In the phase 3 ALLURE trial, the selective T-cell co-stimulation modulator abatacept was not superior to placebo on the primary study endpoint of complete response at one year in patients with active proliferative class III or IV lupus nephritis. However, compared with placebo, treatment with abatacept resulted in more rapid improvement in proteinuria. ALLURE was a randomized, multicenter, double-blind study with an open-ended, blinded, long-term extension. The trial – the largest ever in lupus nephritis – included 405 patients (baseline mean age 33 years, UPCR 3.78 g/g, serum creatinine 0.93 mg/dl and GFR 95 ml/min). Patients were randomized to either placebo or intravenous abatacept 30 mg/kg for three months, followed by ~10 mg/kg every four weeks. All patients received mycopheno-
late and glucocorticoids. David Jayne (Cambridge, United Kingdom) reported that after one year’s treatment, 35.1% of abatacept patients and 33.5% of placebo patients achieved complete remission (p = 0.75). However, sustained complete remission occurred earlier and more frequently in abatacept-treated patients. These benefits resulted from improved proteinuria that was seen as early as three months and was driven by a rapid effect on urine protein concentration. Abatacept had no negative effect on renal function. Consistent with previous studies, major differences were seen in the effects of abatacept compared to placebo on immune markers, specifically anti-double stranded DNA antibodies and complement levels, confirming the predicted influence of abatacept on lupus biology. There was a trend to more infections with abatacept, which was consistent with the drug’s known safety profile. Serious adverse effects were lower with abatacept than with placebo (6% versus 13%). "Despite failing to achieve its primary endpoints the ALLURE trial has set a new standard in the design of lupus nephritis trials through its size and duration, and has observed differences in key disease-related markers,” concluded David Jayne.
In the PEXIVA trial, compared to standard-dose glucocorticoids, treatment with a reduced dose resulted in fewer serious infections and did not substantially increase the risk of death or end-stage renal disease in severe ANCA-associated vasculitis (AAV). Plasma exchange did not reduce the risk of death or end-stage renal disease in these patients. PEXIVAS was a multicenter, international, open-label, randomized controlled trial with a 2 × 2 factorial design and including 702 patients with severe AAV. The aim was to separately evaluate the efficacy and safety of plasma exchange and two different regimens of oral glucocorticoids. The patients were randomly assigned to seven treatments of plasma exchange and two different regimens of glucocorticoids. All patients were treated with immunosuppression. Patients were followed up to seven years for the primary composite outcome of death from any cause or end-stage renal disease. The primary composite outcome, death from any cause or end-stage renal disease, occurred in 28% of patients receiving plasma exchange compared to 31% in the no-plasma-exchange group (hazard ratio 0.86, 95% CI 0.65–1.13; p = 0.27). The primary outcome occurred in 28% of patients in the reduced glucocorticoid group and 26% in the standard glucocorticoid group (absolute risk difference 2.3%, 90% CI –3.4% to 8.0%), meeting the non-inferiority hypothesis. Serious infections in the first year occurred less often in the reduced glucocorticoid group compared to the standard group (incidence rate ratio 0.70, 95% CI 0.52–0.94; p = 0.02). The investigators concluded that in the largest ever trial in AAV, a reduced dose of glucocorticoids was non-inferior to a standard dose and resulted in fewer serious infections. However, infection rates remained high, and further research is needed.

In the phase 3 ALLURE trial, the selective T-cell co-stimulation modulator abatacept was not superior to placebo on the primary study endpoint of complete response at one year in patients with active proliferative class III or IV lupus nephritis. However, compared with placebo, treatment with abatacept resulted in more rapid improvement in proteinuria. ALLURE was a randomized, multicenter, double-blind study with an open-ended, blinded, long-term extension. The trial – the largest ever in lupus nephritis – included 405 patients (baseline mean age 33 years, UPCR 3.78 g/g, serum creatinine 0.93 mg/dl and GFR 95 ml/ min). Patients were randomized to either placebo or intravenous abatacept 30 mg/kg for three months, followed by 10 mg/kg every four weeks. All patients received mycophenolate and glucocorticoids. David Jayne (Cambridge, United Kingdom) reported that after one year’s treatment, 35.1% of abatacept patients and 33.5% of placebo patients achieved complete remission (p = 0.73). However, sustained complete remission occurred earlier and more frequently in abatacept-treated patients. These benefits resulted from improved proteinuria that was seen as early as three months and was driven by a rapid effect on urine protein concentration. Abatacept had no negative effect on renal function. Consistent with previous studies, major differences were seen in the effects of abatacept compared to placebo on immune markers, specifically anti-double stranded DNA antibodies and complement levels, confirming the predicted influence of abatacept on lupus biology. There was a trend to more infections with abatacept, which was consistent with the drug’s known safety profile. Serious adverse effects were lower with abatacept than with placebo (6% versus 13%). “Despite failing to achieve its primary endpoints the ALLURE trial has set a new standard in the design of lupus nephritis trials through its size and duration, and has observed differences in key disease-related markers,” concluded David Jayne.
Treatment with the somatostatin analog lanreotide did not improve rate of eGFR loss in the DPCAKI trial in patients with late-stage autosomal dominant polycystic kidney disease (ADPKD). Lanreotide was also associated with an increased incidence of adverse events, predominantly injection site related, gastrointestinal, and hepatic cyst infections.

Ferric citrate improved multiple aspects of abnormal mineral metabolism and raised hemoglobin in patients with advanced autosomal dominant polycystic kidney disease (CKD), regardless of their baseline serum phosphate, hemoglobin or iron sufficiency. Furthermore, in the ferric citrate group, time to renal replacement therapy (RRT) or death was significantly longer in AKD patients compared to those treated with standard care. The ERA-EDTA is the first medical association to try and implement ‘greener’ health care as suggested by the Step-Stop-IgAN trial, urinary DKK3 concentrations were significantly associated with CKD progression, and significantly improved prediction of loss of eGFR as compared to eGFR or albuminuria alone. Urinary DKK3 > 4,000 pg/mg creatinine and > 1,000 pg/mg creatinine were associated with a mean annual eGFR decline of 2.4 % (95 % CI: –4.6 to –0.2 %; p = 0.007) and 7.6 % (95 % CI: –10.9 to –4.2 %; p < 0.001), respectively, which was independent of eGFR and albuminuria. In the STOP-IgAN trial, urinary DKK3 > 1,000 pg/mg creatinine was independently associated with a mean eGFR decline of 12.2 % (95 % CI: –16.9 to –7.4 %; p = 0.003) during the six-month run-in phase (n = 96). In the subsequent first six months of the treatment phase (n = 57), a rise in urinary DKK3 concentration was associated with a significant (p = 0.001) eGFR decline, whereas stable or decreasing urinary DKK3 indicated a more favorable course. This result was independent of randomization to the intervention arms.

How does the ERA-EDTA contribute to a more environmentally friendly healthcare sector? First step is to create awareness with its members of the challenges that we are facing in patient care, research and education. Two examples from the field of nephrology are dialysis and self and home care. Hemodialysis is very energy-consuming, uses large quantities of water (usually at least 120 liters per patient per session, which is heated up to 37 °C and is thereafter discarded), and creates substantial waste. Various dialysis industries have already launched initiatives in this respect. The ERA-EDTA is open to collaboration with industries to boost these initiatives. A second example is the implementation of e-health, promoting self and home care on a much larger scale in nephrology, reducing the need for patients to come to the hospital. The ERA-EDTA will function as a platform for end-users and industries to support these initiatives.

Another key word is ‘sustainable healthcare education’. ‘We need to design new educational tools and programs using modern technologies to prepare our students and doctors for the health care of the future. This way, we hope to reduce the nephrologists’ carbon footprint’, explains Monica Fontana, ERA-EDTA’s executive manager.

The ERA-EDTA is the leading society in Europe for physicians working in the field of care for patients with kidney disease. The organization traditionally focuses on a broad range of activities aimed at improving the quality of patient care. Economic issues have not been on the agenda until now. The ERA-EDTA is the first medical association to try and implement ‘greener’ health care as suggested by the ‘Lancet Countdown’ group, a collaboration among 24 academic institutions and intergovernmental organizations, which tracks progress on health and climate change and provides an independent assessment of the health effects of climate change and the actions that are developed to stop it [1].

The relation between health care and the environment/climate change is bi-directional. Not only does a polluted environment cause various diseases, but also the converse: at the global level, the health care sector also has a clear negative impact on the environment, explains Professor Peter Blankesjön, who has just published an editorial on this issue in Nephrology, Dialysis, Transplantation (NDT) [2]. This is in conflict with the guiding principle for all physicians of primum non nocere, meaning ‘first, do no harm’. According to Blankesjön: ‘The health profession not only has the ability but also the responsibility to act as public health advocates by communicating the threats and opportunities to the public and policy makers and ensuring climate change is understood as being central in human well-being. Therefore, every doctor needs to contribute to the development and implementation of ‘greener’ health care.’

References

01. Watts N et al. The Lancet Countdown on health and climate change: from 25 years of inaction to a global transformation for public health. Lancet 2018; 393: S51-630
02. Blankesjön P, Peter et al. ERA-EDTA invests in transformation to greener healthcare. Nephrol Dial Transplant 2018; published online on 25 May
Nephrology reaches beyond!

We have asked the five medical disciplines which are closest to nephrology, if and how kidney diseases impact their specialty.

**Diabetes**

Professor Sally Marshall, European Foundation for the Study of Diabetes

“Diabetes is the single most common cause worldwide of kidney failure requiring dialysis. At present I am the President of the European Diabetic Nephropathy Study Group, in which professionals from diabetology and nephrology work closely together. The aim is to assemble researchers from different backgrounds who are interested in diabetic renal disease in order to study the epidemiology, pathology, pathophysiology and treatment of this complication of diabetes mellitus. The present projects range from genetics studies about diabetes and diabetic kidney disease to treatment studies. The ultimate goal is to prevent kidney disease in patients with diabetes.”

**Hypertension**

Professor Konstantinos P. Tsiofis, President of the European Society of Hypertension

“It is well established that there is a bidirectional cause-effect relationship between hypertension and chronic kidney disease. Prevalence of hypertension among patients with chronic disease is almost 87%. CKD is also a serious and unexpected decline in GFR in our patients, meaning every 3–6 months, – and we change the doses of our drugs or apply other therapeutics if the kidneys are involved. We usually do this with a nephrologist.”

**Cardiology**

Professor Giovanni de Simone, Vice Chair, Council on Hypertension of the European Society of Cardiology

“There is a tremendous link between nephrology and cardiology, of course. From the physiological point of view, the two systems – the cardiac and the renal system – are closely related, with one impacting the other. For example, heart function has an enormous impact on renal blood flow. Conversely, the kidneys influence blood pressure and thus indirectly the workload of the heart, via RAAS. But this is only one example of the overlap between the two systems. Heart failure is another condition involving reciprocity kidney and heart, leading to the so-called renal-cardiac/cadio-renal syndrome. Nephrologists and cardiologists cannot ignore this pathophysiological interrelationship, especially since the treatment of one organ always impacts the other. In our clinic, we work closely with nephrologists in the management of our heart failure patients. Of course, cardiologists and nephrologists need to have a certain understanding of the other discipline, too, but I think there should be a ‘culture’ of talking to each other, collaborating and pooling expert knowledge. In certain situations, the involvement of a nephrologist is essential, e.g. in severe deterioration of kidney functions in our heart failure patients or when we need ultrafiltration in our patients with decompensated heart failure and cardiacorenal syndrome.”

