISS trials evaluated 267 patients who had active renal involvement at baseline.[43] A trend towards reduction in the rate of renal flares (1.4% versus 3.0% in the placebo and belimumab 10 mg/kg arms, respectively) and level of proteinuria, as well as increased rates of renal remission (58.7% versus 70.5% in the placebo and belimumab 10 mg/kg arms, respectively), were observed in the belimumab groups over 52 weeks. Efficacy of belimumab was more pronounced in patients receiving MMF or those who were serologically active at baseline. A formal trial of belimumab in active LN is currently underway (NCT01639339).

Two RCTs were recently published comparing costimulation blockade with abatacept against standard of care in active LN. The ACCESS trial[44] found no difference in rates of CRR at 6 months when abatacept or placebo was added to low-dose CYC (Euro-Lupus regimen). In the second study, 298 patients were randomised to abatacept or placebo, both administered on background immunosuppression with MMF 2-3 g/day and oral prednisone.[45] After 12 months abatacept failed to increase the rates of CRR over placebo, although a greater reduction in proteinuria was observed in abatacept-treated patients with nephrotic syndrome at baseline. A post-hoc analysis showed that if less stringent outcome criteria were applied, CR rates would be higher and significant differences (reaching almost 18%) would be noted in favour of abatacept.[46] The use of abatacept in refractory forms of LN has not been tested.

A number of novel therapies are currently in the pipeline for assessment in LN, including interleukin-6 blockade (sirukumab), anti-TWEAK, anti-interferon α (sifalimumab, rontalizumab), and anti-fibrotic agents (fresolimumab), but a detailed review of their preliminary efficacy data is beyond the scope of this article. Figure 1 depicts a diagnostic and therapeutic algorithm for refractory LN.

Maintenance Therapy

Very scant data are available regarding therapeutic options for maintenance of renal response in refractory LN. The choice largely depends on physician experience, but also on the agent used for induction of response. In this regard, if MMF was used for induction and led to renal response, it seems reasonable to continue with it through the maintenance phase.

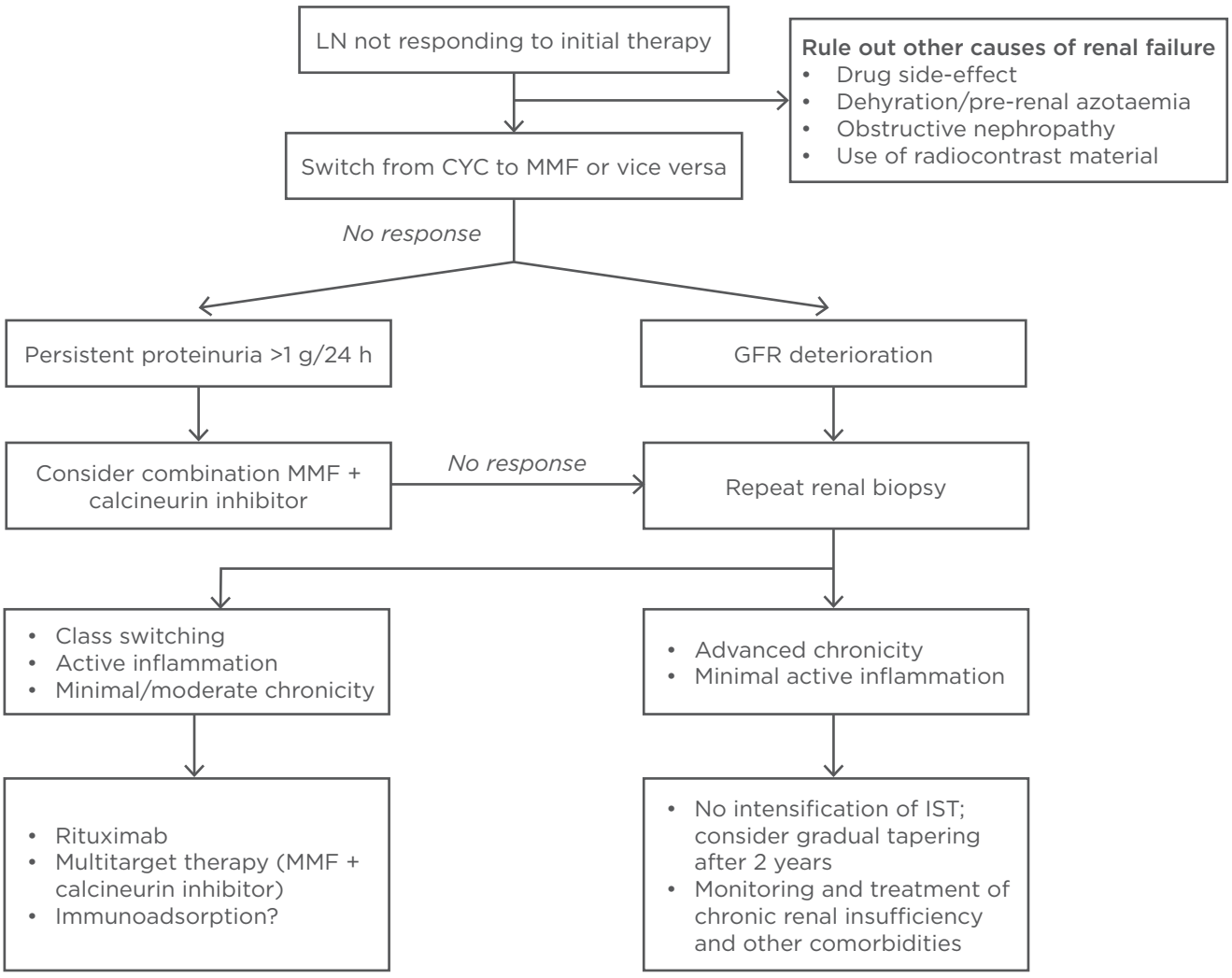

Figure 1: Diagnostic and therapeutic approach to refractory lupus nephritis.
LN: lupus nephritis; MMF: mycophenolate mofetil; GFR: glomerular filtration rate; CYC: cyclophosphamide; IST: immunosuppressive therapy.

In the study by Rivera et al.[26] that tested the efficacy of MMF after CYC failure, nearly 16% of patients (3/19) relapsed after discontinuing MMF. If CYC was used for induction, prolonged IV pulses (bimonthly or quarterly) can be used to consolidate the response. The pivotal initial studies from the National Institutes of Health have shown that prolonged IV CYC pulses are associated with beneficial renal outcomes in the very long term (10 years) with an acceptable safety profile; however, these studies did not specifically target patients with refractory LN.[24,47]

Adjunctive Therapy

The importance of adjunctive treatment in LN cannot be overemphasised. Tight control of hypertension and dyslipidaemia is recommended. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are the agents of choice for the former, based on their antiproteinuric effects. Statins are recommended to treat dyslipidaemia (ideally low-density lipoprotein <100 mg/dl, as in other high-risk populations); a recent study suggested dyslipidaemia to be an independent risk factor for progression to chronic kidney disease in LN.[48] Hydroxychloroquine (HCQ) should be considered an essential component of LN therapy.[49] Thus, evidence suggests that inclusion of HCQ in the therapeutic armamentarium reduces the risk for nephritic flares and renal damage,[50,51] and it may also facilitate the successful withdrawal of immunosuppressives in patients with LN.[52] Finally, adherence to seasonal vaccination schedules and osteoporosis prophylaxis is of utmost importance.

UNMET NEEDS – CONCLUSION

Despite the advances in the field, LN continues to pose considerable therapeutic challenges, since a significant proportion of patients fail to respond to treatment and consequently carry an increased risk for developing chronic renal insufficiency and end-stage renal disease. Contradicting the accumulation of high-quality data in LN over the past decades, well-designed clinical trials have not yet been performed in refractory forms of the disease. The future research agenda will incorporate various issues, including but not limited to i) the identification of reliable surrogate markers to substitute for repeat renal biopsy in relapsing/refractory LN, ii) better clarification of any therapeutic gain from switching between different induction regimens in cases of treatment failure, iii) the precise role of adding calcineurin inhibitors, RTX, or belimumab to standard therapy in cases with residual disease, and iv) the testing of novel biologic agents currently under development. With all this in mind, we are looking forward to a fascinating period in the field.

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ACUTE KIDNEY INJURY: EPIDEMIOLOGY, DIAGNOSIS, PROGNOSIS, AND FUTURE DIRECTIONS

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ABSTRACT

Acute kidney injury (AKI) is a common problem highly associated with hospitalisation. AKI is the cause of harmful short-term consequences: longer hospital stays, greater disability after discharge, and greater risk of in-hospital mortality, as well as adverse long-term outcomes, such as progression to chronic kidney disease, development of cardiovascular disease, and increased risk of long-term mortality. The concept of AKI has changed since the introduction of the 'Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease' (RIFLE) classification. More recently, the 'Kidney Disease Improving Global Outcomes' (KDIGO) classification appears to have provided increased diagnostic sensitivity and outcome-prediction capability. Novel biomarkers and further research on the role of the immune system in AKI may help improve the diagnosis, severity, outcome evaluation, and treatment of the condition. In this review we describe the epidemiology, diagnosis, and prognosis of AKI, as well as possible future directions for its clinical management.

Keywords: Acute kidney injury, biological markers, incidence, mortality, outcome.

INTRODUCTION

Acute kidney injury (AKI) affects one in five hospitalised patients,[1] is associated with high expenditure of resources, and leads to adverse outcomes. Over the last 20 years, great efforts have been made to better unveil and characterise the mechanisms and consequences of AKI. The 'Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease' (RIFLE)[2] criteria were the first consensus criteria for the diagnosis of AKI and have been followed by the Acute Kidney Injury Network (AKIN)[3] and the 'Kidney Disease Improving Global Outcomes' (KDIGO)[4] classifications. These tools have provided more robust knowledge on the epidemiology and outcomes of AKI, especially for the critically ill patient.

A new potential pathway for earlier recognition and better outcome prediction has been opened up by research on more sensitive and specific markers. In addition, the pathogenesis of AKI, namely the role of the immune system, is now less elusive and this knowledge may help further categorise AKI and discover new treatment tools. In this review we discuss the current knowledge on the epidemiology, diagnosis, and prognosis of AKI, and on two fields that we believe will change clinical practice in the future: novel urinary and serum biomarkers, and the role of the immune system in AKI.