**Rheumatology**

Professor Robert Landewe, European League Against Rheumatism

“The involvement of the kidneys has a very important prognostic value in patients with rheumatic diseases: If the kidneys are affected, the patient has a poorer prognosis with regard to quality of life as well as survival. Therefore, we monitor kidney function closely in our patients, meaning every 3–6 months, – and we change the doses of our drugs or apply other therapeutics if the kidneys are involved. Of course, rheumatologists are doctors for internal medicine and as such they know about CKD, but they are very aware of the fact that in the event of renal problems arising, or in the case of proteinuria in our patients, rapid intervention is imperative and may improve the prognosis of patients. So whenever there is a serious and unexpected decline in GFR or a rise in creatinine, we are used to bringing in a nephrologist. Besides, there is often an overlap in the pathogenesis of rheumatologic and nephrologic diseases, so joint research is often far more efficient. Many joint studies, e.g. on lupus erythematosus (SLE), lupus nephritis or ANCA-associated vasculitis have been initiated. In Horizon 2020, some calls aim at the identification of joint pathways, and the projects involve rheumatologists, nephrologists as well as scientists from other disciplines.”

**General practice/family medicine**

Professor Amanda Howe, President of the World Organization of Family Doctors

“To involve a kidney function check in general health assessments is important, because in the early stages of chronic kidney disease many people do not have symptoms. So we see what appears to be a healthy person and the only way we know that they may have a problem with their kidneys is when it shows in the blood test. But what we have to debate about is whom to test and at what age and what stage to perform the test. We should be thinking if there are any risks, have there been any previous problems, even as a child? Or does the patient have another condition like diabetes or hypertension, that might, particularly, increase the risk of developing renal problems? This selection is important, because as general practitioners we do not want to “over-medicalise” people’s lives and perform tests which are not necessary. But on the other hand, we do not want to be too late in diagnosing CKD. Therefore, in many countries nephrologists, in collaboration with family doctors, have developed sensible screening guidance.”

**Cardiovascular Disease**

Professor Robert Landewe, European League Against Rheumatism

“Of course, rheumatologists are doctors for internal medicine and as such they know about CKD, but they are very aware of the fact that in the event of renal problems arising, or in the case of proteinuria in our patients, rapid intervention is imperative and may improve the prognosis of patients. So whenever there is a serious and unexpected decline in GFR or a rise in creatinine, we are used to bringing in a nephrologist. Besides, there is often an overlap in the pathogenesis of rheumatologic and nephrologic diseases, so joint research is often far more efficient. Many joint studies, e.g. on lupus erythematosus (SLE), lupus nephritis or ANCA-associated vasculitis have been initiated. In Horizon 2020, some calls aim at the identification of joint pathways, and the projects involve rheumatologists, nephrologists as well as scientists from other disciplines.”

**Association**

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Research

It is time to take action to eliminate HCV
Hepatitis C virus in CKD/ESRD: challenges and opportunities

The recent availability of direct-acting antiviral agents (DAAs) able to cure hepatitis C virus (HCV) infection in >95% of patients, not only in the general population but also in chronic kidney disease stage 4 and 5, including dialysis patients, is a major breakthrough. Yet translating this breakthrough into lower morbidity and mortality in this vulnerable population entails a number of challenges.

Firstly, in order to be treated, HCV infection should be diagnosed. Whereas hemodialysis (HD) patients are regularly screened for HCV in many countries, much remains to be done to screen every chronic kidney disease (CKD) patient at least once! The reasons for doing so include the potential role of HCV in the progression of chronic kidney disease in patients with chronic kidney disease (CKD) and the high risk of hepatic complications in the dialysis population. Although controversial, the concept that even the metabolic shutdown of epithelial cells and tubular necrosis in proportions that have clinical consequences (DDG) if the cold ischemia time is sustained (the threshold of 18 hours has been found to be highly relevant). In a recent analysis of a large European cohort of kidney recipients, the anastomosis time, considered as warm ischemia, has been found to be another determinant of long-term graft fibrosis and function.

Progression from AKI to CKD

Although controversial, the concept that even a resolving episode of AKI is a strong risk factor for subsequent chronic kidney disease (CKD) has been confirmed in native kidneys as well as in renal grafts. Here again, cold and warm ischemia may induce epithelial and endothelial lesions that will apparently heal in a matter of days. These lesions, however, may be followed by a reprogramming of cells that will accelerate graft fibrogenesis in the following months or years, and hence impair renal function. Furthermore, danger signals that are expressed during AKI of renal grafts, and the inflammation that characterizes acute tubular necrosis, may potentiate allo-immune recognition and thereby contribute to humoral rejection and graft failure.

Perspectives

Shortening cold ischemia time has already been successfully achieved in the last decade. Reducing the anastomosis time is a new challenge, requiring greater professionalization of surgical procedures. Whether the grafts should be stored static or under perfusion, with or without oxygen carriers, and at a cold temperature or in normothermic conditions, are major points to consider in order to reduce DGF and, more importantly, AKI of renal grafts. The mechanisms at stake in the reprogramming of renal cells subjected to an ischemic injury are another potential target: the metabolic shutdown of epithelial cells and the epigenetic impact of AKI are currently under close scrutiny and will hopefully lead to the development of drugs that will halt graft fibrogenesis. To what extent the immune system will be modulated (positively or otherwise) by the manipulation of these molecular events is undoubtedly key.

JADOUR MICHEL

Brussels, Belgium

SVERRE E. KJELDOSEN

Oslo, Norway

Looking for optimal target blood pressure: What are the implications of the recent trials?

Recent studies have led to renewed attention on blood pressure (BP) treatment targets, and the debate on whether an aggressive or a conservative approach is most favorable is yet again under scrutiny. In the aftermath of the publication of the Systolic Blood Pressure Intervention Trial (SPRINT) study in the fall of 2015, the tendency towards more aggressive BP control has grown stronger. The results of SPRINT (specified target BP of 120/80 mmHg in high-risk hypertensive patients) gained widespread attention upon its publication, both within the academic community and in the tabloid press, but the SPRINT results have also met considerable criticism. The main criticism of SPRINT is based on the study’s method of unob- served BP measurement and the primary endpoint being driven by the ‘soft’ endpoint of ‘heart failure’ in a trial with a major difference in ‘heart failure-protecting antihyper- tension drugs’ between the two randomized arms. Still, latest American guidelines (recently published) lowered the recommend-
We have reasonable parameters for kidney disease, with no clinical or laboratory evidence of compromised glomerular filtration rate, hypertension or proteinuria in adolescence, was associated with a significantly increased risk of ESRD in adulthood (HR 4.19, 95% CI 3.52–4.99)."

The study results suggest that even a subclinical degree of kidney parenchymal injury secondary to childhood kidney conditions can lead to enhanced susceptibility to future CKD. These findings are clinically relevant in the current global CKD epidemic, as the care of patients with CKD is also aimed at identifying at-risk individuals and asymptomatic patients in early disease stages, in order to initiate timely treatments and preventive measures that can mitigate prognosis.

"Our study highlights mild childhood kidney diseases as a newly appreciated risk factor for future CKD," concludes Dr Vivante. ▶

References

S 2.2 Paediatric nephrology Saturday, 08.00–09.30, C1-M1-2

Acute kidney injury in disasters – How can we prevent deaths from crush syndrome-related AKI?

Disasters are very heterogeneous and, in parallel with this heterogeneity, the spectrum of acute kidney injury (AKI) during disasters shows wide variation. The vast majority of these cases are not specific i.e. not directly related to the disaster. For example, any injured disaster victim may suffer from excessive bleeding, which may result in hypovolemic shock and prerenal AKI similar to injuries in routine daily practice. Postrenal AKI may also develop, as a consequence of supravesical or intravesical obstruction due to pelvic trauma. Last, but not least, intrarenal AKI (both ischemic and toxic) are frequent in these patients because of prolonged shock, sepsis, frequent usage of nephrotoxic agents and blood transfusions. Since over all management of these ‘non-disaster specific’ AKIs do not differ significantly from routine daily practice, I will not focus on these cases.

Crush syndrome (CS)-related AKI, however, quite unique to disasters. This pathology results in renal hypoperfusion, which is unique, I will focus on CS.

CS may be defined as systemic manifestations of traumatic rhabdomyolysis. Its incidence varies between 2% and 3% of all casualties, and it is the second most frequent cause of death after asphyxia. Mortality figures are around 15–20%, while this figure has been reported up to 40% in some series. The pathogenesis of CS-related AKI is complex. The most important mechanism is volume depletion due to development of traumatic rhabdomyolysis-induced compartment syndrome. This pathology results in renal hypoperfusion, ischemic damage and acute tubular necrosis.

Clinical features of crush-related AKI can be classified as: (1) local findings in the traumatized muscles, (which include pain, pressure, paresthesia, paresis or paralysis, pallor and paresthesia), and (2) systemic manifestations (which include, but are not limited to, hypovolemic shock, AKI, respiratory failure, fluid-electrolyte/acid-base disturbances and heart failure).

On laboratory examination, there is a dirty-brown discolouration of the urine. Abnormal findings in the blood chemistry are related to increased serum levels of substances (e.g. muscle enzymes, urea and creatinine) released from the injured muscles. However, the most important laboratory finding is hyperkalemia, which is a main cause of death in many patients.

Treatment of crush victims is complex. Since volume depletion is of primary importance in pathogenesis, the most useful therapeutic intervention is giving IV fluids at the earliest occasion. Although, bicarbonate-hypotonic saline is the ideal fluid, it cannot be easily found in chaotic disaster circumstances. Therefore, most frequently isotonic saline is used for volume resuscitation. There are inconsistent reports about the efficacy of mannitol in traumatic rhabdomyolysis patients. Treatment should be initiated as soon as possible, ideally even when the victims are still buried under the rubble. Before rescue, an infusion rate of 1 L/hr is appropriate in most victims. Fluids should be continued both during and after extrication, and overall 3–6 L of fluids are given initially taking into consideration many variables. Afterwards, the volume of fluids should be decided based on urine response; according to some reports this volume may be as high as 20 L/day.

Since crush-related AKI is a highly catastrophic disorder, dialysis is frequently needed. All dialysis modalities have both medical and logistic advantages and drawbacks; however, intermittent hemodialysis is the most commonly applied treatment.

When treating disaster crush victims, there is a shortage of medical material and personnel, and also because of overwhelming chaos there are several logistic difficulties. Despite all these drawbacks, however, deaths due to crush-related AKI can be reduced by appropriate medical and logistic management. ▶

S 8.1 Hot topics in hypertension Saturday, 08.00–09.30, Hall A1

Acute kidney injury in various circumstances Saturday, 08.00–09.30, Auditorium 15
Factors affecting adherence in CKD Patients’ perspectives on taking their medication

In this presentation I will first introduce the concept of adherence and how it is measured. One widely used definition of adherence to medications is: the process by which patients take their medications as prescribed, composed of initiation, implementation and discontinuation.

Research on non-adherence (or non-compliance as the concept is also known) has been ongoing for a number of decades, but the problem has not yet been solved in spite of much effort. The prevalence of non-adherence to medications ranges from 20% to 80% and is highest with groups of medications that are meant for prevention (such as statins, 50–80%), and chronic disease treatment (30–60%), and lowest in acute disease treatment (20–40%).

Needless to say, the clinical and economic implications of non-adherence are tremendous.

Non-adherence has been shown to increase the risk of all-cause mortality by 50% for patients on beta-blockers, 85% for those using statins, and 74% for those using ACE-inhibitors. Economic implications can be seen in a new US study from 2018 on the impact of adherence to chronic disease medications on health service utilization.[1] This study found that full adherence was associated with 8–26% fewer hospitalizations and 3–12% fewer emergency department visits among those with congestive heart failure, hypertension, diabetes, and schizophrenia/bipolar. No studies of the impact of non-adherence have been done directly on chronic kidney disease (CKD) patients, but one can assume that the implications of non-adherence are not smaller for them than for other patients.

We have been working on understanding the CKD patients’ perspective on cardiovascular medications in collaboration with Rigshospitalet in Copenhagen. I will present what is known about how patients think about their antihypertensive medications by comparing CKD patients with patients who do not have CKD. We have also conducted a qualitative interview study to prepare to improve adherence in this patient group.