EPIDEMIOLOGY

The definition of AKI's epidemiology has been, and is still, limited by the lack of studies evaluating AKI in the community setting, as well as a lack of comparisons between intensive care unit (ICU) patients and non-ICU patients.[1] AKI is more common in the ICU and after cardiac surgery.[1] According to a recently published meta-analysis of 312 studies representing almost 50 million patients, the pooled incidence and mortality of AKI in hospitalised adult patients is 21.6% and 23.9%, respectively.[1] The incidence of AKI in critically ill patients has increased over the years,[5]

as has the incidence of dialysis-requiring AKI, especially among the elderly, the male gender, and the black population.[6] Overall, mortality has declined for the critically ill,[5] but the reverse has occurred for AKI patients who need dialysis.[6]

The typical AKI patient is more complex clinically than they were 30 years ago,[7] and is also more complex than the non-AKI patient;[8-12] AKI tends to affect people of older age, who tend to have a higher rate of comorbidities and a greater likelihood of developing severe disease, multiple organ failure, and sepsis. The leading cause of AKI is sepsis, followed by nephrotoxin use and ischaemia. Septic AKI can be considered a separate clinical entity from non-septic AKI. Septic AKI patients are less likely to have pre-existing renal dysfunction and be dependent on dialysis at discharge, but their disease burden is greater and they are more prone to concomitant non-renal dysfunction, require mechanically assisted ventilation and vasoactive drugs, are prone to longer hospital stays, and their probability of dying is higher during their stay in hospital.[13-15]

Given the growing incidence of AKI and consequent increased healthcare burden,[5] measures to prevent AKI have been sought. Some interventions may help reduce mortality in patients with or at risk of AKI, such as perioperative haemodynamic optimisation, albumin in cirrhotic patients, spontaneous bacterial peritonitis, and terlipressin for Type 1 hepatorenal syndrome.[16] In contrast, positive fluid balance, hydroxyethyl starch, and loop diuretics may have deleterious effects in patients with or at risk of AKI.[16] Unfortunately, prediction of the risk of AKI is difficult or even impossible in many situations today, which limits prophylactic action.

DIAGNOSTIC CLASSIFICATIONS

The first definition of AKI, the RIFLE classification, was published in 2004 (Table 1).[2] This classification categorises AKI into three severity classes (risk, injury, and failure) based on serum creatinine (SCr) or on estimated glomerular filtration rate (eGFR), on urine output changes, and two outcome classes - loss of kidney function and end-stage renal disease based on time of dependence of renal replacement therapy. For AKI to be present, renal function deterioration must occur over a period of 7 days and persist for longer than 24 hours. When baseline SCr is unknown and a previous history of chronic kidney disease (CKD) is absent, a baseline eGFR of 75-100 ml/min/1.73 m^2 should be assumed and the Modification of Diet in Renal Disease equation should be used to calculate baseline SCr.

Because even small increases in SCr are associated with poor outcomes,[17] mathematical formulae that estimate GFR presume a steady state that is absent in AKI, and because the accessibility and indications for starting renal replacement therapy differ between institutions and countries, the AKIN classification, also known as 'modified RIFLE', was published in 2007 (Table 2).[3] Instead of relying on either SCr or eGFR, the AKIN classification depends only on the former and requires at least two measurements taken during a 48-hour period, which removes the need for baseline SCr observations. Also, prior to the diagnosis of AKI, urinary obstruction must be excluded and an adequate hydration status must be attained, and no outcome classes are defined. Despite having higher diagnostic sensitivity, AKIN has not yet been proven to confer any advantages over RIFLE with regard to defining the severity and outcomes of AKI.[10,18-24]

Recently, the RIFLE and AKIN classifications have been merged into the KDIGO classification in order to provide simpler and more unified criteria that can be used in clinical activity, research, and public health surveillance[4] (Table 2). In this classification, disease severity has been staged similarly to AKIN except for a simplification of the criteria needed to be classified as Stage 3. Two recent publications, one from a prospective multi-centre study with 3,107 patients[25] and another from a retrospective single-centre study with 49,518 patients,[26] show that the KDIGO classification has better diagnostic sensitivity than RIFLE and AKIN, and an accuracy for predicting mortality that is at least similar to these two classification systems.[25,26]

The aforementioned AKI classifications rely on SCr, eGFR, and urine output, which are surrogate, unspecific, and often unreliable markers of renal dysfunction. Also, they do not take into account the duration or cause of the disease. However, it is essential when using these tools to recognise AKI in clinical practice and to characterise its epidemiology and outcomes in the research setting.

OUTCOMES

Multiple studies have shown patients with AKI experience poorer early outcomes than patients

without renal dysfunction,[8-12,17-30] namely longer lengths of ICU and hospital stay, higher in-hospital and post-discharge mortality, and increased likelihood of discharge to an extended-care facility. Although AKI patients have more comorbidities than non-AKI patients,[8,11,12] this does not seem to account for all of the increased early AKI-associated mortality.[31] Moreover, if even small increases in SCr lead to worse outcomes,[17] then other factors apart from AKI should probably be taken into consideration. Thus, AKI is increasingly thought of as being part of a systemic disease: underlying mechanisms mediate organ crosstalk, leading to multi-organ dysfunction that includes the kidney.[32,33] These systemic mechanisms, and not just AKI, could help explain the decreased survival observed in AKI patients.

The deleterious effects of AKI persist beyond hospitalisation and AKI patients have a greater risk of long-term mortality than non-AKI patients.[34-39] A large, retrospective, multi-centre study suggests that AKI is an independent risk factor for long-term mortality in critically ill patients[35] and a prospective cohort study showed that even Stage 1 AKI is associated with worse adjusted 10-year survival rates.[36]

If the acute insult is inadequately resolved following AKI, persistent inflammation, increased transformation of pericytes into myofibroblasts in response to tubular injury, and build-up of extracellular matrix and vascular rarefaction[40] lead to permanent changes in renal structure and function,[41,42] and ultimately to CKD. The risk of development or quicker progression of CKD occurs in a stepwise pattern according to the severity of AKI.[43] After AKI there is also an increased risk of proteinuria and arterial hypertension.[44,45] These two signs, and GFR decline, are known risk factors for cardiovascular disease,[46-48] which may contribute to the decrement in survival observed among AKI survivors. In fact, development or progression of CKD contributes to increased long-term mortality, even in ICU AKI patients who did not require dialysis at the time of the acute event.[49] Long-term outcomes appear to be more influenced by pre and post-AKI renal function than by the event itself.[50] In the future, pharmacological interventions with the ability to alter the maladaptive response to injury, such as drugs that affect profibrotic pathways,[40] may provide great impact on morbidity and mortality following AKI. Further understanding of the impact of AKI on long-term outcomes and of the causative mechanisms of AKI will have great impact on treatment and risk stratification during hospitalisation, and will guide follow-up care after hospital discharge.

FUTURE DIRECTIONS

Biomarkers

The RIFLE, AKIN, and KDIGO classifications rely on SCr, eGFR, and urine output, which are surrogate unspecific markers of renal dysfunction. Firstly, SCr can be influenced by factors that regulate its synthesis and elimination, such as age, sex, diet, and muscle mass. Tubular secretion is responsible for up to 40% of creatinine elimination and changes in GFR and certain drugs can modulate this mechanism. Additionally, haemodilution caused by fluid overload and inhibition of creatinine synthesis by sepsis can cause a decrease in SCr.[51]

Table 1: 'Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease' (RIFLE) classification of acute kidney injury.[2]

Class	Glomerular filtration rate	Urine output
Risk	↑ SCr × 1.5 or ↓ GFR >25%	<0.5 ml/kg/h (>6 h)
Injury	↑ SCr × 2 or ↓ GFR >50%	<0.5 ml/kg/h (>12 h)
Failure	↑ SCr × 3 or ↓ GFR >75% or if baseline SCr ≥353.6 µmol/l (≥4 mg/dl) ↑ SCr >44.2 µmol/l (>0.5 mg/dl)	<0.3 ml/kg/h (>24 h) or anuria (>12 h)
Loss of kidney function	Dialysis dependence for at least 4 weeks	
End-stage kidney disease	Dialysis dependence for at least 3 months	

GFR: glomerular filtration rate; SCr: serum creatinine.

Table 2: Acute Kidney Injury Network (AKIN)[3] and Kidney Disease Improving Global Outcomes (KDIGO)[4] classifications of acute kidney injury.

Stage	Serum creatinine		Urine output	
	AKIN	KDIGO	AKIN	KDIGO
1	↑ SCr ≥26.5 µmol/l (≥0.3 mg/dl) or ↑ SCr ≥1.5-2×	↑ SCr ≥26.5 µmol/l (≥0.3 mg/dl) or ↑ SCr ≥1.5-2×	<0.5 ml/kg/h (>6 h)	<0.5 ml/kg/h (>6 h)
2	↑ SCr >2-3×	↑ SCr >2-3×	<0.5 ml/kg/h (>12 h)	<0.5 ml/kg/h (>12 h)
3	↑ SCr >3× or if baseline SCr ≥353.6 µmol/l (≥4 mg/dl) ↑ SCr ≥44.2 µmol/l (≥0.5 mg/dl) or initiation of renal replacement therapy	↑ SCr >3× or ↑ SCr to ≥353.6 µmol/l (≥4 mg/dl) or initiation of renal replacement therapy	<0.3 ml/kg/h (24 h) or anuria (12 h)	<0.3 ml/kg/h (24 h) or anuria (12 h)

SCr: serum creatinine.

The evaluation of SCr can also be mildly compromised by the presence of certain compounds (e.g. acetoacetate accumulation in diabetic ketoacidosis).[52] In the presence of renal injury, there is a time lag until renal function begins to decline.[53] In addition, the percentage rise in SCr needed to establish the diagnosis of AKI occurs later in CKD patients when compared with others without previous renal dysfunction.[53] For this reason, using only SCr delays the diagnosis of AKI with respect to the initial insult and may be insufficient to identify AKI when CKD is present.

Secondly, large changes in GFR can be associated with only small changes in SCr[53] and using formulae to estimate GFR is inadequate since they presume a steady state that is absent in patients with AKI. Thirdly, urine output is highly influenced by diuretics. There are nonoliguric forms of AKI: calculating diuresis as a function of body weight can induce diagnostic error in obesity and in cachexia, so a urinary catheter is needed for its accurate measurement and most studies do not evaluate this parameter.[54]

To surpass the limitations of known functional markers, novel biomarkers have been studied: cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), interleukin 18, urinary kidney injury molecule 1, clusterin, liver-type fatty-acid binding protein, and osteopontin. Some of these have been shown to offer great advantages over the clinical classifications: earlier diagnosis of AKI (1-3 days),[55] identification of the probable aetiology of injury,[56] monitoring of treatment,[57] and prediction of outcome.[58] Subclinical AKI, an entity whose diagnosis depends on the rise of these novel biomarkers without changes in SCr and urine output, has been previously associated with poor prognosis,[59] unravelling the potential of outperformance of functional markers.

Nonetheless, strong evidence for the clinical applicability of single biomarkers is still lacking, proper cut-offs remain to be defined, and their specificity may be compromised by concomitant conditions, for example, plasma NGAL is also elevated in sepsis and in cardiac failure.[60,61] The development of studies using biochemical patterns of markers that could anticipate the diagnosis of AKI, assist with differential diagnosis, and predict outcomes was proposed at the 10th Acute Dialysis Quality Initiative (ADQI) meeting.[62] In fact, a study using the relative changes in different urinary biomarkers over time demonstrated that such a combination could help predict short-term outcomes.[63] To date, biomarkers are still not recommended for clinical decision making.[62] However, biomarkers show great promise for changing the course of AKI through early detection of injury and implementation of therapy, which may help decrease the associated health burden.

The Immune System in AKI

Purely haemodynamic or toxic actions appear to be insufficient to explain the pathogenesis of AKI in most cases. Especially in the critically ill, multifactorial mechanisms take place and non-haemodynamic factors such as neurohormonal

pathways and immune activation play an active and important role in AKI and associated multi-organ dysfunction.[33] For example, septic AKI results from an interaction between inflammatory pathways, microcirculatory changes, cellular energetic responses, and tubular cell adaptation to injury.[64]

Multiple key players of innate immunity have been shown to participate in AKI[65] and this may explain why AKI patients are more prone to infection.[9,29] After acute injury, inflammation mediates further renal damage and dendritic cells appear to be key players in summoning action from other immune cells.[66] During resolution after injury, cytokines, growth factors, and peptide molecules regulate M1 and M2 macrophages to cause either regeneration of renal tissue or evolution to fibrosis.[66]

T cells also have a role in AKI: CD4+ cells during the early stages of injury, and CD4+/CD25+/FoxP3− regulatory cells and the newly discovered kidney CD4−/CD8− cells apparently through protective mechanisms.[67] Finally, immune activation following AKI, among other mechanisms, appears to negatively influence function of other organs, such as the lungs, the liver, and the heart.[32,33] The modulation of the immune system could provide a therapeutic route to decrease the severity and improve the outcomes of AKI,[67,68] and potential therapeutic targets are already being sought.

CONCLUSION

Over recent decades, landmark studies and consensus criteria have helped improve our knowledge of AKI and understand its clinical relevance. In the future, the key research priorities must be focussed on earlier diagnosis, better prediction of outcomes, and new treatment modalities. The KDIGO classification aims to unify practice and has been shown to represent an improvement over the previous classifications. Nevertheless, novel biomarkers hold the promise of change from a renal function-based diagnosis towards an injury-defined, subclinical diagnosis, which could help improve outcomes. In addition, these markers could represent more accurate tools for outcome prediction. Further research on the role of the immune system might provide insights into the pathogenic steps behind the acute injury and its consequent resolution, which can become targets for disease and outcome-modifying treatment tools.

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IgA NEPHROPATHY: NEW ASPECTS IN PATHOPHYSIOLOGY AND PATHOGENESIS

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ABSTRACT

Knowledge of the pathophysiology of immunoglobulin A nephropathy (IgAN) has progressed significantly, with this disease being clearly identified as an autoimmune disease with a peculiar autoantigen (galactose-deficient IgA1 [Gd-IgA1]), specific autoantibodies (IgG and IgA1 anti-glycans), and formation followed by mesangial deposition of circulating immune complexes with the involvement of other players, such as mesangial transferrin receptor (TfR), monocyte Fcα receptor (CD89), and glomerular transglutaminase 2 (TG2). The pathogenesis still requires additional clarifications in order to explain the initiation of the disease and to establish the respective role of genetics, environment, and hazard concordance in the cascade of events/steps. The clinical application of this new knowledge is spreading slowly and includes possible measurement of serum Gd-IgA1, IgG anti-Gd-IgA1, IgA anti-Gd-IgA1, soluble CD89, and soluble TfR in the urine of patients with IgAN.

Keywords: IgA nephropathy, autoimmune disease, IgA1 molecule, glycosylation, genetics, pathogenesis, pathophysiology.

INTRODUCTION

Immunoglobulin A nephropathy (IgAN) was first described in 1967 by Jean Berger,[1] a general pathologist in Paris. The primary form represents 90% of all cases and was also called Berger's disease. The secondary forms are seen in Henoch-Schönlein purpura (HSP), in a few cases of systemic lupus erythematosus-induced nephritides, and also in some cases of nephritis associated with overt liver cirrhosis. The classification between primary and secondary forms is based exclusively on clinical grounds. The definition[2,3] is pathological in nature and still requires a renal biopsy in order to accurately establish the diagnosis. The biopsy should be processed for both immunofluorescent (IF) and optical microscopies. The characteristic lesions observed in IF microscopy are mesangial IgA deposits with the following patterns: granular, coarse, generalised, or diffuse, and these patterns can also be dominant or codominant with other immunoglobulin deposits (IgM and/or IgG) or complement-factor deposits (mainly C3). Examination by light microscopy allows the evaluation of elementary lesions and establishment of an International/Oxford classification[4] using 'MEST' scoring: M for mesangial hypercellularity (M0 or M1), E for endocapillary hypercellularity (E0 or E1), S for segmental glomerulosclerosis (S0 or S1), and T for tubular atrophy/interstitial fibrosis (T0, T1 or T2); by combining these indices, the maximal score is 5 (M1+E1+S1+T2). The MEST score has been validated as an independent risk factor for prediction of progression to end-stage renal failure (dialysis or Stage 5 estimated glomerular filtration rate), with renal lesions indicative of poor prognosis being present when the MEST score is ≥2 (unpublished data from our group).

This pathological risk factor should be evaluated with the two other independent clinical risk factors already described and internationally approved: proteinuria ≥1 g/day and the presence of arterial hypertension, and this has permitted our group[5] to establish the absolute renal risk (ARR) for

dialysis/death. We demonstrated that these three simplified risk factors: proteinuria ≥1 g/day (yes or no), arterial hypertension (yes or no), and severe pathological score (≥8 for our local classification or MEST ≥2 for the Oxford classification; yes or no), were independent and equipotent in the prediction of dialysis/death. The scoring of ARR is simply the number of these three risk factors that are present at initial diagnosis (0, 1, 2, or 3); this ARR allows an accurate estimation of the risk of dialysis/death at 10 years post-diagnosis or at 20 years post-disease onset: approximately 5%, 10%, 20%, and 60% for ARR 0, 1, 2, or 3, respectively. This ARR scoring was also validated for IgAN secondary to HSP.[6]

PATHOPHYSIOLOGY OF IgAN

Mesangial Deposits of IgA1 Subclass

The main characteristic of IgAN is the deposition of IgA in the mesangial area, it has been known since 1980[7] that this deposition is highly selective and concerns only the IgA1 subclass and not IgA2. In normal individuals, the majority (approximately 84%) of serum IgA is monomeric with IgA1 being predominant, although these percentages are highly variable (range: 65-94%).

IgA1 Subclass and Unique Hinge Region

The major difference between IgA1 and IgA2 resides in the presence of a unique long hinge region in IgA1 (Figure 1). This hinge region is a chain of 18 amino acids (5 serine, 4 threonine, and 9 proline) that can attach up to six lateral sugar chains fixed to the threonine or serine residues by an oxygen linkage (O-glycosylated chains). A complete glycosylated chain is composed of a first molecule of sugar, the N-acetylgalactosamine (GalNAc) fixed on either threonine or serine by a specific enzyme called GalNAc transferase 2, the second molecule of sugar is galactose (Gal) fixed on GalNAc by a specific enzyme called β1,3-galactosyltransferase (β1,3GT), and a third molecule of sialic acid (also called N-acetylneuraminic acid) can be attached to the terminal Gal by a specific enzyme called α2,3-sialyltransferase (α2,3ST) and/or attached to the lateral GalNAc by the specific enzyme called α2,6-sialyltransferase (α2,6ST).

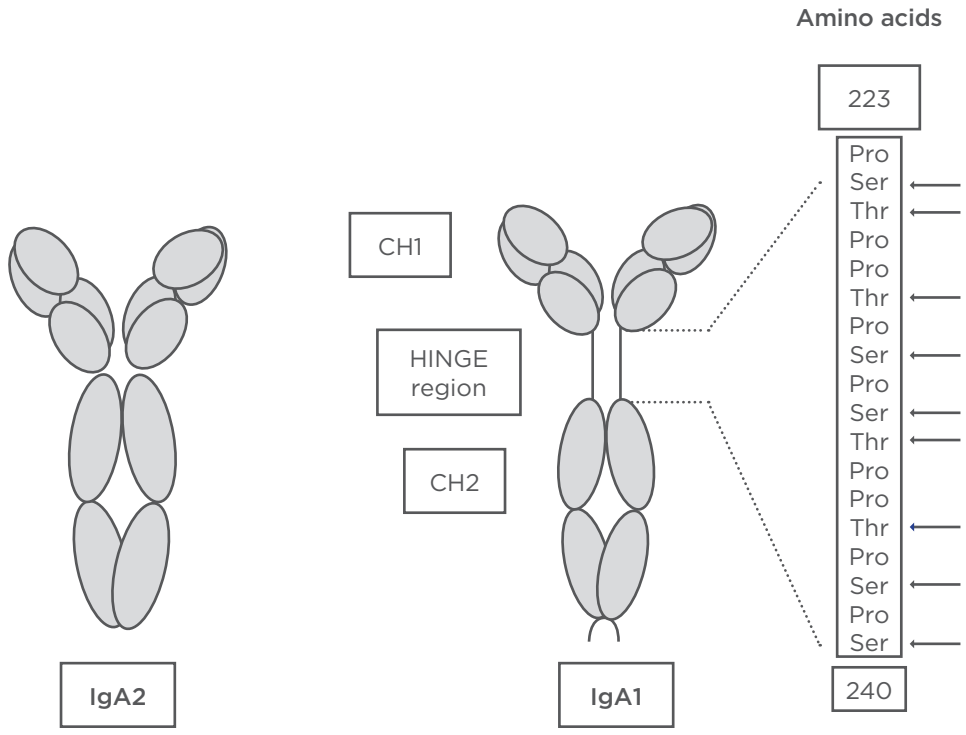

Figure 1: Molecular differences in IgA1 and IgA2.
IgA1 molecules are characterised by the presence of a hinge region that can bind lateral sugar chains on the main protein chain, and which is composed of 18 amino acids. The binding is exclusively possible on serine or threonine residues with an oxygen linkage, the O-glycosylated lateral chains. There are nine potential sites for fixation, but only up to six lateral chains are attached.
IgA: immunoglobulin A; CH: constant heavy chain domains; Pro: proline; Ser: serine; Thr: threonine.