In order to intervene it is also useful to build upon behavioral models that can explain and increasing the patient’s knowledge about the disease and the importance of the medication.

I will end the presentation with a few take-home messages about CKD patients’ perspectives and how these can be interfaced with general knowledge about non-adherence. I hope this information is helpful for nephrologists and clinicians who prescribe medications for CKD patients.

References

1. O’Reeuck MC, Koestner RJ, Dougherty JS. Impact of medication adherence on health services utilization in Medicaid. Med Care 2018;56:266–273

What is the role of CRRT in the intensive care unit? Questions remain about continuous renal replacement therapy in critical illness

Acute kidney injury (AKI) occurs in up to 25% of patients in the intensive care unit (ICU), and approximately a 6% will require renal replacement therapy (RRT) during their ICU stay. Sepsis and septic shock is present in about 50% of ICU patients requiring RRT, and mortality approaches 80% in these cases. Once a patient requires RRT, several options can be considered: intermittent hemodialysis (IHD) (conventional and sustained low-efficient dialysis) and continuous RRT (CRRT).

Initially, in the late 1970s, continuous RRT was developed for those critically ill patients (around 10%) who could not tolerate intermittent techniques because of hemodynamic instability. In the past three decades, CRRT has become a routine technique for critically ill patients, with specialized monitors that combine ease of use and control by ICU nurses and staff, as well as safety for the patient, and in some parts of the world it has now become the leading form of RRT in the ICU.

However, evidence about advantages of CRRT over IHD regarding mortality, length of ICU stay, recovery of kidney function and even hemodynamic tolerance is still lacking, since the few clinical trials comparing both techniques have demonstrated their equivalence.

In spite of this, CRRT has its role in the support of ICU patients with AKI, because of its perceived clinical advantages: adequate fluid balance with continuous control, and better hemodynamic stability during fluid removal. Therefore, it is recommended for patients with hemodynamic instability, fluid overload, catabolism, or sepsis with AKI.

CRRT can be offered as a purely diffusive technique (continuous hemodialysis) with preferential removal of small molecules, a convective technique (continuous hemofiltration) with additional removal of middle molecules, and as a combination (hemodiafiltration). There are not enough data to recommend one form of CRRT over another, but hemodilution has become the preferred modality in some countries.

With respect to prescription of the technique, there are major issues to be considered. First, there is no clear recommendation about the timing of initiation of RRT; since two recent clinical trials have shown opposite results. However, traditional indications for RRT initiation (hyperkalemia, pulmonary edema) have been replaced by urine output criteria and dynamic evaluation of patient’s condition and response to conservative measures. Second, the currently accepted dose of replacement is set to a minimum of 25 ml/kg/h of effluent (that is, the sum of dialysate and ultrafiltrate), since the RENAL and VAD-NIH studies demonstrated that higher doses did not improve survival. An unanswered question is whether patients need the same dose during the entire time that CRRT is needed, since critical illness is a dynamic process and overdosing may produce complications such as hypophosphatemia, hypokalemia, and hemodynamic instability among others.

Last, but not least, is anticoagulation. Coting of the circuit is the most frequent complication of CRRT and the use of heparin is associated with hemorrhagic complications as well as thrombocytopenia. Regional citrate anticoagulation is devoid of these complications and is the technique recommended by KDIGO. However, as of today, it has not gained full acceptance and heparin still remains the most frequently used anticoagulant.

Finally, since dose or initiation do not seem to affect survival, new developments must be evaluated. CRRT can offer a broad spectrum of advanced technologies (high-cut-off continuous hemodialysis, CRRT coupled to hemoperfusion or plasma-adsorption, bioartificial kidney) that still need to be evaluated in future clinical trials.
Improved survival for children on RRT
But access to treatment and outcomes continue to vary within Europe

Although other patient-related outcomes such as growth, psychosocial development, and quality-of-life are of major importance, prolongation of patient survival may be arguably the most relevant clinical goal. Fortunately, survival in the pediatric end-stage renal disease (ESRD) population has improved substantially over the past decades, especially in the youngest patients.

In European dialysis patients, the five-year mortality risk fell by 12% in children aged over five years and by 36% between 1990 to 2010, with each five-year increment decreasing mortality by 12% in children aged over five years and by 20% in children aged less than five years. At present, the overall five-year survival for pediatric renal replacement therapy (RRT) patients is good, at approximately 90% across high-income countries. Nonetheless, mortality remains at least 30 times higher than in healthy peers.

Over the past years, various (inter)national registries, such as the ESPN/ERA-EDTA, have been instrumental in providing epidemiologic evidence for both patient- and country-level factors affecting survival in this population. First and foremost, patient survival is dependent on access to RRT. As economic welfare is a key determinant of health and access to health services, the provision of chronic RRT is a key determinant of health and access to health services. With permission from Elsevier via Copyright Clearance Center.

References

Figure 1: Crude five-year country mortality rates. Mortality rates that lie within the central grey segment of the plot do not differ significantly from the European average. Countries that fall outside the 95% and 99% control limits are performing either better or worse than the European average.[2] With permission from Elsevier via Copyright Clearance Center.
Albinuria as an endpoint? The debate continues in clinical trials in Nephrology

RON T. GANSEVOORT
Groningen, The Netherlands

Chronic kidney disease is a significant global public health problem, but progression is often slow and there are few specific symptoms until the stage of kidney failure has been reached. There is general agreement that surrogate markers, rather than kidney failure, are needed, to, among others, study whether new drugs slow the progression of kidney disease. The two most widely studied biomarkers are glomerular filtration rate (GFR) and albuminuria—maximizing the information on both is desirable.

Recent work showed strong relationships between change in GFR and kidney failure and mortality in observational studies. Based on analyses from past clinical trials and simulations, it has been proposed that a 30% or 40% decline in GFR would be an acceptable alternative endpoint in clinical trials.

Unfortunately, the application of this endpoint is limited at higher baseline GFR and for agents that cause an ‘acute effect’ on GFR. As such, these alternative endpoints are less applicable in drug development for drugs targeted at earlier stages of kidney disease and for many drugs with potential hemodynamic effects. Strategies to overcome these limitations include assessing change in proteinuria as an earlier marker of kidney disease progression.

Proteinuria occurs earlier in the disease course than a change in GFR in many diseases, and proteinuria is one of the most powerful markers of CKD and its progression, as well as complications, in particular cardiovascular disease. However, use of change in proteinuria as a surrogate endpoint is also limited, because the relationship between change in proteinuria and kidney disease progression has been shown to vary among different causes of kidney disease. In addition, unlike a decrease in GFR, an increase in proteinuria is not necessarily a signpost to kidney failure.

Previous work has examined whether change in proteinuria can be used as a surrogate outcome and/or treatment target for clinical trials, but definitive conclusions have not been reached and recent debate has highlighted significant controversy.[2,3]

For these reasons it was felt that a scientific workshop focused on reviewing the available data related to changes in proteinuria was important, timely and likely to make progress. This workshop was organized in March 2018 by representatives of the United States National Kidney Foundation, the Food and Drug Administration, the European Medicines Agency, industry, and academia.

During this presentation, I will review some of the topics that were discussed during this workshop, including: Pathophysiological mechanisms by which proteinuria causes kidney damage and may be an appropriate target of therapy; Associations of treatment effects on early change in proteinuria with later treatment effects on established endpoints in clinical trials; The consistency of these associations across subgroups.

References


S 4.6 Focus on surrogate endpoints in Nephrology
Saturday, 15.00–16.30, Auditorium 10-11-12

Should ADPKD patients drink more water? Low-osmolar diet and adjusted water intake in ADPKD

ALBERT C. M. ONG
Sheffield, United Kingdom

Autosomal dominant polycystic kidney disease (ADPKD) is the fourth most common cause of end-stage renal failure, accounting for up to 10% of prevalent patients on renal replacement therapy. Until recently, ADPKD was considered an untreatable disease. Recent data from the REPRISE trial has confirmed earlier results from the TEMPO3/4 study showing that the vasopressin type 2 receptor (V2R) antagonist, tolvaptan, significantly slows the rate of renal function decline (measured as eGFR change from baseline) by ~36%.

These studies confirm preclinical data indicating that genetic or pharmacological inhibition of vasopressin action is beneficial in ADPKD models, and should accelerate the adoption of tolvaptan as part of standard care for ADPKD patients with evidence or risk of rapid disease progression (eGFR slope > 2.5 ml/min/year).

(1) Hypothetical side-effects of tolvaptan may be poorly tolerated and the risk of idiosyncratic liver toxicity requires monthly monitoring. Thus not all patients may choose to take tolvaptan.
Lunch will be provided during this symposium

**Programme**

**13.15** Welcome  
*Professor Tilman Drüeke (France)*

**13.20** Understanding the complexity of CKD-MBD  
*Professor Pieter Evenepoel (Belgium)*

**13.35** Using our understanding of the evolution of SHPT to choose the right target at the right time  
*Professor David Goldsmith (UK)*

**13.50** Balancing theoretical targets with practical considerations for phosphate management  
*Professor Mario Cozzolino (Italy)*

**14.05** Panel discussion and closing remarks  
*Professor Tilman Drüeke (France)*

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A promising alternative would be to suppress plasma arginine vasopressin (AVP) through increased daily fluid intake. In a recessive PKD model (Pck rat), high water intake (3.5-fold increase) for 10 weeks suppressed urinary AVP, reduced cyst burden (by 38%) and improved renal function.[2] So should ADPKD patients be advised to drink more water and would this be effective in slowing the course of disease?

A pilot study of water loading over one week (3L/d) in a small group of ADPKD patients (n = 13) with preserved renal function (mean eGFR 94 ml/min/1.73 m²) was able to achieve reductions in 24-hour urine osmolality to 270 mOsm/L, suggesting full suppression of AVP action.[3] Surprisingly reductions in urinary cAMP (as a surrogate for AVP action) were, however, only observed in a subset of patients and did not correlate with changes in urine volume or osmolality. This could indicate that other cAMP-mobilizing agonists (apart from AVP) may be equally or more active in some patients.

Ultimately, definitive evidence awaits a randomized controlled trial in ADPKD. Indeed, a recent non-randomized study suggested that high water intake might paradoxically enhance disease progression. PREVENT-ADPKD is a current RCT using MRI measured total kidney volume (TKV) as a primary end-point to test whether an increase in individualized fluid intake to reduce urine osmolality to < 270 mOsm/L would be effective over three years in ADPKD patients with stages 1–3 CKD.[4] Of potential relevance, dietary reductions in sodium (80–100 mmol/d) and protein (0.75–1 g/kg/d) will be instituted to reduce obligate urine volumes needed for daily solute clearance and hence total adjusted daily water intake.

What about salt? A post hoc analysis of the HALT studies, where a reduction in dietary sodium (< 100 mmol/d or 2.4 g/d) was instituted as part of the protocol, reported a significant positive correlation between annual TKV slope (Study A) or hazard ratio for a composite renal endpoint (Study B) and average and time-varying urine sodium excretion.[5] The results suggest a causal relationship between sodium intake and kidney growth (independent of blood pressure), confirming an association first observed in the CRISP cohort. Nonetheless, they are surprising given that very modest reductions in daily sodium intake were achieved in both trials (7–14%) – indeed > 80% still had mean 24h urine sodium > 100 mmol/d despite dietary advice.

In the meantime, what should we advise our patients? Based on limited evidence, a pragmatic policy would be to suggest a moderate increase in daily water intake (3L/d) alongside a moderate reduction in daily salt intake (< 100 mmol/d or 2.4 g/d) and protein intake (< 1 g/kg/d). More motivated patients could monitor their urine osmolality regularly to achieve a specific gravity of 1.010 equivalent to a urine osmolality of < 270 mOsm/L. How these dietary changes will influence actual disease progression remain uncertain.