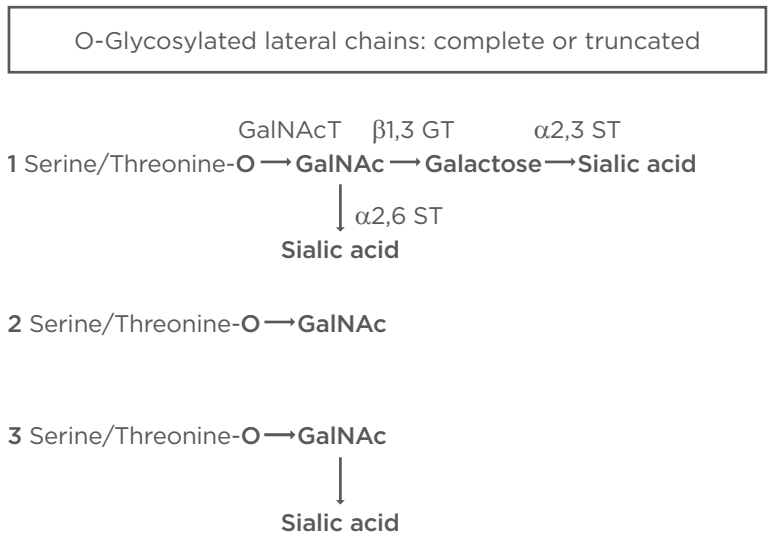

Figure 2: Complete or truncated lateral sugar chains.
The first step is the binding of an N-acetyl galactosamine (GalNAc) molecule to serine/threonine residues, which is controlled by the enzyme GalNAc transferase (GalNAcT). The second step is the transfer of a galactose (Gal) molecule, which is controlled by the enzyme β1,3-galactosyltransferase (β1,3GT). The final step is the addition of a terminal sialic acid molecule to Gal, which is controlled by the enzyme α2,3-sialyltransferase (α2,3ST), and the GalNAc molecule can be laterally sialylated under the control of the enzyme α2,6-sialyltransferase (α2,6ST). In IgA nephropathy, these sugar chains are often lacking Gal, and are referred to as Gal-deficient IgA1. These chains are truncated with the loss of Gal and the terminal sialic acid, if present; the simplest chain is O-GalNAc.

Besides these complete sugar chains, there are incomplete sugar chains lacking terminal or lateral sialylation or lacking Gal; the simplest chain is O-GalNAc (Figure 2).

Differences in O-glycosylation of IgA1 Between Controls and IgAN Patients

Compared with healthy individuals, there is a significant decrease in the number of completely glycosylated lateral chains, with a loss of Gal (under-galactosylation), in serum samples from IgAN patients; this is a quantitative but not a qualitative difference. In healthy individuals, the majority of O-chains are complete with Gal (i.e., at least four of the six chains are complete), while the majority of chains in IgAN patients are incomplete or truncated (i.e., no more than two of the six chains are complete). This IgA1 abnormality in IgAN patients was first described by Hiki et al. in 1998,[8,9] largely confirmed by many other groups,[10-12] and is now a well-established fact.

This under-galactosylation of IgA1 molecules in IgAN patients is not only evident in circulating (serum) IgA1, but is also present in mesangial-deposited IgA1,[13,14] IgA1 produced by B lymphocytes (peripheral or in bone marrow), in musoca-associated lymphoid tissue (MALT), and in IgA1 extracted from tonsils.[15] Therefore, this is a generalised abnormality. Compared with healthy individuals, an increased number of sialic acid molecules in the serum of IgAN patients has been described,[16] and this was despite the loss of Gal molecules with possible terminal sialic acid moieties; this implies an increase in lateral sialylation of GalNAc. There is currently a lack of consensus regarding this observed abnormality.

Differences Between IgAN Patients and Controls at the Enzyme and Gene Levels

Three enzymes control the addition of sugar molecules to the O-glycosylated lateral chains:

i) The enzyme β1,3GT controls the transfer of Gal molecules to GalNAc and its activity is diminished in lymphocytes from IgAN patients.[17-19] This enzyme requires a chaperone molecule, referred to as CosmC, to gain full activity,[20] and the genes encoding these two proteins have been identified: *C1GALT1* and *C1GALT1C1*, respectively. There is decreased gene expression of *C1GALT1* and also

an association with a particular gene polymorphism in IgAN patients;[21] the results for the *C1GALT1C1* gene are discordant.

ii) The enzyme α2,6ST controls the lateral binding of sialic acid molecules to GalNAc. In IgAN patients, its activity is increased with an increased expression of the gene *ST6GALNAC2*,[22] but with a controversial paper.[23]

iii) The enzyme α2,3ST controls the terminal binding of sialic acid molecules to Gal. No difference between this enzyme's activity in IgAN patients and healthy individuals has been found.

The IgAN Autoantigen

The hallmark of IgAN patients is an under-(hypo-)galactosylation of circulating IgA1 (Gal-deficient IgA1, Gd-IgA1) compared with healthy individuals and with patients with other renal diseases. The consequence is an 'overexposure' of terminal GalNAc molecules, which are often sialylated, and these glycans become immunogenic and constitute the autoantigen. The measurement of this autoantigen within serum samples is either very sophisticated, e.g. by mass spectrometry techniques,[8,13] and therefore limited, or by a more simple indirect enzyme-linked immunosorbent assay (ELISA) that relies on the specific binding of the lectin *Helix aspersa* agglutinin (HAA) to terminal GalNAc molecules; the percentage binding/reactivity to HAA is proportional to the amount of Gd-IgA1 within the sample.[24,25]

For clinical use, this assay should be performed on desialylated samples (pretreated with neuraminidase) and the total Gd-IgA1 calculated by multiplying the normalised HAA binding (units) obtained by the amount of IgA1 in the sample (units/ml). The serum level of Gd-IgA1 is significantly elevated in IgAN patients versus healthy individuals and patients with other renal diseases; subsequently, an association was shown with the subgroup of progressive IgAN patients.[26,27] It should be remembered that total serum IgA is globally increased in IgAN patients compared with healthy individuals, with a significant individual increase (over 350 mg/dl) in more than 50% of patients. It has subsequently been shown that this is also true for total IgA1, with the majority being polymeric and more anionic.

The Specific Autoantibodies in IgAN: IgG and IgA Subclasses

Specific anti-glycan antibodies were first described by the group of Jan Novak,[22,24,28] with IgG anti-Gd-IgA1 and IgA (including IgA1) anti-Gd-IgA1; circulating immune complexes were also demonstrated. Therefore, IgAN is clearly an autoimmune disease, similar to membranous glomerulonephritis in which the most common autoantigen is phospholipase A2 receptor and there is specific IgG autoantibody. In the clinical situation, it is possible but difficult to measure serum IgG and serum IgA anti-Gd-IgA1 by specific ELISA assays.[26,29] The results were normalised (units per 0.5 µg of IgG or per 1 µg of IgA) and then multiplied by the amount of IgG or IgA in the sample (units/mg). We recently demonstrated that the respective serum levels of Gd-IgA1 and of the autoantibodies (IgG and IgA subclasses) are associated with potential progression of the disease, which is reflected by the ARR for dialysis/death.[26] Hastings et al.[30] provide a thorough review of these clinical results.

Circulating Immune Complexes and Monocyte Fcα Receptor (CD89) Amplification Loops

Before reaching the kidneys, immune complexes composed of Gd-IgA1–IgG and Gd-IgA1–IgA can bind to the receptor CD89 expressed on the surface of monocytes and macrophages in the circulation; this receptor is a specific ligand for the Fcα chain and has been well described by the group of Renato Monteiro in Paris, France.[31] These complexes can then be transported by these cells or circulate freely as a tri-molecular complex composed of antibody, antigen, and soluble CD89 (sCD89); this sCD89 is a truncated chain of the receptor. This constitutes the systemic CD89 amplification loop. Recently, it was shown that this tri-molecular complex can bind directly to the transferrin receptor (TfR) within the mesangium,[32] locally initiating the expression of a new molecule, transglutaminase 2 (TG2),[33] with a local amplification loop (increased expression of TfR with greater IgA1 deposition). In the clinical situation, serum levels of sCD89 have been measured with conflicting results: one study showed elevated levels in IgAN patients compared with healthy individuals,[31] whereas others showed lower sCD89 in progressive IgAN or no differences between the non-progressive IgAN patients versus healthy individuals or patients with other renal diseases.[34,35]

Gd-IgA1 Mesangial Deposition and Creation of Renal Lesions

These Gd-IgA1 molecules and immune complexes have modified characteristics and are more prone to deposit passively within the kidney (because they are more 'sticky'), as well as actively within the mesangium due to the presence of TfR that can bind IgA1 (non-specific ligand), and which results in an overexpression of these receptors. Binding of Gd-IgA1 to TfR is increased compared with normal IgA1. As described above, sCD89 can also bind TfR with a local amplification loop. In the clinical situation, it has been possible to measure soluble TfR in concentrated urine: the median value was higher in progressive IgAN and HSP nephritis (HSPN) compared with quiescent IgAN/HSPN and all other renal diseases.[36]

The initiation of renal lesions is dependent on the activation of humoural and cellular mediators of inflammation,[37,38] the role of complement deposition, and the local production of cytokines and receptors such as interleukin (IL)-6, IL-4, tumour necrosis factor α, Toll-like receptor, and many others. The details of this process are not well understood but it allows the initiation of acute kidney lesions starting at the glomerular/mesangial level (increased matrix, mesangial, and endocapillary proliferation, focal and segmental hyalinosis, crescent formation, etc.). These lesions will not spontaneously heal, but instead lead to a chronic process with arteriolar, interstitial, and tubular lesions and their clinical consequences (massive proteinuria, hypertension, and progressive renal failure). This chronicity could be the result of different acute episodes or a permanently low level of stimulation.