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Clinical consequences of hypervolemia in CKD
Fluid overload is a promising and potentially modifiable risk factor in non-dialysis CKD patients

Spinning the thread of life – Klotho and endocrine FGFs: markers of CKD progression and cardiovascular complications?
**An open question – High convective volume and haemodiafiltration outcomes**

Standard low-flux haemodialysis (IF-HD) is effective in removing low molecular weight (MW) molecules, such as urea and creatinine, but it cannot remove solutes of higher MW like β2-microglobulin and protein-bound molecules; thus, it is not a very efficient detoxification technique compared to healthy kidneys. This may be one of the reasons why HD patient morbidity and mortality are still very high.

Online haemodiafiltration (OL-HDF) is considered the most efficient dialysis technique, as clearance of small solutes, like urea, may be slightly higher, and clearance of middle solutes, like β2-microglobulin, are much higher than in IF-HD. It has been suggested that OL-HDF (particularly if high convective volumes are performed) reduces mortality compared to haemodialysis (HD), possibly due to more effective removal of larger uremic retention solutes. However, despite clear theoretical advantages, to date the evidence that the addition of large convective volumes can improve survival in HD patients is still conflicting.

Only one of the three largest randomized trials was able to demonstrate a positive effect of OL-HDF on patient survival in comparison to those randomized to HD. Interestingly, post-hoc analyses of these studies consistently showed that the patients randomized to OL-HDF, who received the highest convection volumes, had a lower risk of mortality and cardiovascular events than those randomized to HD.

Recently, the HDF Pooling Project Investigators performed a pooled individual patient analysis of four prospective trials and compared tertiles of delivered convection volume with HD. All-cause mortality was also reduced when the convective dose was standardized to body surface area, given the confounding effect of body size (hazard ratio and 95% confidence intervals of 0.74 (0.58–0.93) for those receiving higher convective doses). Standardization by body weight or body mass index gave no significant survival advantage. The largest survival benefit was seen in patients receiving the highest delivered convection volume, i.e. > 231 L/m² body surface area per session. However, other studies did not confirm these conclusions.

An important criticism of the possible role of the rate of fluid replacement on survival is that this relationship may be actually be due to a selection bias, since high convection volumes are only achievable in the healthier patients; i.e. in those with a lower mortality risk. It is true that, even after extensive statistical adjustments, residual confounding always remains. While the pooled individual meta-analysis addressed the selection bias due to informative censoring, the other limitations of the single trials persist and residual confounding still remains. Another point to consider is that the threshold of convection volume above which there is a lower risk of mortality is not uniform across studies.

At present no convincing data are available concerning a positive effect of OL-HDF on survival and morbidity in HD patients. However, post-hoc analyses suggest, although not consistently, that high convection may be crucial for improving patient outcomes. Randomized controlled trials targeting different convection volumes are required to definitively determine a dose–response effect, and whether this may translate into a clinical benefit in everyday clinical practice, considering the lowering risk of selection bias of the patients. These studies should also further clarify the effect of online HDF on survival and morbidity of HD patients, and determine whether high convection volumes are actually a crucial aspect for achieving better outcomes with HDF in comparison to HD, including high flux dialysis, in everyday clinical practice.
A personalized approach to treatment of IgA nephropathy

IgA nephropathy (IgAN) is a common glomerular disease with a variable course that ranges from remission of clinical features, indolent and non-progressive course, to rapid progression and end-stage renal disease (ESRD), mimicking vasculitis. At one extreme, these cases are easily identified by minor urinary and pathology changes or, at the opposite extreme, by severe proteinuria, progressive decrease in renal function and hypertension. However, most patients with IgAN have a progressive disease and 10–30% will reach ESRD by 10 years after diagnosis. Slowly progressive cases have a variable rate of decline in renal function. Hence the diagnosis of IgAN has little significance for the individual patient. Clinicians need a prognosis of the potential progression of the renal disease in each patient so that they can prescribe personalized therapy.

Since the decision about the need for treatment and the choice among various possibilities come after the results of the renal biopsy, much interest has been focused on the identification of pathology features that are associated with risk of progression and are potentially reversible after targeted therapy.

The multicenter VALIGA study, promoted by the Immunonephrology Working Group of the ERA-EDTA, involved 1,147 European patients who were followed up for 4.7 years. In this large cohort, the prognostic value of the lesions identified by the Oxford classification IgAN (the MEST score: mesangial hypercellularity [M], endocapillary hypercellularity [E], segmental glomerulosclerosis [S], and tubular atrophy/interstitial fibrosis [T]), was confirmed. The strongest predictive value was the presence of irreversible, extensive T lesions in > 25% of the renal biopsy tissue (T1 and T2), but data also indicated the value of reversible pathology risk factors.

Interest is now being focused on trying to find the way of selecting therapy, not only on the basis of persistent proteinuria, but also on the activity and reversibility of lesions found at renal biopsy. A critical analysis of multicenter collaborative studies and some important recent reports suggest a possible personalized approach to treatment of patients with IgAN that takes into account the pathology features in addition to the classical clinical risk factors.

To sum up the message of the lecture As demonstrated by the STOP-IgAN randomized controlled trial (RCT), protracted and rigorous supportive care, including blockade of the renin-angiotensin system (RAS) to address blood pressure and proteinuria, and metabolic and lifestyle targets, can be of benefit in one-third of patients with IgAN with proteinuria > 0.75–3.5 g/day and who are at high risk of rapid progression.

Is additional corticosteroid therapy needed? No, when proteinuria is 0.75–1.5 g/day and MEST scores are negative, as shown in a large multicenter study of 200 patients including VALIGA, Oxford and North America collaborative studies. Yes, when IgAN is progressing with rapid loss of GFR or when crescents are present in > 25% of glomeruli, as shown by a collaborative study on 3,000 patients from VALIGA, Chinese and Japanese cohorts. Probably yes, when risk factors are present, with persistent proteinuria > 1 g/day or when proteinuria < 1 g/day with M1 or E1 or S1 with podocytopathy, based on the value of risk factors observed in validation studies in young and adult subjects and in untreated cohorts.

The addition of alkylating agents/antimetabolites to corticosteroids is not indicated in non-vasculitic-like progressive forms, particularly when GFR < 50 ml/min/1.73 min. To apply more aggressive therapies, the rapidity of GFR loss over the previous weeks/months must be considered, taking into consideration active and potentially progressive pathology lesions.

The addition of corticosteroids to supportive care induces reduction in proteinuria and possible renal-protective effects in the long term, with an increase in adverse events, which mostly occurs in patients with impaired renal function. Systemic exposure to corticosteroids and their adverse events may be avoided or greatly limited by using the target-eluted, enteric formulation of budesonide, which acts on the intestinal immune system highly expressed at the Peyser’s patches near the ileo-cecal junction. A phase 2 RCT showed favorable results without serious steroid side effects. There is interest in this approach for its possible indication for early cases without irreversible sclerotic lesions.

In conclusion, clinical trials often do not consider baseline renal biopsy features. In the era of precision nephrology, pathology lesions – particularly mesangial proliferation, podocytopathy leading to segmental glomerulosclerosis, epithelial crescents and the extent of tubulo-interstitial damage – may represent a useful criterion for designing clinical trials aimed at curbing the risk of kidney failure in IgAN patients with a high risk of progression.

References


From the laboratory to the bedside The role of experimental models in developing new treatment options

Despite large investments in drug development, the overall success rate of drugs during clinical development remains low, notably for inflammatory renal diseases such as glomerulonephritis. One prominent explanation is flawed preclinical research. Therefore, critical evaluation and selection of a validated and predictive animal model are essential to address clinical questions. For many years, limitations of animal models of IgA nephropathy (IgAN) were highlighted by the absence of the IgA1 isotype and of its receptor, the CD89, in the mouse. Indeed, in IgAN patients, several researchers worldwide have identified abnormalities of IgA1 and its receptor, such as galactose deficiency of IgA1 and release of soluble CD89, that participate in nephrotic immuno-complex formation.

To improve the clinical relevance for translation, a humanized mouse model was generated expressing human IgA1 and CD89, the α1KICD89Tg mice, which spontaneously develops clinical features typical of IgAN, including mesangial IgA1 deposits, herniation and proteinuria.[1] This humanized model of IgAN was essential for translation of drug findings from bench to bedside. We have demonstrated, for example, that recombinant IgA1 protease can reverse the disease by clearing IgA1 deposits, thus opening new avenues for future treatment.[2] Similarly, this mouse model allowed us to test whether food antigens (i.e. gliadin) were deleterious for disease development. A gluten-free diet was beneficial in preventing IgAN development in the α1KICD89Tg mice,[3] confirming results obtained in patients with a gluten-free diet in the early 1990s by Professor Coppo’s group. They re-applied the efficacy of such treatment by showing that it may have preventive, rather than curative, effects, as it acted mainly on animals with normal renal function by prevention of disease development. Thus, excluding gluten from the diet could be a simple therapeutic approach for patients with preserved renal function, especially those with sensitivity to gluten. A new clinical trial is now under way in France.

Animal models can also provide new clues on the pathogenesis of the disease. For example, observed prevention of IgAN in the α1KICD89Tg mice following oral antibiotic treatment our group, indicating that the microbiota is directly implicated in disease development. This again opens new avenues for understanding the disease pathophysiology and for future treatments by modulating human microbiota.

Although preclinical testing of a drug in an animal model is not a prerequisite for regulatory agencies before entering clinical trials, it unquestionably provides valuable data on the expected clinical performance of the drug. Inclusion of safety parameters in animal models will help to build the required safety data package of drugs in development. Finally, our experience brings encouragement for new procedures seeking to introduce key disease-driven pathogenic factors in the mouse to generate valuable humanized spontaneous models of human diseases.

References

The pathogenesis of IF/TA is multifactorial, encompassing immunologic and non-immunologic factors. The process already starts in the period of organ procurement and is closely associated with donor-dependent kidney quality, driven by age, and cold and warm ischemia time. Multiple biomarkers are applied to demonstrate the magnitude of ischemic-reperfusion injury and to predict chronic allograft damage; e.g., the novel epigenetic DNA hypermethylation.

It should be emphasized that the renal graft needs to carry the workload of two previously intact kidneys. This task must be fulfilled despite a diminishing pool of functioning nephrons due to ischemia-reperfusion injury, which simultaneously triggers the recipient immune response. In addition to optimal logistics in graft transportation, hypothermic and normothermic perfusion machines are currently being used, with aim of diminishing cold ischemia damage. Kidney surface cooling during implantation can be performed to eliminate warm ischemia.

Protocol biopsies have become the standard tool for follow-up of ongoing graft injury. Recent observations suggest the application of ultrasonography and magnetic resonance elastography as novel noninvasive measures of the fibrosis burden of the entire allograft. Determination of donor-specific antibodies (DSA) has also been included in standard care by multiple transplant centers. It has revealed chronic antibody-mediated rejection (ABMR) as the leading cause of progressive IF/TA. Recent years have brought significant developments in establishing the biologic impact of DSA; e.g., based on their ability to activate complement.

It is currently clear that IF/TA is not a static, inert occurrence, but appears as the effect of active coexisting processes: immunologic inflammation (in a large part driven by chronic ABMR), non-immunologic factors (hypertension, diabetes, calcineurin inhibitor toxicity, vascular aging), and repair events. The goal of the future research is to find reliable indicators of IF/TA resulting from different causes. At present a wide array of potential biomarkers is under investigation. Promising examples include:

- mRNA profiling of urinary cells
- Expression of epithelial to mesenchymal transition (EMT) markers vimentin and b-catenin in surveillance biopsy and their mRNA measurement in urinary cells
- High-mobility group protein B1, transforming growth factor-b1, nuclear factor-kb staining intensity within the graft
- Transforming growth factor-b1 and connective tissue growth factor urinary excretion.

Today, identification of the links between the complex fibrosis process and the pathophysiologic pathways that are the main contributors in each case has no direct therapeutic consequences due to the lack of specific agents. Therefore, the remaining options are strict matching of the immunosuppressive regimen with the intensity of the immune response, and rational non-specific interventions, such as metformin and mineralocorticoid antagonists.

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S 4.4 Interstitial fibrosis and mechanisms of CKD progression
Sunday, 08.00–09.30, C1-M3
Recent international heart failure guidelines introduced a novel classification of heart failure (HF) based on left-ventricular ejection fraction (EF). This novel classification now encompasses three entities: HF with reduced ejection fraction (HFrEF), preserved EF (HfPEF) or mid-range EF (HfMefEF). These three HF groups represent far more than simple nomenclature; they have an impact upon our practical approach to our patients. Moreover, since chronic kidney disease (CKD) and arterial hypertension are among the leading causes of left-ventricular dysfunction and hypertrophy, it is especially the nephrology field that may benefit from this modified classification.

We need to acknowledge that the best and most substantiated treatment guidelines and algorithms exist for HFrEF patients. The development of and adherence to these guidelines have improved outcomes substantially in recent years. Dramatic improvements in survival have been achieved. Nephrologists, however, are well aware that not all guideline recommendations also apply to CKD or end-stage renal disease (ESRD) patients; either specific contraindications exist or the number of tested patients is not sufficient to transfer the recommendations directly to CKD/ESRD patients.

One additional aspect merits attention: a thorough cardiac work-up of CKD patients will identify a huge proportion of our patients as having left-ventricular dysfunction attributable to either one of the three subgroups. That means the novel classification helps us as nephrologists to categorize our patients correctly. Of note, a formally normal EF does not exclude the presence of diseased myocardium – the contrary. So the clear and straightforward definition of HFRoEF helps to increase awareness of how many patients are actually affected by a "true" disease. That leads to another advantage: even if currently treatment recommendations in HFRoEF and HFRoEF are sparse, the definition of affected patients as 'sick' clearly supports the initiation of studies designed to overcome the unmet medical need in these patients.

A specific role for nephrologists in the HF business is to encourage studies that tackle the distinct side effect profile of standard medications; that investigate the unique urmic risk profile; and, finally, that introduce evidence-based medicine into those subgroups of HF patients with normal or close-to-normal EF but clinical signs of HF.

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S 5.8 The diagnosis of Heart Failure in End Stage Kidney Disease (ESKD): a lingering dilemma Sunday, 08.00—09.30, Hall A1

More than just a signature of IgG deposition

The implications of complement activation in the kidney

Complement in a session on chronic kidney disease (CKD), hypertension and pregnancy; isn’t that a mistake? We recognize the complement system as an important part of our innate defense mechanism against pathogens. At the same time it is also known as a pathogenic mechanism of (auto)-immunity in many diseases, including several renal diseases. Why is it interesting to hear more about complement?

Complement can be activated by three different pathways, the classical, lectin and alternative pathways, that are activated by antibodies, sugar moieties and bacterial surfaces, respectively. When considering the importance of complement in renal diseases, the traditional focus has been on antibody-mediated diseases, such as lupus nephritis or IgA nephropathy, and there is increasing recognition of complement’s role in antibody-mediated allograft rejection. In addition, alterations in complement regulatory proteins, such as factor H, have been linked to atypical HUS and C3-glucomerulonephropathy. These two conditions bring us closer to complement’s potential role in hypertension and pregnancy. The hallmark of all these conditions is local activation of complement, with deposition of C3 as a common finding in the renal biopsy. However, since C3 is the central factor of the complement system and all pathways converge at this level, this does not indicate how the complement activation cascade was initiated. Recently, it has become clear that the role of the alternative pathway as a local amplification system is of importance, and might for instance also be driven by alterations in endothelial cells or endothelial glycoalyx. This brings us into the middle of thrombotic microangiopathy (TMA).

More information about which pathways are driving pathogenic complement activation and which effector mechanisms are important for renal injury is not just a semantic discussion. The availability of complement-directed therapeutics, with novel strategies in development, will provide the opportunity to intervene at different levels. In the current lecture I will give a systematic overview of the complement system and how it goes beyond antibody-mediated renal pathology and might also contribute to conditions such as hypertension-associated TMA or complement deposition in kidneys of women with pre-eclampsia.

S 2.3 Pregnancy, CKD and hypertension Sunday, 08.00—09.30, Hall A3

Statin-based therapy reduces the risk of atherothrombotic events, but no treatments have been shown to reduce admissions with heart failure, arrhythmias, sudden death and other events commonly observed in patients with more advanced CKD.

Nephrilysin is the enzyme responsible for the degradation of natriuretic and other vasoactive peptides. Natriuretic peptides have a positive association with heart failure outcomes such that inhibition of nephrilysin has been investigated as a treatment for heart failure. Early efforts failed because the treatments also inhibited angiotensin-converting enzyme (ACE) and, as both ACE and nephrilysin degrade bradykinin, development of such drugs was ceased due to excess angioedema. Nevertheless, some animal experiments also demonstrated that such agents reduced progression of CKD and proteinuria (compared to ACE inhibition alone), raising the possibility that nephrilysin inhibition might be good for the kidney, as well as the heart.

The development of LCZ696 (now known as sacubitril/valsartan) has allowed these hypotheses to be tested, because it combines a nephrilysin inhibitor with an angiotensin-receptor blocker (which do not increase bradykinin concentrations). Sacubitril/valsartan was compared withenalapril in the largest-ever trial in heart failure, PARADIGM-HF. The trial was stopped early because of clear evidence of benefit, with a highly significant 16 % reduction in all-cause mortality (HR 0.84, 95 % CI 0.76–0.93), leading to rapid approval for use of sacubitril/valsartan in patients with heart failure and reduced ejection fraction.

It is therefore very pertinent to ask the question whether sacubitril/valsartan could reduce cardiovascular outcomes in patients with CKD, and also whether it could slow the prolixting of the renal biopsy. However, since C3 is the central factor of the complement system and all pathways converge at this level, this does not indicate how the complement activation cascade was initiated. Recently, it has become clear that the role of the alternative pathway as a local amplification system is of importance, and might for instance also be driven by alterations in endothelial cells or endothelial glycoalyx. This brings us into the middle of thrombotic microangiopathy (TMA).

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CKD. Its focus was on the effects on kidney progression of CKD. Among patients with heart failure, sacubitril/valsartan actually increases albuminuria, so before large numbers of patients could be entered into a clinical outcome trial, the UK HARP-III trial was designed to compare sacubitril/valsartan with irbesartan in a pilot trial among patients with CKD. Its focus was on the effects on kidney function over one year, safety and tolerability and the effects on cardiac biomarkers. At the 2018 ERA-EDTA Congress in Copenhagen, there will be a new important closing session that you will not want to miss.

The duration of this session will be of 90 minutes (12.30–14.00) with 5 internationally recognized speakers talking about the latest updates and novelties in Nephrology. The clinically oriented presentations will focus on the previous year’s research and achievements in important fields of interest.

You are cordially invited to this exciting event.

NEW closing session at ERA-EDTA on May 27

Nephrology Pearls

Starting with the 2018 ERA-EDTA Congress in Copenhagen, there will be a new important closing session that you will not want to miss.

The duration of this session will be of 90 minutes (12.30–14.00) with 5 internationally recognized speakers talking about the latest updates and novelties in Nephrology. The clinically oriented presentations will focus on the previous year’s research and achievements in important fields of interest.

You are cordially invited to this exciting event.

From genetics to pathophysiology in IgA nephropathy

IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis in the world. The diagnosis of IgAN is based on evaluation of renal biopsy, with characteristic predominant or co-dominant glomerular deposition of IgA, usually with complement C3 and variable amounts of IgG and/or IgM, often with mesangial hypercellularity observed by light microscopy. IgA in the glomerular immunodeposits is exclusively of IgA1 subclass.

IgAN exhibits heterogeneous clinical and pathological features with variable progression, although only a minority of IgAN patients enters sustained clinical remission. As there is no disease-specific treatment, 20–40 % of patients with IgAN progress to end-stage renal disease within 20 years of diagnosis. Moreover, the disease recurs in > 50 % of patients by five years after kidney transplantation. Clinical data suggest that the primary pathogenic defect in IgAN is of extra-renal origin and that IgA1-containing immune complexes are implicated. Clinical and laboratory studies indicated that most IgAN patients have immunologic defects resulting in generation of pathogenic IgA1-containing immune complexes. These immune complexes contain IgA1 with some hinge-region O-glycans deficient in galactose (Gd-IgA1). However, Gd-IgA1 alone is not sufficient to induce IgAN. A second critical step to generate renal injury is the development of autoantibodies (IgG or IgA) that bind Gd-IgA1 to form pathogenic immune complexes. These conclusions have been supported by the findings that in patients with IgAN: (i) IgA1 glomerular immunodeposits are enriched for Gd-IgA1; (ii) serum levels of Gd-IgA1 (autoantigen) and the corresponding autoantibodies each correlate with disease severity and progression; and (iii) serum levels of Gd-IgA1 correlate with the levels of corresponding IgA autoantibodies. A multi-hit mechanism was proposed to explain these autoimmune features of IgAN, where in the kidneys are damaged as innocent bystanders: immune complexes consisting of Gd-IgA1 bound by Gd-IgA1-specific autoantibodies form in the circulation and deposit in the glomeruli, activating mesangial cells and inciting injury. IgAN has contributing environmental and genetic factors. In many patients, disease onset is often characterized by synpharyngitic hematuria. Contribution of genetic factors first emerged from the discovery of familial cases, followed by identification of disease susceptibility alleles that encodes for proteins involved in antigen-processing and presentation pathways.

Ongoing and future studies will clarify involvement of different pathways in the pathogenesis of IgAN by elucidating the origin of IgA1 glycosylation defects as well as the autoimmune responses to Gd-IgA1. The evidence arising from gene-mapping efforts will likely enable generation of a unified pathogenesis model that would incorporate biochemical, functional, and genetic data, providing potential biomarkers and treatment targets.

References


IgA nephropathy: from genes to therapeutic controversies

Sunday, 08.00–09.30, Hall A2

The diagnosis of Heart Failure in End Stage Kidney Disease (ESKD): a lingering dilemma

Sunday, 08.00–09.30, Hall A1

Basic Science and Translational Nephrology
Paola Romagnani, Florence, Italy

Epidemiology and Clinical Nephrology
Ziad Massy, Paris, France

ESKD and Dialysis
Peter Blankestijn, Utrecht, Netherlands

Kidney Transplantation
Daniel Abramowicz, Antwerp, Belgium

Hypertension and Diabetes
Peter Rossing, Gentofte, Denmark

Join! Today!
Hypoxia Inducible Factor Stabilizers

Recent Clinical Trials

David Wheeler
London, United Kingdom

Hypoxia Inducible Factor (HIF) stabilizers, also known as HIF prolyl-hydroxylase inhibitors (HIF PHIs), are a new class of drug developed to treat the anaemia associated with chronic kidney disease. Their principle mechanism of action is to inhibit breakdown of HIFs, the primary regulator of hypoxia-induced gene expression. Enhanced transcription of one of these genes, the erythropoietin gene, leads to proliferation of erythroid progenitor cells in the bone marrow and increases circulating haemoglobin concentrations. Other actions of HIF stabilizers include enhanced gastrointestinal uptake of iron, thereby increasing iron availability for erythropoiesis. Potential advantages of HIF stabilizers over erythropoiesis stimulating agents (ESAs) include their oral route of administration and “physiological” mode of action, targeting the two key components of ESA-associated anaemia (deficiency of erythropoietin and lack of available iron). Oral administration avoids exposing patients to high blood levels of erythropoietin, a phenomenon thought to explain some of the unwanted side effects of ESAs. Furthermore, HIF stabilizers are cheaper to produce than ESAs and may prove to be more cost effective. However, the concept of switching on hypoxia-responsive genes, particularly growth factors, has raised safety concerns. Clinical depression of the dipping phenomenon. Night time systolic BP and the night–day ratio is related to left-ventricular hypertrophy and CV events in the general population and also in CKD patients. There are striking data collected for over a decade showing that a major part of renal transplant patients are poor-dippers, non-dippers or even reverse dippers; furthermore, the dipping status is a dynamic entity that can change in the duration after transplantation. Interestingly, recipients of other solid organ transplants – such as heart and liver – are also prone to the loss of circadian BP variations. The causes for this phenomenon are multiple. Diurnal rhythmicity of the BP relies mainly on the interplay of the kidney and the renin-angiotensin-aldosterone system, the blood vessels, the heart and the nervous system. Our pre-programmed biological clock in the region of the suprarectal nucleus controls the individual biological clocks of different organs in order to prepare the organism for the periodic changes of night and day, rest and activity. In the kidney the activity of different pumps of solute excretion and reabsorption is under strict diurnal control. The absorption of different drugs by the gut and their metabolism by the liver is under diurnal control, as is the activity of the central and autonomous nervous system. Additionally, some drugs used after transplantation (mainly the calcium antagonists and steroids) directly and indirectly affect the physiological diurnal cycles, while their metabolism in turn may also be influenced by circadian cycles. After kidney transplantation, the increased workload of the heart due to nocturnal hypertension does not only affect the heart muscle, but it may also add to the burden of arteriosclerosis assessed by the evolution of IMT in function of the dipping phenomenon. Night time systolic BP and the night–day ratio are independently associated with IMT. Furthermore, night-time BP after renal transplantation is the strongest indicator of the risk of decline in glomerular filtration rate (GFR).