PATHOGENESIS OF IgA NEPHROPATHY

Systemic Disease

The mechanism of this disease is systemic with two long-known clinical situations in favour: IgAN is prone to recurrence after renal transplantation in patients with biopsy-proven IgAN in the native kidney and in those who progressed to end-stage renal disease and dialysis.[39] After renal transplantation, one-third to one-half of these patients exhibit clinicopathological recurrence at 10 years post-transplant with typical IgAN on transplant biopsy.[40] Two renal recipients may have inadvertently received a donor kidney containing subclinical mesangial IgA deposits, in this situation the IgA deposits usually disappear rapidly as proved by subsequent graft biopsy.[41]

Implication of Mucosal IgA1 and Bone Marrow IgA1 Production with Crosstalk

The typical presentation of patients (about one-third) with such disease is the occurrence of gross haematuria episodes at the time of a mucosal infection (tonsillitis, intestinal infection, etc.). At that time, increased production of Gd-IgA1 with probable specific autoantibodies was demonstrated. This implies a predominant role of MALT in local production of protective secretory IgA molecules, followed in these IgAN patients by a rapid production of Gd-IgA1 at the mucosal site and also by a systemic production in the bone marrow. The connections between mucosal and bone marrow B lymphocytes (plasmocytes) are complex and partly unknown: direct migration of lymphocytes and production of cytokines with a special role in homing and addressing.

The Potential Causes of the Early Initiation/Occurrence of the Disease

There are different possibilities, which are not mutually exclusive. The genetic background/predisposition for this disease is based on initial description of familial cases among siblings,[42] followed by specific classical genetic-linkage studies leading to the isolation of the first locus on chromosome 6 within the human leukocyte antigen region, *IgAN1*.[43] More recently, the genome-wide association studies isolated different loci on different chromosomes.[44] The Gd-IgA1 abnormality observed in affected patients was also observed in unaffected family members.[45] Some specific single nucleotide polymorphisms in the genes controlling different humoural and/or cellular mediators of inflammation may potentially be involved. Abnormal microRNA expression may also play a significant role in IgAN.[46] The overall impact of genetics in the occurrence of this disease is complex and multigenic, but probably also limited.

This disease may also be acquired depending on numerous environmental factors: exposure to certain exoantigens (infectious organisms, food, etc.), involvement of specific cytokines that can induce the production of Gd-IgA1, and modification of the different players potentially involved (immune response to autoantigens, abnormalities in receptors such as TfR and CD89, tissue TG2 status, etc.).

In any case, the initiation of the disease is dependent on a 'multi-hit theory',[38] which implies a concordance of events at different steps: exposure to certain antigens; Gd-IgA1 production at the mucosal and bone marrow levels; deposition of mesangial Gd-IgA1; response/activation of the mediators of inflammation, which all ultimately result in acute glomerular lesions with disease expression. The transition to chronicity depends on the repetition of acute events, and also on renal pathology and clinical factors involved in progression. Current treatment for IgAN targets the late renal lesions/inflammation (with steroid treatment) and also the clinical factors for progression (optimal control of hypertension, reducing proteinuria with angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers); in the future the target will be the early pathogenic events.

CONCLUSION

IgAN is clearly an autoimmune disease with a precisely identified autoantigen and specific autoantibodies, and is characterised by circulating immune complexes with mesangial deposition in the kidneys. There is a multi-step, multi-hit process required to achieve the full expression of this clinicopathological disease. The intimate mechanisms involved in the key early events are still obscure and the pathogenesis is not yet fully elucidated.

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PRIMARY FOCAL SEGMENTAL GLOMERULOSCLEROSIS: WHY ARE PIECES OF THIS PUZZLE STILL MISSING?

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ABSTRACT

Focal segmental glomerulosclerosis (FSGS) can be classified as primary or secondary. Moreover, many causes of primary FSGS have been identified in recent years. In this regard, genetic circulating permeability factors and the abnormal podocyte expression of co-stimulatory molecules have been reported. However, the classification of this entity remains difficult to understand, mainly due to the fact that it describes a morphologic pattern of scarring. FSGS is a histological pattern shared by almost all the glomerulonephritides that describes a podocyte lesion and not a disease. Therefore, it should be reclassified according to the new pathophysiological findings and the biomarkers encountered in each triggered pathway.

Keywords: Focal segmental glomerulosclerosis (FSGS), soluble factor urokinase type plasminogen activator receptor (suPAR), B7-1, proteinuria.

MORPHOLOGY AND PATHOPHYSIOLOGY

Since the introduction of kidney biopsy in 1951, the urinary anomalies observed either macro or microscopically, plus the quantification of proteinuria and the clinically diagnosed kidney diseases, were consolidated into one main group in internal medicine: glomerular diseases.[1] Nephrosis and nephritis were better distinguished and classified according to optic microscopy observed patterns, to which electron microscopy and immunofluorescence microscopy added more information. Therefore, morphology was employed as a solid base on which clinical and laboratory findings could be explained and sustained in order to establish diagnosis and to eventually prescribe an available treatment. As recently remarked by Sethi et al.,[2] adequate quantification of the percentage of glomeruli affected by sclerosis can only be made by examination of sufficient glomeruli within a specimen, which helps to ensure that the specimen is reasonably representative of the population of glomeruli in the kidney as a whole. Of course, this ideal situation can be far from possible in a clinical setting.

Despite this often overlooked consideration, the morphological patterns of glomerulopathies have been facing new challenges in the last decades. As the pathophysiological pathways of glomerular diseases have been unravelled, the glomerular diseases have become better understood. As a consequence, the dissection of the molecular mechanisms of disease has started to demonstrate that a similar morphological pattern in a biopsy can be shared by different entities based on quite diverse pathophysiological pathways. This important issue obliged the nephrology community to reconsider the classification of many glomerulopathies, in which the pathophysiology would prevail over the morphological patterns. Moreover, the chain of events is facing a new challenge. The identification of appropriate, specific, and commercially available plasmatic or urinary biomarkers that do not only correlate with the histological variants of a certain glomerulopathy, but also inform the therapeutic approaches to be followed.

THE COMPLEX DEFINITION OF PRIMARY FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Focal segmental glomerulosclerosis (FSGS) is even more complex, as it refers to a morphological pattern that can not only be present in its primary variants, but also occur as a consequence of secondary insults and as a common final pattern of glomerular obliteration.

FSGS is a morphological pattern of glomerular injury primarily directed at the podocyte and defined by the presence of sclerosis in parts (segmental) of some (focal) glomeruli, as observed by light microscopy of a renal biopsy.[2] However, the name itself is misleading. Morphometric analysis of complete glomeruli from renal biopsies obtained from patients with FSGS shows that the volume of the sclerotic lesions averages just 12.5% of the entire glomerular volume.[3] Moreover, as remarked by Sethi et al.,[2] renal biopsies with <15 glomeruli cannot exclude FSGS with confidence. This is further complicated by the well-known fact that the inner (deep) juxtamedullary glomeruli are preferentially affected in the early phases of primary FSGS.[4] A biopsy specimen containing only cortical glomeruli may underestimate the frequency of FSGS lesions in the whole kidney. In order to maximise accuracy, the diagnostic set should be comprised of consecutive sections selected from 12-15 routinely cut serial sections[5,6] and should contain a minimum of 8 glomeruli.[3]

Another point frequently overlooked is that the electron microscopy-observed changes are the initial phase of the pathological process; only with time will the characteristic sclerotic lesion develop. This can explain the absence of FSGS lesions in an initial biopsy while a second biopsy, performed months or even years later, clearly demonstrates lesions of FSGS.[7] The 'bottom line' is that the lesion of FSGS observed by light microscopy, which is how FSGS is defined, is not really segmental and is only rarely truly focal in its distribution. While FSGS is not a very common cause of nephrotic syndrome (NS) in the elderly,[8] some of these patients may present with NS and with an FSGS as the only apparent lesion in optical microscopy. Finally, evaluation of non-sclerosed glomeruli by electron microscopy can be helpful in identifying a primary podocytopathy, and can support the use of immunosuppressive therapy in the setting of widespread foot process effacement.

GENETIC CAUSES OF FOCAL SEGMENTAL GLOMERULOSCLEROSIS

Currently, mutation analysis is expensive and single genes are analysed separately. Therefore, a cost-effective approach requires information on the prevalence of causative mutations in a given population.[9] However, certain concepts must be taken into account when a genetic cause of FSGS is suspected. The genetic causes of FSGS comprise proteins that are mainly expressed in the podocyte or in the slit diaphragm itself and are engaged either in the organisation of the slit diaphragm or the podocyte actin cytoskeleton, thus regulating glomerular membrane permeability and selectivity. FSGS caused by mutations in nephrin (*NPHS1*), podocin (*NPHS2*), CD2-associated protein (*CD2AP*), phospholipase C epsilon-1 (*PLCe1*), and myosin 1e (*MYO1E*) is characterised by an autosomal recessive pattern of inheritance. As a rule, the onset of disease occurs in childhood. In contrast, mutations in *ACTN4, TRPC6,* and *INF29* cause autosomal dominant FSGS. In most patients, onset of disease is in adulthood, and many patients do not develop a full-blown nephrotic syndrome. FSGS can also be caused by mutations in genes that encode proteins that are expressed not only in the podocytes but also, or even more so, in other tissues and cell types. In these syndromic forms of FSGS the extrarenal manifestations are most prominent and often diagnostic, and in some of these diseases FSGS may be the only or the presenting manifestation, thus mimicking isolated FSGS. Well-known examples are mutations in the transcription factor Wilms tumour 1 (*WT1*) and certain mitochondrial mutations.[9]

PRIMARY FOCAL SEGMENTAL GLOMERULOSCLEROSIS PATHOPHYSIOLOGY: suPAR

FSGS is a major cause of chronic kidney disease in children and adults.[10-12] It can occur as a primary disorder (called primary acquired FSGS) as a consequence of genetic mutations in podocyte-specific or slit diaphragm proteins (also called primary genetic FSGS), or as a secondary disorder.[13,14] In recent years, much of the progress obtained in unravelling the pathophysiological events in FSGS has been focussed primarily on the identification of genetic mutations of membrane and podocyte slit diaphragm proteins and on immune factors, but the real identity of the

primary acquired variant apparently caused by circulating permeability factors remains elusive. In this regard, the role of these permeability factors in the pathogenesis of proteinuria has also shown progress in recent years, although the results are not entirely convincing and appear to lack specificity for a unique type of glomerular disease, as has been found in other glomerular diseases such as minimal change disease and membranous nephropathy.[15] Lately, the soluble factor urokinase-type plasminogen activator receptor (suPAR) has become one of the most studied permeability factors with a potential pathophysiological involvement in FSGS. It is reported to be responsible for the contraction of podocytes and their eventual detachment from the glomerular basement membrane, which denudes it and causes proteinuria in the majority of primary acquired cases of FSGS.[16]