Diagnosis of nocturnal hypertension using ABPM should be a regular tool in the follow-up of patients after any solid organ transplanta-

Non-dippers, poor dippers or reverse dippers?
Nocturnal hypertension and renal function loss in kidney transplant recipients

George S. Reusz
Budapest, Hungary

Renal transplantation is the treatment of choice to replace functionality of failed kidneys. However, even after a successful transplant, patients are often faced with a reduction in the quantity of functioning nephrons. The transplanted kidney often undergoes compensatory hypertrophy and hyperfiltration that can lead to deleterious consequences in the long run. Cardiovascular (CV) morbidity and mortality are among the leading consequences of progressing chronic kidney disease (CKD). Clinically, CV risk in these recipients can be quantified by looking at hard endpoints such as death, myocardial infarction or stroke. Currently, surrogate markers such as intima-media thickness (IMT), pulse wave velocity (PWV) and calcification scores are used during research protocols but not in current clinical practice.

Routine use of ambulatory blood pressure monitoring (ABPM) is a useful tool to diagnose hypertension and its variants such as white-coat and masked hypertension. It is well known that the loss of about 10% of the fall in night-time BP (non-dipping or even reverse dipping) is related to left-ventricular hypertrophy and CV events in the general population and also in CKD patients. There are striking data collected for over a decade showing that a major part of renal transplant patients are poor-dippers, non-dippers or even reverse dippers; furthermore, the dipping status is a dynamic entity that can change in the duration after transplantation. Interestingly, recipients of other solid organ transplants – such as heart and liver – are also prone to the loss of circadian BP variations. The causes for this phenomenon are multiple. Diurnal rhythmicity of the BP relies mainly on the interplay of the kidney and the renin-angiotensin-aldosterone system, the blood vessels, the heart and the nervous system. Our pre-programmed biological clock in the region of the suprarectal nucleus controls the individual biological clocks of different organs in order to prepare the organism for the periodic changes of night and day, rest and activity. In the kidney the activity of different pumps of solute excretion and reabsorption is under strict diurnal control. The absorption of different drugs by the gut and their metabolism by the liver is under diurnal control, as is the activity of the central and autonomous nervous system. Additionally, some drugs used after transplantation (mainly the calcium antagonists and steroids) directly and indirectly affect the physiological diurnal cycles, while their metabolism in turn may also be influenced by circadian cycles. After kidney transplantation, the increased workload of the heart due to nocturnal hypertension does not only affect the heart muscle, but it may also add to the burden of arteriosclerosis assessed by the evolution of IMT in function of the dipping phenomenon. Night time systolic BP and the night–day ratio are independently associated with IMT. Furthermore, night-time BP after renal transplantation is the strongest indicator of the risk of decline in glomerular filtration rate (GFR).

Diagnosis of nocturnal hypertension using ABPM should be a regular tool in the follow-up of patients after any solid organ transplanta-

S 5.4
New methods of anaemia management in CKD patients
Sunday, 10.45—12.15, Hall A1

Four agents, Roxadustat (developed by Astellas, AstraZeneca and FibroGen), Vadadustat (Akebia and Otsuka), Daprodustat (GalaxoSmithKline) and Molidustat (Bayer) have undergone testing in phase II studies and all except Molidustat have entered into phase III programmes. The available phase II data demonstrate that Roxadustat, Vadadustat and Daprodustat increase haemoglobin concentrations in ESA naïve non-dialysed and dialysis-dependent CKD patients in a dose-dependent manner compared to placebo. Studies in patients previously receiving ESAs indicate that with appropriate dose titration, haemoglobin can be maintained within a pre-specified target range with a HIF stabilizer over several weeks. All 3 agents reduced hepcidin, a circulating inhibitor of iron absorption. Available data on Molidustat are more limited with two trials in non-dialysis CKD patients. These demonstrate a dose-dependent haemoglobin response and successful maintenance of haemoglobin after switching from Darbepoetin. Measurements of erythropoietin are available from some of the phase II studies and indicate blood levels within the physiological range normally observed after acute bleeding or at high altitude. All 4 of these HIF stabilizers have been well tolerated, with no drug-related serious adverse events emerging so far, albeit in short-term studies.

Phase III studies of Roxadustat, Vadadustat and Daprodustat are ongoing and will test the efficacy and safety of these agents in a wide range of CKD patients over extended periods up to 5 years. After our experience with ESAs, some of these studies will examine cardiovascular outcomes as well as the development of malignancies. Preliminary 8-week data from two Roxadustat phase III studies conducted in China have been released and are consistent with phase II results. It is likely that this drug will be the first to gain a license for the management of CKD-associated anaemia, but we will need to wait several years before we can be sure that the benefits of these new agents are not offset by long-term safety issues.

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Chronotherapy – treatment tailored according to the diurnal rhythm – is a reasonable option to restore the physiological rhythmicity of the patient’s BP.

Messages
(1) ABPM should be a regular tool in the follow-up of patients with solid organ transplantation. (2) The loss of the dipping status affects the heart, vasculature and the kidneys. (3) Prospective studies are needed to establish the value of chrono-pharmacotherapy on cardiovascular and renal consequences of nocturnal hypertension after kidney transplantation.

Approximately 11% of patients on dialysis worldwide use peritoneal dialysis (PD), although this proportion varies across countries, from less than 1% in Egypt to around 75% in Hong Kong. While PD is associated with lower health care costs and offers patients more autonomy and flexibility compared to hemodialysis, technique failure remains a major challenge to its success. Moreover, since PD is usually performed in the home by the patient or caregiver, the daily and ongoing responsibilities can be overwhelming, which can then lead to patient and caregiver burnout. These issues emphasize the need for care that is informed by research relevant to patients, caregivers and clinicians. Improvements in care and outcomes are likely to be mediated by randomized trials of innovative therapies, but will be limited if the outcomes measured and reported are not important for patients and clinicians. The Standardised Outcomes in Nephrology-Peritoneal Dialysis (SONG-PD) study aims to establish a set of core outcomes for trials in patients on PD based on the shared priorities of all stakeholders, so that outcomes of most relevance for decision making can be evaluated and interventions can be compared reliably.

The five phases in the SONG-PD project include a systematic review to identify outcomes and outcome measures that have been reported in randomized trials involving patients on PD; focus groups using nominal group technique with patients and caregivers to identify, rank and describe reasons for their choice of outcomes; semi-structured key informant interviews with health professionals; a three-round international Delphi survey involving a multi-stakeholder panel; and a consensus workshop to review and endorse the proposed set of core outcome domains for PD trials.

The establishment of three to five high-priority core outcomes, to be measured and reported consistently in all trials in PD, will ultimately enable patients and clinicians to make informed decisions about treatment, based on outcomes of common importance.

References
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A bidirectional interaction The pathogenic roles of lipoproteins and apolipoproteins in kidney diseases

The classical physiological role of lipoproteins is the transport of esterified fatty acids and cholesterol from the site of their resorption (intestine) or synthesis (mostly liver) to the site of their consumption (striated muscle, adipose tissue, liver, steroidogenic organs) or excretion (liver, intestine). Disturbed lipoprotein metabolism frequently causes storage of lipids or lipoproteins in various cell types, including macrophages in the arterial wall, as well as mesangial cells, tubular epithelial cells, podocytes, or vascular cells of the kidney. In addition to apolipoproteins and phosphatidylcholines needed for formation and processing of lipoproteins and their cargo (cholesterol, triglycerides), lipoproteins contain dozens of quantitatively minor lipids and proteins, some of which exert very specific functions even beyond lipid transport; for example in the regulation of function and survival of various cell types, including renal cells. From a clinical perspective, the interactions of lipoproteins and the kidney are bidirectional.

On the one hand, the kidney regulates metabolism and plasma concentrations of lipoproteins. This is best illustrated by the findings of hypertriglyceridemia, low HDL cholesterol and elevated lipoprotein(a) levels in chronic kidney disease (CKD), as well as mixed hyperlipidemia in nephrotic syndrome. In addition, uremia and the proinflammatory state in many renal diseases modify composition and components of lipoproteins. For example, CKD was found to convert vasoprotective activities of HDL into damaging ones. The quantitative and qualitative changes in plasma lipoproteins likely contribute to the very high risk of atherosclerotic cardiovascular disease (ASCVD) in CKD patients.

On the other hand, lipoproteins or their constituents affect kidney function and contribute to the development and progression of renal diseases. In general, the severity of dyslipoproteinemias is associated with worsening prognosis of CKD. More specific examples include renal lipidoses caused by genetic variants of apoE, nephrotic syndrome and renal failure in patients with deficiency of lecithin-cholesterol acyltransferase, and the association of focal glomerulosclerosis with frequent variants of apoL1 in sub-Saharan Africans. The histological appearance of clear cell renal cell carcinoma is caused by the accumulation of lipoprotein-derived lipids.

Despite the strong evidence from observational and genetic studies, intervention studies with lipid-modifying therapies did not provide strong evidence that correction of dyslipoproteinemia reduces the very high risk of ASCVD or end-stage renal disease in CKD patients. Several hypotheses have been suggested to explain the discrepancy between observational and interventional studies. One of them – the need of more pronounced lowering of LDL cholesterol – can now be tested with PCSK9 inhibitors. In addition, the anti-sense oligonucleotide drugs, which are currently in development, lower lipoprotein(a) or triglycerides more effectively than currently available drugs.

More generally, it will be important to find out whether enhanced lipid or lipoprotein accumulation in vascular, parenchymal or cancer cells of the kidney is causal and rate limiting for the onset or progression of associated kidney diseases. This will be the prerequisite for the development of therapies that specifically target the interaction of renal cells with lipoproteins or their minor components (e.g. ApoL1).

ARNOLD VON ECKARDSTEIN
Zurich, Switzerland

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Rituximab in IgAN: what’s the evidence? Clinical trials have generally been disappointing

A key event in the current understanding of the pathogenesis of IgAN is the development of IgG and/or IgA autoantibodies against polymeric galactose-deficient IgA1 (Gd-IgA1), the levels of which are elevated in the circulation of most patients with IgAN. Because B cell-depleting therapies are known to be effective in many renal diseases mediated by the presence of autoantibodies (for example, membranous nephropathy and ANCA-associated vasculitis), the hypothesis that depleting antibody–producing B-cells and, presumably, the autoantibodies that drive progression of IgAN, is attractive.

In an open-label, multicenter study conducted over one-year follow-up,[2] Lafayette et al randomized 34 adult patients with biopsy-proven IgAN and proteinuria > 1 g/d, main- taining levels of Gd-IgA1 and anti-Gd-IgA1 antibodies. Serum levels of Gd-IgA1 or anti-Gd-IgA1 antibodies, suggesting that the increased circulating levels of anti-Gd-IgA1 IgG autoanti- bodies may originate from plasma cells, and not CD20+ B-cells, in the bone marrow. On the other hand, rituximab appears to be benefi- cial in patients with a vasculitic form of IgAN.[3]

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References


Too much nephrology? The CKD epidemic is overstated

Many epidemiological studies have assert- ed that the incidence and/or prevalence of chronic kidney disease (CKD) have reached ‘epidemic’ proportions. The data from these studies are largely based on a misleading definition of CKD. Indeed, such definitions al- locate CKD status to all patients with a GFR below 60 mL/min/1.73 m², regardless of age (over 20 years) and even in the absence of other signs of kidney damage. Also, the defini- tion of CKD requires that decreased GFR persists for at least the 3 months. The dura- tion requirement is commonly missing in ep- idemiological studies. Data from UK (RRID), Norway (RENIS) and Morocco (MAREMAR) have shown that in at least 30 % of subjects with GFR below 60 mL/min/1.73 m² CKD will not be confirmed by a second test.

The CKD definition based on an absolute GFR threshold (< 60 mL/min/1.73 m²) is also questionable. First, GFR declines physiolog- ically with normal aging, and occurs even in ‘super’ healthy populations (living kidney donors) and in the healthy general popula- tion (both with measured GFR or estimat- ed [eGFR]). This implies that some healthy elderly subjects are falsely diagnosed with CKD.

From the US NHANES study, CKD preva- lence in 2011–2014 was claimed to be about 14.9 %, but when patients with any abnor- mal albuminuria are excluded, the CKD preva- lence is about 5.0 %. Specifically, the CKD prevalence of patients in category G3A1 (GFR between 45 and 60 mL/min/1.73 m² and no albuminuria) is 3.9 %, or about 26 % of all CKD or 6 – 10 million of subjects in the USA alone. However, most of these patients are older than 65 years, in whom the re- duced GFR may be a normal phenomenon.

Second, a common argument for the single absolute 60 mL/min/1.73 m² threshold for GFR is that such GFR values (below 60 mL/ min/1.73 m²) are associated with increased mortality or other adverse events (the ‘prog- nosis’ argument). Using data from large cohort studies with a single normal refer- ence value or one representing the mean for a given age group, a higher relative risk of mortality is observed in the apparently healthy aging population when the GFR falls below about 45 mL/min/1.73 m², in the ab- sence of albuminuria.

Alternative definitions of CKD, based on an age-stratified threshold of GFR or age-specifi-
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Please join our expert Faculty who will share their real-world clinical experience of:

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We look forward to seeing you there.

Professor Thomas Benzing
Department II of Internal Medicine, University of Cologne, Germany

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker/Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:45</td>
<td>Welcome and introduction</td>
<td>Professor Thomas Benzing, Germany</td>
</tr>
<tr>
<td>09:50</td>
<td>The ERA-EDTA guidelines in clinical practice</td>
<td>Dr Roser Torra, Spain</td>
</tr>
<tr>
<td>10:05</td>
<td>Identifying patients with ADPKD at risk of worsening renal function – the GERMAN Experience</td>
<td>Dr Roman-Ulrich Müller, Germany</td>
</tr>
<tr>
<td>10:20</td>
<td>Clinical scenarios – a practical approach</td>
<td>Professor Yannick Le Meur, France</td>
</tr>
<tr>
<td>10:35</td>
<td>Questions, summary and close</td>
<td>Panel Discussion led by Professor Thomas Benzing, Germany</td>
</tr>
</tbody>
</table>

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The 400-year-old Renaissance castle was built by Christian IV whose colorful personality left a strong mark on Danish history. Today visitors can travel back in time and see the crowns of the Danish kings and queens which are kept in special vaults.

www.kongernessamling.dk/rosenberg/

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The English choreographer and dancer Paul James Rooney has created a fairytale ballet about a Chinese girl and boy who fall in love. But the girl is forced to marry someone else and the boy dies of a broken heart. Together they are united – as beautiful, fluttering butterflies.

www.tivoligardens.com

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Especially during summer, Nyhavn is the perfect place to end a long day. With a cold one on the quay like the locals, or at one of the many restaurants. Originally, Nyhavn was a busy commercial port where ships from all over the world would dock. Today restaurants dominate the old port. Enjoy the relaxed atmosphere by the canal, jazz music and great food.
ADPKD Patient Route Map – an interactive new resource to help empower patients and families

ERAL-EDTA 2018 sees the launch of the ADPKD Patient Route Map, an interactive tool designed to help educate and empower people affected by autosomal dominant polycystic kidney disease (ADPKD).

The Route Map explains the types of care and support that patients and families should expect from their health service. The aim is to help patients and carers to manage their own health with their healthcare team, to talk about ADPKD with their nephrologist, to participate in making decisions about their own care, and to make the best use of available care and support services. The Route Map was developed jointly by the European ADPKD Forum (EAF), an international group of experts from the fields of nephrology, genetics, hepatology and advocacy, and PKD International, the international ADPKD patient support group alliance.

‘The ADPKD Patient Route Map is a great example of how patients and experts can work together,’ says Tess Harris, PKD International President and an ADPKD patient. ‘Ultimately the idea is to help everyone affected by ADPKD to cope better with the disease and to get all the care, support and information they need, at the right time.’

The idea for the Route Map came from an EAF Round Table meeting involving representatives from various European-level societies of medical specialists involved in ADPKD care and kidney patient organisations, in January 2016. The resulting ‘Multidisciplinary Position Statement on ADPKD Care’, recently published in the April edition of Nephrology Dialysis and Transplantation, explains the principles and evidence base for the Route Map.

The Route Map explains in lay terms what ADPKD is, how it is diagnosed and assessed, and how it can affect kidney function over time. It shows current approaches to ADPKD management over the course of the disease, from diagnosis through to end-stage renal disease, with a particular focus on the self-care measures patients can take to stay as healthy as possible. It also covers renal complications (e.g. cyst infections and kidney stones), pain management and major non-renal manifestations (e.g. liver cysts and intracranial aneurysms). It gives advice on issues such as genetics and genetic testing, family planning, and coping with the effects of ADPKD on wellbeing, work and finances. Finally, it provides an overview of opportunities for patients to participate in research and highlights the role of the European Rare Kidney Disease Network.

As Prof. Albert Ong (Sheffield, UK), a co-author of the Route Map put it: ‘We’ve tried to map out ADPKD along the course of a lifetime.’

What’s great about the Route Map is that it’s not just a book of facts – it’s attractive and interactive, allowing people to look at different topics according to the different stages of their own journey.’

The Route Map allows readers to reveal further information on key topics and messages of advice, experience and support provided by patients and their family members across Europe.

By providing key information on the disease, its progression and management options, the Route Map is intended to help people affected by ADPKD to participate in their care planning, and coping with the effects of ADPKD on wellbeing, work and finances. The Route Map should be very useful for nephrologists – to help us to inform and empower our patients and to ensure that our services are truly patient-centred.’

Towards precision medicine in the nephrology clinic – The APOL1-associated spectrum of chronic kidney disease

Compared to European-derived populations, African Americans and individuals with recent African ancestry have significantly higher incidence rates of end-stage kidney disease (ESKD). This observation, coupled with the marked familial aggregation of ESKD in African Americans, including disparate etiologies of chronic kidney disease in single families, long supported an inherited predisposition to kidney disease as contributing to observed racial and ethnic disparities in risk. In 2010, the discovery of the apolipoprotein L1 gene (APOL1) association with non-diabetic nephropathy in African Americans powerfully transformed our understanding of ESKD in this population. More than 30% of African Americans with ESKD receiving renal replacement therapy are now known to have APOL1-associated kidney diseases, including patients with hypertension-related nephropathy, focal segmental glomerulosclerosis (FSGS), HIV-associated nephropathy (HIVAN), severe lupus nephritis and the nephropathy associated with sickle cell disease. The autosomal recessive APOL1 gene association with kidney disease exhibits among the strongest observed in a complex disease. Odds ratios for association range from 7.3 with hypertension-attributed nephropathy, to 17 with FSGS and >29 in HIVAN.

The APOL1-associated spectrum of kidney diseases histologically resides in the FSGS family. These kidney diseases can present with absent or low-level proteinuria, for example, with solidified glomerulosclerosis, to high-level proteinuria and more rapid loss of kidney function with collapsing glomerulopathy. Kidneys from deceased donors with APOL1 high-risk genotypes have shorter renal allograft survival after transplantation, an effect that is independent from the APOL1 genotype in recipients. Living kidney donors with APOL1 high-risk genotypes were also reported to have poorer post-donation kidney function and higher rates of ESKD.

Approximately 20% of individuals inheriting two copies of APOL1 renal-risk variants, defining the high-risk genotype, will ultimately develop advanced kidney disease. As such, modifying factors appear to be required for the expression of disease. Inflammatory pathways, including those mediated by interferons, appear to play an important role as second hits or disease modifiers.

The APOL1 breakthrough will likely impact the epidemiology of ESKD and lead to novel therapies. The National Institutes of Health recently initiated the APOLLO Study (APOL1 Long-term Kidney Transplantation Outcomes Network) to assess roles for APOL1 genotyping in deceased-donor kidney transplantation in order to optimize organ allocation and determine the safety of donation in potential living kidney donors with APOL1 high-risk genotypes. Given APOL1 and other recent genetic discoveries, precision medicine is likely to play an expanded role in the Nephrology clinic.
WHY BECOME A MEMBER?

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Potential new targets for antihypertensive therapy
Targeting peripheral and central mechanisms to lower blood pressure

Better understanding of pathophysiological mechanisms and signaling pathways underlying cardiometabolic diseases have provided new targets to treat hypertension. Progress in hypertension management is reflected by novel procedures focused on inhibition of sympathetic overactivity, new molecules and classes of drug, and behavioral lifestyle interventions.

First, the well-established contribution of the neurogenic component of hypertension has led to the introduction of alternative therapies, such as renal denervation and baroreflex activation therapy, aimed specifically at modulation of peripheral neural reflexes mechanisms involved in blood pressure control. However, blood pressure response to these interventions is highly variable, prompting extensive research to define predictors of successful treatment.

Other newer methods have recently emerged. We have shown that carotid body (chemoreflex) modulation might improve blood pressure control in some patients with resistant hypertension. Responding patients had characteristics distinct from those who did not respond, which could allow patient selection for future trials. Endovascular baroreceptor amplification using a dedicated stent-like device has been shown to substantially lower blood pressure, and might become an alternative to baroreflex electric stimulation.

Importantly, there is growing evidence that not only peripheral, but also central neural mechanisms might play an important role in pathogenesis of cardiovascular diseases. Local cerebrovascular dysfunction and altered neuronal anatomical connectivity might predispose to development/progression of hypertension and to accelerated brain aging. Thus, future interventions focused on modulation of central neural mechanisms may improve prevention and treatment of cardiovascular disease.

Secondly, several pharmacological targets (such as vasopressin inhibition, ACE-2 activation and aldosterone synthase inhibition) have been identified with promising preclinical and early clinical phase results. However, the overall development of novel antihypertensive drugs is more difficult than expected. Nevertheless, better understanding of the endothelin system has resulted in development of aproclitan, an orally active, dual endothelin receptor antagonist, that is being investigated in a large phase 3 trial in patients with resistant hypertension. Furthermore, there is growing interest in blood pressure lowering effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors, which might be of particular relevance especially in the setting of double inhibition of SGLT2 and the renin-angiotensin system.