Abnormally high circulating levels of suPAR have been associated with the pathogenesis of acquired primary FSGS, since approximately two-thirds of patients with acquired FSGS have increased circulating levels of suPAR.[16] suPAR then binds to and activates αvβ3 integrin in podocytes by a lipid-dependent mechanism,[17] leading to alterations in the morphology and dynamics of the metabolism of podocytes and foot process effacement, detachment and podocyturia, finally resulting in proteinuria and the beginning of glomerulosclerosis, nephrotic syndrome, and renal insufficiency.[17,18] According to Li et al.,[19] steroid responsiveness may be related to the levels of suPAR in some primary FSGS cases. The authors propose a suPAR concentration of 3,400 pg/ml to be used as an optimal cut-off value for corticosteroid therapy.[19]

What is the cellular origin of this increased membrane urokinase-type plasminogen activator receptor (uPAR) and circulating suPAR in FSGS? Wei et al.[17] suggest that neutrophils and monocytes may be culprits, but another possibility lies in circulating T cells, since there is an association between T cell activation and systemic proteinuria. In turn, and as mentioned above, not all cases of idiopathic acquired FSGS display increased circulating levels of suPAR. This is another confirmation that histological FSGS is not a disease but a form of kidney damage characterised by common histopathological features and with completely different pathophysiological pathways.[20] In other words, FSGS is a morphological description that is denoting podocyte injury; it is a lesion and not a disease.[2]

With regard to suPAR and FSGS, this concept is not shared by others who question whether elevated levels of suPAR are indeed pathogenic or are merely markers of a split uPAR (CD87) molecule. Moreover, proteinuria does not occur in other clinical settings in which suPAR is elevated.[21-23] An elevated concentration of suPAR is not a specific marker of FSGS as levels can also be high in patients with other glomerulopathies, as well as in patients without glomerular derangement. In addition, elevated suPAR levels are not always encountered in recurrences of FSGS following transplantation.[21-23] Finally, some authors suggest that it is the presence of suPAR in urine that is the real cause of primary acquired FSGS.[20-23]

Various molecules can activate uPAR, including urokinase-type plasminogen activator (uPA), plasminogen, chymotrypsin, various metalloproteinases, and some elastases.[24-27] Studies are generally based on the action of these molecules on uPAR but, as suPAR slightly shares the same molecular structure as uPAR, these proteases are also likely to cleave suPAR fragments. Furthermore, suPAR or uPAR are capable, once activated, of catalysing the conversion of plasminogen to plasmin, which is an important molecule in fibrinolytic processes and in the activation of several matrix metalloproteinases, in the recycling and degradation of the extracellular matrix, in cell activation, migration, contraction, vasculogenesis, and in vitronectin degradation.[28-31] This phenomenon may occur in plasma, on the podocyte surface, or in renal distal tubular cells.[18-32] It is noteworthy that patients with NS present with elevated serum levels of plasminogen and plasmin.[33] In turn, and after being filtered, urinary plasminogen is converted to plasmin by podocyte or distal renal tubular epithelial uPA/uPAR.

At this distal location, plasmin has been reported to function as a regulator of water and sodium absorption, which is a key event in the pathogenesis of oedema, and also as a mediator in calcium tubular transport.[32,34,35] It is known that uPAR is needed to activate the integrin αvβ3 in podocytes, which promotes cell motility and activation of small GTPases that control cell division, such as cdc42 and cdc40. If αvβ3 integrin is activated, the podocyte contracts and proteinuria ensues. However, it is believed that suPAR has

inhibitory properties on adhesion and uPAR-dependent migration but not on cell contraction. Thus, it would be able to interact with αvβ3 integrin, vitronectin, or plasmin.[36,37]

PRIMARY FOCAL SEGMENTAL GLOMERULOSCLEROSIS PATHOPHYSIOLOGY: B7-1

A new and provocative proposal recently came onto the scene when expression of the B7-1 molecule on podocytes was found to be present in patients with primary FSGS.[38] B7-1 is a 53 kDa membrane-associated protein that, in the glomerulus, is localised exclusively in podocytes, although it can also be found in renal tubules.[39,40] It is better known for its role in the immune system as a co-stimulatory receptor involved in T cell activation.[40] Activation of B7-1 by puromycin in cultured podocytes was found to attenuate expression of nephrin and results in foot process effacement and retraction.[41] The ability of B7-1 to regulate podocytes' filtering capacity is also shown when lipopolysaccharide (LPS) is injected into mice, which results in increased B7-1 expression and proteinuria; proteinuria does not occur in B7-1 knockout mice.[39] Therefore, the immune stimulatory role of B7-1 within the glomerulus would support the idea that it may modulate immune-mediated injury to podocytes.[42]

T cells require two signals to become activated. The first signal comes from the interaction between the antigen-presenting cell (APC) and the T cell receptor via the major histocompatibility complex. This signal alone leads to anergy or tolerance.[43] The second signal is named the co-stimulatory or accessory signal, and is mediated via interactions between CD28 expressed on the surface of T cells and the lymphocyte activation antigens B7-1 or B7-2 (also known as CD86) expressed on the surface of APCs.[44] B7-1 modulates the activity of responding CD4+ and CD8+ T cells by alternatively binding to the surface glycoprotein CD28 co-stimulator, which is constitutively expressed on the surface of naïve and activated T cells, or the cytotoxic T lymphocyte-associated protein 4 (CTLA 4) co-inhibitor, which is inducibly expressed on both CD4+ and CD8+ T cells upon activation. As mentioned above, podocytes do not express the B7-1 molecule on their extracellular membrane in normal conditions. However, various rodent models of glomerular diseases are associated with an upregulation of B7-1 in podocytes.[45-48] In this respect, the podocyte would act as an APC to T cells, which would then activate other T cell populations as well as B cell populations, triggering antibody synthesis and also potentially influencing the synthesis or release of suPAR from leukocytes. These findings and speculations may portend relevant implications for the role the second signal should be playing at the initial steps of the immune response involved in glomerulopathies.

In this regard, there are at least two implications related to the podocyte expression of B7-1. First, the APC role of podocytes in abnormal conditions; second, B7-1+ podocytes have a reduced capacity to attach to the surrounding matrix (the glomerular basement membrane) through β1 integrin.[49,50] Whereas in T cells B7-1 acts by binding to CD28 or CTLA-4 through its extracellular domains, in podocytes the cytoplasmic tail of B7-1 is necessary and sufficient to block β1-integrin activation by competing with talin for β1-integrin binding.[51,52] B7-1+ podocytes change their morphological characteristics and their function, promoting podocyte migration through inactivation of β1 integrin and leading to detachment of their foot processes from the glomerular basement membrane, podocyturia, and proteinuria.[53] This is a result of the interaction between T cells and podocytes through B7-1 and B7-2. The inhibition of β1-integrin activation in podocytes by abatacept could be a potential mechanism that could explain the underlying antiproteinuric action of this drug.[53]

B7-1 can be detected and measured in the urine and may be a potential biomarker of podocyte injury, but, as mentioned above, its origin could be either podocytic or tubular.[39,40] Urinary levels of B7-1 in patients with relapsed minimal-change disease are higher when compared with those in patients with minimal change disease in remission, lupus (with and without proteinuria), other glomerulopathies (FSGS, membranoproliferative glomerulonephritis, immunoglobulin A nephropathy, and membranous nephropathy), and healthy control patients.[40] Data from a second study by the same group showed that urinary B7-1 was increased in patients with minimal change disease in relapse compared with patients with minimal-change disease in remission or those with FSGS.[54] Additionally, the level of urinary B7-1 mRNA was found to be enhanced in patients with glomerular kidney disease compared with that of healthy patients.[55] Promising data describing the utility of urinary B7-1 as a biomarker of

podocytopathy have been reported; however, the fact that B7-1 can also be derived from tubular epithelium reduces confidence in its specificity.[40] Moreover, immunohistochemical detection of B7-1 is technically difficult using paraffin-embedded tissue samples.[56] This highlights the need for the development of improved techniques for routine widespread use.

Recently, Yu et al.[38] administered abatacept in one or two intravenous doses of 10 mg/kg to four patients with recurrent FSGS after kidney transplantation and to one patient with primary FSGS.[40] The patients with recurrent FSGS underwent concurrent plasmapheresis. The conclusions from this study must be taken with utmost caution as only five patients were included. Nonetheless, the results were interesting and encouraging: these patients experienced a remission that lasted 10-48 months. As the therapy was beneficial, B7-1 staining of kidney biopsy samples from patients with glomerular diseases was assessed and podocyte B7-1 expression was observed. In the non-transplant patient with primary FSGS, treatment with abatacept 10 mg/kg on Day 1, 15, and 30, and monthly thereafter, was associated with partial remission and proteinuria decrease at 12 months. Several hypotheses for this response could be proposed. Firstly, abatacept is capable of modulating the immune response by affecting B7-1 and CD28 co-stimulation, which in turn could decrease leukocyte-derived circulating factors, such as suPAR, and consequently protect podocytes from contraction.[20] Secondly, abatacept might bind to podocyte B7-1, thus altering the cellular downstream function of this receptor in relation to the roles of actin and integrin in podocyte contraction.[20,38] Thirdly, plasmapheresis could have removed a circulating factor and this removal induced remission independent of podocyte B7-1 expression and/or abatacept infusion.[20,49] In summary, a small subset of patients with primary FSGS who are B7-1+ may prove to be responsive to abatacept. It cannot be concluded that abatacept is a specific treatment for FSGS.

Finally, abatacept could play a role in podocyte toll-like receptor (TLR) signalling through B7-1 interaction or independent of B7-1. This mechanism could be, for example, via the endogenous calprotectin system composed of TLR4 agonists S100A8/S100A9 and present in monocytes.[57] These proteins have been shown to play critical roles in LPS-induced sepsis, vasculitis, and certain types of glomerulonephritis.[58,59] To my knowledge, this hypothesis has not been explored in this field. Although the podocyte B7-1 pathway seems to play an important role in some glomerular diseases, clinical results suggest that targetting this mechanism needs further study in randomised controlled trials. As commented by Haraldsson,[59] the relevance of distinguishing B7-1+ from B7-1– glomerulopathies could predict the response to abatacept.

THE REASON WHY PRIMARY FSGS IS A DIFFICULT PUZZLE TO COMPLETE

Histopathologic morphological patterns have played a valuable and critical role in the classification and comprehension of glomerulopathies. However, as the dissection of the pathophysiological pathways of glomerular diseases continue to be revealed, the classical morphological classifications must be aligned with the biomarkers involved in the development of glomerular injuries and changed to a molecular-based classification. Immunohistochemistry can add important functional information to the morphological patterns. So long as FSGS is considered a disease, the completion of the puzzle will remain elusive. FSGS is a morphological lesion. Many new pathophysiological advances have taken place in recent years that can justify the splitting of this entity into a more comprehensive classification. Morphology has paved the road for nephrologists to face proteinuria. However, with respect to FSGS, the newly discovered pathophysiological pathways and the different adjunctive biomarkers are showing that new roads are stretching out ahead, which will require a new classification of this erroneously denominated disease. Therefore, more than one puzzle could be made, in which the pieces would be fewer and ought to fit more easily and smoothly.

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CHRONIC KIDNEY DISEASE AND ENDOTHELIUM

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ABSTRACT

The endothelial cell layer is responsible for molecular traffic between the blood and surrounding tissue, and endothelial integrity plays a pivotal role in many aspects of vascular function. Cardiovascular disease (CVD) is the main cause of death in patients with chronic kidney disease (CKD) and its incidence and severity increase in direct proportion with kidney function decline. Non-traditional risk factors for CVDs, including endothelial dysfunction (ED), are highly prevalent in this population and play an important role in cardiovascular (CV) events. ED is the first step in the development of atherosclerosis and its severity has prognostic value for CV events. Several risk markers have been associated with ED. Reduced bioavailability of nitric oxide plays a central role, linking kidney disease to ED, atherosclerosis, and CV events. Inflammation, loss of residual renal function, and insulin resistance are closely related to ED in CKD. ED may be followed by structural damage and remodelling that can precipitate both bleeding and thrombotic events. The endothelium plays a main role in vascular tone and metabolic pathways. ED is the first, yet potentially reversible step in the development of atherosclerosis and its severity has prognostic value for CV events. Therefore, evaluation of ED may have major clinical diagnostic and therapeutic implications. In patients with CKD, many risk factors are strongly interrelated and play a major role in the initiation and progression of vascular complications that lead to the high mortality rate due to CVD.

Keywords: Chronic kidney disease, endothelium, endothelial dysfunction.

INTRODUCTION

In patients with chronic kidney disease (CKD), the endothelium plays a pivotal role, not only with respect to their cardiovascular (CV) morbidity and mortality, but also with regard to progression of the disease. It has become clear from experimental studies that vascular rarefaction in the capillary system of the renal medulla as a result of endothelial damage is a central step towards tissue hypoxia and kidney damage.[1] Renal insufficiency may be a constituent and/or cause of a systemic subclinical atherothrombotic process.[2] Endothelial dysfunction (ED) is an early phenomenon that precedes structural changes and clinical manifestations of atherosclerosis, contributing to both plaque initiation and progression.[3,4] The severity of ED has been shown to have prognostic value for CV events.[5] Additionally, several risk markers have been associated with ED in CKD.[6]

Therefore, it is correct to consider ED as a heterogeneous syndrome, which can be focussed upon either as a local or a systemic condition as in CKD, with subclinical or clinical manifestations, being reversible or irreversible according to its severity, and with many related aetiological mechanisms.[7] In CKD, ED is characterised by increased plasma concentrations of endothelium-derived molecules, an imbalance between circulating endothelial cells and bone-marrow endothelial progenitor cells (EPCs), or reduced endothelium-dependent vasodilatation.[8] As renal function deteriorates, an atherogenic milieu is generated due to the accumulation of uraemic toxins with a direct impact on the endothelium and the vessel wall, contributing to oxidative stress (OS) and enhancing a subclinical inflammatory state. In CKD, these initial steps in ED may perpetuate if not identified at the early subclinical stages, leading to atherogenesis. Decreased endothelial function (EF) is thought to primarily

reflect a decreased bioavailability of nitric oxide (NO), a molecule with vasodilatory and antiatherosclerotic properties.[9] Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of NO synthase, is involved in atherogenesis, is primarily cleared by the kidney, and is elevated in CKD.[10] ADMA is considered as an independent predictor of ED and poor outcome in dialysis patients.[11] Thus ADMA, as well as its catabolising enzyme dimethylarginine dimethylaminohydrolase, could be a potential treatment target in clinical trials aimed at reducing the loss of kidney function in CKD patients. Various mechanisms have been implicated in the impaired endothelium-dependent relaxation.

Endothelin-1 (ET1) has two direct renal actions: causing renal vasoconstriction (via endothelin type A [ETA] receptors) and tubular sodium and water loss (via endothelin type B [ETB] receptors), which probably reflect separate sites of production in renal blood vessels and tubules. ETA antagonism alone, and/or combined ETA/ETB blockade, reduces CKD progression. Based on strong pre-clinical data, several clinical trials using ETA antagonists were conducted. Small trials involving acute intravenous endothelin receptor blockade suggest that ETA but not ETB blockade exerts protective renal and vascular effects in CKD patients. A large Phase III trial (A Study of Cardiovascular Events in Diabetes [ASCEND]) examined the effects of avosentan, an endothelin receptor antagonist, on renal disease progression in diabetic nephropathy.[12] Proteinuria was reduced after 3-6 months of treatment. Several Phase II trials using avosentan at lower doses than in ASCEND, atrasentan, or sitaxsentan (the latter two being highly ETA-selective) showed reductions in proteinuria in addition to renin-angiotensin system blockade. Infrequent and clinically insignificant fluid retention was observed at the most effective doses. Additional trials using ETA blockers are ongoing or being planned in patients with diabetic nephropathy or focal segmental glomerulosclerosis.[12,13] There is much optimism regarding their clinical benefit, although 'hard' renal outcomes analysing renal function remain to be determined. Finally, consideration needs to be given to conducting trials examining the effects of ETA receptor blockers in dialysis patients.

Additionally, albuminuria is a predictor of increased CV risk. Albuminuria is strongly associated with increased levels of pentraxin 3, an inflammatory mediator predominantly produced by endothelial cells, macrophages, and adipocytes in response to pro-inflammatory signals.[14] This suggests that it may have an additional role in the atherogenic process common to inflammatory mediators.[15] Because of its extrahepatic synthesis, pentraxin 3 levels are believed to be an independent indicator of disease activity occurring directly at sites of inflammation and linked to ED. Detached circulating endothelial cells may serve as potential markers of endothelial damage in CKD. In CKD there exists an impaired migratory activity and/or decreased numbers of these cells, which may have a role in neovascularisation of ischaemic tissue and the progression of atherosclerosis and cardiovascular disease (CVD).[16] An imbalance between the numbers of circulating endothelial cells and EPCs seems to exist in CKD.[15] This imbalance may contribute to the pathogenesis and progression of atherosclerosis.

The Endothelium and Oxidative Stress

Uraemia is a pro-oxidant state. Lipid peroxidation, oxidative modification of proteins and carbohydrates, and certain uraemic toxins themselves have been implicated in ED in CKD.[17] Moreover, numerous defects in antioxidant systems lead to a decrease in the depuration of reactive oxygen species. OS appears to start early in CKD,[18] but total antioxidant capacity has been observed to be exceeded only in end-stage renal disease (ESRD), suggesting that production of reactive oxygen species starts overcoming its clearance at the beginning of the decline in renal function. Reactive oxygen species react with and deactivate NO. Reduced bioavailability of NO as a resultant of ED enhances the development and maintenance of hypertension by augmenting systemic vascular resistance by increasing adrenergic tone, volume expansion and vascular smooth muscle cell proliferation, matrix accumulation, and vascular remodelling, which are inhibited by NO and promoted by free radicals.[19] OS increases production of ET1 and the cytosolic concentration of calcium, thereby increasing vascular smooth muscle tone, systemic vascular resistance, arterial pressure, and accumulation of matrix proteins.[20]

The Endothelium and Inflammation

The causes of the high prevalence of inflammation in ESRD are multifactorial and include decreased renal function, volume overload, comorbidities, intercurrent clinical events, and dialysis-associated factors.[21] An acute-phase reaction may be a

direct cause of vascular injury. Pro-inflammatory cytokines play a central role in the genesis of both CVD and malnutrition in ESRD.[22] Inflammation (which is interrelated to OS, ED, wasting, and insulin resistance) has been suggested to be a significant contributor to CVD in ESRD. It is difficult to define systemic inflammation in CKD patients because there is not a 'gold standard' inflammatory marker. Several different inflammatory biomarkers, such as high-sensitivity C-reactive protein (CRP), have been shown to independently predict mortality in these patients.[21] Although CRP is the most frequently used in clinical trials, it is at the end of the inflammatory cascade and many early inflammatory processes are underdiagnosed. Therefore, several authors adopted the coincidental elevation of CRP and a pro-inflammatory cytokine (e.g. interleukin 6 [IL-6], matrix metallopeptidase 9, tumour necrosis factor alpha [TNF-α]) plasma level as definition of inflammation. Elevated CRP relates to long-term prognosis in both patients with coronary artery disease and in apparently healthy men due to a blunted systemic endothelial vasodilator function. CRP has also been suggested to be a mediator of atherogenesis.[23] Therefore, the identification of elevated CRP levels as a transient independent risk factor for ED might provide an important clue to link a systemic marker of inflammation to atherosclerotic disease progression.[20] Chronic inflammation therefore emerged as a potential mediator between microalbuminuria and macrovascular disease. Pentraxin 3 is an inflammatory mediator produced by endothelial cells that may have a role in atherogenesis. In two cohorts: Stage 5 CKD and Type 2 diabetes with normal renal function, pentraxin 3 was found to be independently associated with proteinuria. Moreover, both pentraxin 3 and proteinuria were associated with ED in patients with Type 2 diabetes.[22]

The Endothelium and Uraemic Toxins

During the development of the uraemic syndrome, loss of kidney function is accompanied by deteriorating organ function attributable to the accumulation of uraemic retention solutes. Compounds that exert an adverse biological impact are called uraemic toxins.[24] Uraemic toxins provoke OS, inflammation, hypertrophy, constriction, and coagulation through various mechanisms.[25] Uraemic toxins can activate the endothelium to produce the following effects: vasoconstriction (via ADMA, advanced glycation end products [AGEs], and homocysteine), inflammation (via indoxyl sulfate and AGEs), OS (via ADMA, AGEs, and homocysteine), or procoagulant activity. The procoagulant effect of endothelium is characterised by increased procoagulant factors (increased plasminogen activator inhibitor-1 and von Willebrand factor) and reduced anticoagulant factors. It follows then that a diverse group of toxins act on a variety of cell types to provoke OS, inflammation, vascular smooth vessel proliferation and constriction, ED, and coagulation, which account for some of the manifestations of the uraemic syndrome that include hypertension and accelerated atherosclerosis.[25] Regulation of vascular tone is also impaired, with decreased endothelium-dependent vasodilatation. CKD also induces OS and inflammation in endothelial cells and production of reactive oxygen species in cultured endothelial cells by the protein-bound uraemic toxin indoxyl sulphate.

The Endothelium and Haematological Alterations

An important intermediary in the continued activation of endothelial cells is the interaction of the endothelium with platelets. The activation of glycoprotein IIb/IIIa on the surface of platelets induces the expression of factors such as P-selectin that promote activation of the endothelium.[26] EPCs contribute to the repair and structural maintenance of the vascular system. From Stage 1 CKD, a decrease in EPC number and function (hampered adherence, reduced endothelial outgrowth potential, and reduced antithrombogenic function) is observed. This alteration, which may hinder vascular repair and add to the CVD risk, becomes more significant with CKD progression.[27]

Endothelial microparticles (EMPs) may be a reliable marker of subclinical atherosclerosis and arterial stiffness. In children on peritoneal dialysis, lower levels of EMPs and more favourable CV indices were observed when compared with patients on haemodialysis (HD). In these studies, blood pressure (BP) was the most important risk factor for atherosclerosis, and EMPs and BP the most important predictors for arterial stiffness.[3]

Compared with erythropoietin-naïve patients, anaemic patients treated with erythropoietin display increased levels for IL-6 and IL-8, CRP, and TNF-α. Long-term administration of erythropoietin has been associated with decreased levels of

TNF-α in dialysis patients, but also with enhanced inflammation and ischaemia-induced neovascularisation via increased mobilisation of EPCs.[28] Furthermore, erythropoietin activates vascular smooth muscle cells, endothelium, and platelets, thus enhancing thrombogenicity and causing a loss of vasodilatory potential. In addition, this could be one explanation for the observation of an increased risk for all-cause and CV mortality in patients with higher haemoglobin levels targeted with higher doses of erythropoiesis-stimulating agents.[29]

The Endothelium and Protein-Energy Wasting

There has been an increase in understanding of the mechanisms causing syndromes of wasting, malnutrition, and inflammation, as well as their interrelationships in individuals with CKD. Approximately 18-75% of patients on chronic dialysis show evidence of wasting.[16] This phenomenon has been referred to as uraemic malnutrition, cachexia, and malnutrition–inflammation atherosclerosis syndrome. In CKD, there are conditions resulting in loss of lean body mass not related to reduced nutrient intake and due to nonspecific inflammatory processes, intercurrent catabolic illnesses, nutrient losses into dialysate, and anaemia or its treatment.[30] Among the number of disorders that can cause wasting in patients with CKD, inflammation, OS, acidaemia, nutrient losses into dialysate, anaemia, hyperparathyroidism, and retention of uraemic toxins interplay, which, as shown in previous sections, causes ED leading to atherogenesis and CVD. Elevated CV and haemodynamic markers of disease and endothelial stress, such as pro-brain natriuretic peptide or troponin T, are associated with wasting and inflammation in dialysis patients.[31]

The Endothelium and Vascular Calcification

Vascular calcification is responsible for the higher prevalence of CVD in dialysis patients. Consequently, its early detection is truly relevant in this population. Vascular calcification has been historically classified as i) intima calcification associated with atheroma plaques, or ii) medial calcification associated with CKD and disturbances in the metabolism of calcium, phosphorus, and vitamin D (VD). Age, dialysis, past medical history of CVD, atherosclerosis, and inflammation are variables significantly influencing calcification.[32] Recently, the term ossification rather than calcification of both the arterial intima and media has been proposed for kidney patients.[15] The presence of artery ossification is associated with functional estimates of arterial dysfunction, such as NO-dependent vasodilatation in dialysis patients and pulse-wave velocity.[33] Vascular ossification should be considered as a CV risk marker and not an aetiological factor of CVD in CKD.[15] Serum levels of calcium and phosphorus have become established risk markers.[34,35] Hyperparathyroidism has also been suggested as a risk factor for and a marker of vascular ossification,[35] and VD deficiency is associated with increased early mortality. The best-studied inhibitor of vascular ossification is fetuin-A, the major carrier of calcium ions in the circulation. Only in CKD Stage 5 are low levels of fetuin-A associated with adverse CV outcomes.[36] The ossification regulators matrix Gla-protein, bone morphogenic proteins, osteopontin, and osteoprotegerin promote an early and extensive vascular ossification process, and have been shown to interfere with EF by decreasing NO production and altering the normal anatomy of the vessel wall, rendering the endothelial surface prone to calcium deposition, prothrombotic events, and a more rigid vessel wall.[37]

Endothelium in Diabetics

Diabetic nephropathy is the leading cause of ESRD. Diabetes mellitus is characterised by generalised ED. However, recent data also emphasise the role of local renal ED in the pathogenesis of diabetic nephropathy. Hyperglycaemia triggers a complex network of signal-transduction molecules, transcription factors, and mediators that culminate in ED.[38] In the glomerulus, vascular endothelial growth factor (VEGF)-A-induced neoangiogenesis may contribute to the initial hyperfiltration and microalbuminuria due to increased filtration area and immaturity of the neovessels, respectively. However, a subsequent decrease in the number of podocytes decreases VEGF production resulting in capillary rarefaction and decreased glomerular filtration rate (GFR). Decreased NO availability also plays a significant role in the development of advanced lesions of diabetic nephropathy through disruption of glomerular autoregulation, uncontrolled VEGF action, release of prothrombotic substances by endothelial cells, and angiotensin II-independent aldosterone production.[39] In addition, disturbances in the endothelial glycocalyx contribute to decreased

permselectivity and microalbuminuria, whereas there is recent evidence that reduced glomerular fenestral endothelium leads to decreased GFR levels. Endothelial repair mechanisms are also impaired in diabetes since the number of circulating EPCs is decreased in diabetic patients with microalbuminuria. Finally, and in the context of elevated profibrotic cytokine transforming growth factor-β levels, endothelial cells also contribute to the detrimental process of fibrosis in advanced diabetic nephropathy through endothelial-to-mesenchymal transition.

THE ENDOTHELIUM AND RENAL REPLACEMENT THERAPY

The role of residual renal function (RRF) in the elimination of excess pro-inflammatory molecules has not generated much attention, and it seems that RRF protects dialysis patients from the excess of pro-inflammatory molecules.[40] Effectively, the changes in endothelial damage and function markers caused by inflammation are more severe in those with less RRF. Volume overhydration is independently associated with worse ED in peritoneal dialysis (PD) patients. In addition, normalised extracellular water together with the product of phosphate times calcium and dialysis vintage were independent determinants of flow-mediated dilatation in PD patients, suggesting that ED might link volume overhydration and CV events in dialysis patients.[41]

A number of studies have reported that PD is associated with lower levels of OS and inflammation when compared with HD. However, an association with vascular or myocardial structure and function could not be established. Some studies have shown that PD is associated with a lower mortality than HD in the first 1-2 years, but thereafter it may actually be higher in PD than in HD.[42] In PD patients, inflammation induces ED as estimated by elevation of endothelial damage markers. In addition, pro-inflammatory cytokines are associated with elevations in pro-coagulable and pro-atherosclerotic mediators in plasma.[40] PD patients without known atherosclerosis show ED and their advanced oxidation protein product (AOPP) levels independently predict EF level.[43] Acute inflammation assessed by high-sensitivity CRP is associated with a temporary increase in peritoneal solute transport rate, as determined by the peritoneal equilibration test in PD patients. This may be caused by intraperitoneal inflammation through the IL-6 system or AOPP.[44]

EF was shown to be better in transplanted patients than in dialysis patients. However, despite correction of uraemia after renal transplantation, substantial ED, structural alterations of the arterial wall, and disturbed mechanical vessel-wall properties persist.[43] ED is more prominent among patients with failed transplants, which are usually complicated by inflammation, suggesting that the failed allograft may be responsible for this abnormality.[45]

New Biomarkers of Endothelial Dysfunction

Alterations in mineral metabolism may play a major role in deranged EF in patients with ESRD because changes in 25-hydroxy (25-OH) VD, serum phosphate, and fibroblast growth factor 23 levels brought about by restored renal function after kidney transplantation correlate with improved endothelium-dependent vasodilatation.[46,47] Cross-sectional studies associated 25-OH VD, 1,25-dihydroxy (1,25-$[OH]_2$) VD, and endothelium-dependent vasodilatation with Stage 3-4 CKD[48] as well as those with ESRD, suggesting that VD insufficiency or deficiency may have adverse effects on the vascular system. Paricalcitol is a synthetic analogue of 1,25-$(OH)_2$ VD endowed with several actions impinging on vascular function. VD receptor activation by this compound ameliorates endothelium-dependent vasodilatation in subtotally nephrectomised rats, an effect which is completely independent of BP and parathormone levels.[49]

As improvement in ED preludes regression of atherosclerosis in primates and signals a reduction in the risk of CV events, the findings in Zoccali's study[50] represent evidence that paricalcitol favourably affects a biological phenomenon of major relevance for atherosclerosis in humans, and add new experimental evidence in support of the hypothesis that VD may exert favourable effects on the CV system in patients with CKD.[50]

Over the last decade the biological interference of uric acid with the CV system and the kidney has been intensively investigated, and several experimental studies in animal models and *in vitro* documented that hyperuricaemia may trigger hypertension and incite ED, vascular damage, and renal disease.[51] A substantial proportion of epidemiological studies are compatible with the hypothesis that hyperuricaemia may be noxious

to both the CV system and the kidney.[52] However, there are still no well-powered trials testing whether uric acid-lowering interventions may reduce BP or attenuate the risk of adverse CV and renal outcomes.[53] Evidence still remains largely insufficient to recommend changes in the current policy of not prescribing uric acid-lowering drugs to individuals with asymptomatic hyperuricaemia.

CONCLUSION

The endothelium plays a major role in vascular tone and metabolic pathways. ED is the first, yet potentially reversible step in the development of atherosclerosis, and its severity has prognostic value for CV events. Therefore, evaluation of ED may have major clinical diagnostic and therapeutic implications. In patients with CKD, many risk factors are strongly interrelated and play a major role in the initiation and progression of vascular complications, leading to the high mortality rate attributable to CVD. Even initial CKD should result in intensive prevention of CV risk since risk of death due to CVD is much higher than that from ESRD.

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