Interestingly, studies using copeptin as a proxy for vasopressin secretion suggest its role in the pathogenesis of cardiometabolic and renal diseases, and resistance to antihypertensive treatment. Future interventions might go beyond pharmacological modulation of vasopressin production. In the 20–25% of the population with the highest copeptin concentrations, the most likely cause is low water intake. Consequently, ongoing studies are testing whether increasing water intake in these subjects may prevent diabetes, hypertension and cardiometabolic disease.

Finally, our treatment options are likely to expand to new areas, including management of stress and sleep deprivation, and to strengthening motivational and other self-management skills of our patients.

Minimal change disease (MCD) is a major cause of idiopathic nephrotic syndrome (INS), and is characterized by intense proteinuria leading to edema and intravascular hypovolemia. In adults, it accounts for approximately 15% of INS cases, but reaches approximately 15% of INS cases, but reaches up to 70–90% in children above 1 year of age.

In the pediatric setting, a renal biopsy is usually not performed if presentation is typical and the patient responds to therapy with oral prednisone at conventional doses. Nevertheless, better understanding of the endothelin system has resulted in development of aproclitan, an orally active, dual endothelin receptor antagonist, that is being investigated in a large phase 3 trial in patients with resistant hypertension. Furthermore, there is growing interest in blood pressure lowering effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors, which might be of particular relevance especially in the setting of double inhibition of SGLT2 and the renin-angiotensin system.

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Iron supplementation in CKD patients What is the optimal dose and route of administration in 2018?

Iron replacement is commonly used in CKD patients, since many of them, particularly those on chronic haemodialysis, are in significant negative iron balance. The two routes of administration for replacing iron are oral and intravenous.

Oral iron has been widely used for over three centuries in the general population, and up until recently has mainly consisted of simple iron salts, such as ferrous sulphate, iron succinate, iron polymalate, etc. There are two main problems with using oral iron in patients with advanced CKD, namely a fairly high incidence of gastrointestinal side-effects, of the order of 20–30%, as well as poor iron absorption from the gut which becomes more severe, the greater the degree of uraemia. More recently, an additional potential adverse consequence of oral iron therapy has emerged, namely the ability of oral iron to alter the gut microbiome and metabolome which is already affected by the uraemic state. In general, intravenous iron has provided a faster and greater response than oral iron in CKD, but two recent randomised controlled trials unfortunately generated conflicting results on the safety of IV iron.

In recent times, a number of newer oral iron preparations have appeared, including ferric citrate, ferric maltol, heme iron polypeptide, and liposomal (sucrosomal) iron, each aspiring for potentially greater efficacy in CKD patients. With the exception of ferric citrate, results of recent trials in CKD patients have been disappointing.

In the haemodialysis setting, intravenous iron has for nearly 30 years now been standard-of-care as the means of supplying iron replacement to patients on chronic haemodialysis. The main debate here is how much iron to administer, with concerns that too much...
Bone: a new endocrine organ CKD-MBD, the calcium-sensing receptor and calcimimetics

Chronic kidney disease-mineral and bone disorders (CKD-MBD) constitute an important systemic disorder that nephrologists are very well aware of. In fact, because CKD represents a human model of accelerated vascular disease and vascular calcification, we are ‘teaching’ other physicians that bone is a new endocrine organ at the heart of CKD-MBD, and that knowledge derived from CKD-MBD has important implications for cardiovascular health and even aging in the general population.[1-2] Among other significant advances in pathophysiology, the discovery in 1993 of the calcium-sensing receptor (CaSR) – the only ion-sensing receptor discovered to date – and the rapid development of a new class of drugs (calcimetics) have both contributed to important changes in the drug management of CKD-MBD.

Currently, an integrated pharmacological approach to CKD-MBD requires prevention of the progression of vascular calcification, in addition to an appropriate management of the CKD-associated phosphate imbalance and control of PTH levels (both phosphate and PTH are also considered uremic toxins). Consequent to the novel 2017 KDIGO CKD-MBD guidelines suggest not only (a) the use of calcium-containing phosphate binders should be restricted and that the presence of vascular/valvular calcifications may still be considered relevant to CKD-MBD management decision making; but also (b) that any antiparathyroid-agent (or combination) is acceptable as the first-line option for PTH control in CKD-SD.

This significant change is in part attributable to the availability for the first time of an anti-parathyroid family (calcimetics) capable of decreasing calcium, phosphate, FGF23 and PTH levels (despite inducing hypocalcemia!), but in addition it has been made on the basis of the important results of two randomized clinical trials (ADVANCE and EVOLVE) performed with cinacalcet. Although these studies did not strictly meet their primary endpoint, many nephrologists are reluctant to exclude potentially important benefits of calcimetics for CKD-SD patients based on subsequent prespecified analysis. Thus, these studies showed that it may be possible to slow the progression of vascular/valvular calcifications and to improve survival in CKD-SD patients with secondary hyperparathyroidism by use of a single drug. However, cinacalcet is not exempt from significant clinical problems affecting tolerance (and therefore compliance) of patients with this treatment.[3] The newly developed oral calcimimetic evocalcet and the potent intravenously administered etelcalcetide may at least partially circumvent some of these clinical problems.

Finally, it is worth emphasizing several points regarding the CaSR: (1) in my opinion, the importance of vitamin D (VD) cannot be discounted despite the striking absence of randomized clinical trials. As a matter of fact, active VD increases not only the expression of the VD receptor but also the expression of the CaSR; (2) CaSR is widely expressed (including in the cardiovascular system); (3) the crystal structure of the CaSR is now known and it is necessary to emphasize that CaSR contains multiple binding sites for phosphate as well as calcium ions (inducing different active and inactive conformations).[4] These findings may provide new clues for the understanding of PTH hypersensitivity in the presence of CKD.[5]

References


Thrombotic microangiopathies: outcomes are improving

Managing thrombotic thrombocytopenic purpura/hemolytic uremic syndrome

Thrombotic microangiopathies (TMAs) are a group of life-threatening disorders characterized by microangiopathic hemolytic anemia (MAHA) with schistocytes, thrombocytopenia and generalized microvascular thrombosis leading to ischemic tissue injury and a variable degree of end-organ dysfunction. TMAs are described as hemolytic-uremic syndrome (HUS) when acute kidney injury (AKI) is present, or as thrombotic thrombocytopenic purpura (TTP) when neurological manifestations are predominant. Although the clinical overlap of HUS and TTP is considerable, these two disorders have distinctive pathophysiology and treatment. The most common typical HUS develops following an infection with Shiga toxin-producing bacteria. Atypical HUS is the result of excessive activation of the alternative pathway of the complement system due to genetic mutations in complement regulatory proteins or anti-complement factor H autoantibodies. TTP is caused by a severe deficiency of the enzyme ADAMTS13, either due to acquired circulating autoantibodies, or genetic mutations. Given the risks of morbidity and mortality and the potential benefit of plasma exchange (PEX) in several clinical settings associated with TMA, immediate initiation of PEX should be considered while the diagnostic workup is in progress. While mortality was almost certain in early reports of TTP/HUS, rates have been reduced to 10 – 20 % in the last 20 years, largely associated with the use of PEX with fresh frozen plasma replacement. PEX is usually supplemented by immunosuppressant drugs, corticosteroids and/or rituximab. When complement-mediated TMA is suspected, anti-complement therapy (e.g. eculizumab) should be started as soon as possible (within 24 to 48 hours). Future research will require multinational collaboration and large, well-designed registers.

View the ERA-EDTA 2018 Broadcast on the YouTube playlist here.
The probability of developing amyloid light-chain (AL) or primary amyloidosis significantly increases with age, and people older than 65 are at the highest risk. The optimal management of patients with AL amyloidosis requires early diagnosis, correct assessment of the type of amyloid, effective treatment with supportive therapy and very careful follow-up. The therapy should be tailored according to the whole spectrum of factors, including age, renal and cardiac status, and the number of affected organs because 'one size does not fit all'. Patients who achieve complete hematologic response after therapy have the best prognosis.[1]

Standard treatment with melphalan and dexamethasone remains the therapeutic option for patients at intermediate risk (about 50–60% of patients), but has been replaced with newer regimens in many cases. These regimens include drugs used for the treatment of multiple myeloma: proteasome inhibitors (bortezomib, carfilzomib and ixazomib) or immunomodulatory inside drugs (IMiDs; thalidomide, lenalidomide and pomalidomide). The most frequently used combinations are bortezomib, melphalan and dexamethasone or cyclophosphamide, bortezomib and dexamethasone. In 15–20% of high-risk patients (NT-proBNP > 8,500 ng/L) low-dose regimens are recommended (reduced doses of dexamethasone from 40 to 20 mg/day) where bortezomib is preferred due to the rapidity of action. High-dose melphalan, supported by autologous stem cell transplantation (HDM-ASCT), remains the therapeutic option for the approximately 15–20% of patients with low-risk status. Bortezomib induction can be considered before ASCT, particularly in patients with a higher clonal burden (bone marrow plasma cell infiltrate > 10%). End-stage renal disease can complicate ASCT, especially in patients with hypoalbuminaemia and eGFR < 40 mL/min/1.73 m², and significantly increase treatment-related mortality.

Drugs that can interfere with amyloid fibrillogenesis seem have great potential in patients with AL amyloidosis. Some, such as 4′-ido-4′-deoxydoxorubicin or doxycycline, have been tested in the past, while the newer epigallocatechin-3-gallate (a phenol of green tea) is the subject of a clinical trial. Other drugs recently tested in AL amyloidosis include monoclonal antibody targeting plasma cell antigen CD38 (daratumumab), NEOD001 (a humanized version of 2A4 mouse monoclonal antibody raised against a cryptic epitope of mouse SAA), and 11-1F4 (monoclonal antibody directed against human amyloidogenic light chains). Antisense oligonucleotides (ASOs) or small interfering RNA (siRNA) have also been studied in pre-clinical models. New treatment modalities including novel hematologic drugs and immunotherapy represent a promising perspective, with hope of better survival for this formerly incurable disease.

One size does not fit all Current best practice in managing primary amyloidosis

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RESEARCH

S 3.3 Plasma cell dyscrasias and the kidney Sunday, 15.00–16.30, C1-M1-2

View the ERA-EDTA 2018 Broadcast on the YouTube playlist here.
Complex and heterogeneous: MiG-associated kidney disease
Successful diagnosis and management depend on close collaboration

Monoclonal immunoglobulins (MiG) result from proliferation of plasma cells or B-cells. The MiG can then cause renal disease, although it should be noted that renal disease occurs in only a small subset of patients with MiG. MiG-associated renal diseases are complex and heterogeneous in their clinical, pathogenic, pathologic, and prognostic findings. Thus:

- Patients may present with acute renal failure, rapidly progressive glomerulonephritis, nephritic or nephrotic syndrome, or slowly progressive renal failure, depending on the type of MiG-associated renal disease.
- The hematologic disease producing the MiG may be a malignant plasma cell condition such as multiple myeloma or a malignant B-cell lymphoproliferative disorder such as lymphoma, or a non-pre-malignant disorder such as monoclonal gammapathy of undetermined significance (MGUS). MGUS causing renal disease is now termed monoclonal gammapathy of renal significance (MGRS).
- The site of deposition, underlying pathology and renal disease are variable and can involve the glomeruli, tubules, interstitium and/or vessels. Glomerular diseases include proliferative glomerulonephritis with MiG deposits, MiG deposition disease (MiDD), and immunotactoid glomerulopathy; tubular diseases include myeloma kidney and light chain proximal tubulopathy, vascular diseases include crystalglobulinemia and thrombotic microangiopathy. Ig-amyloidosis usually involves the glomeruli, interstitium and vessels, and MiDD involves the glomerular and tubular basement membranes.
- In most cases, the renal biopsy demonstrates the MiG (direct mechanism). However, in a small number of patients, the renal disease may be the consequence of the MiG causing dysregulation of the alternative pathway of complement (indirect mechanism). In a few cases, although the kidney biopsy may show the MiG, they are not detected in blood or urine and there is no evidence of a plasma cell or B-cell lymphoproliferative disorder by current standard testing techniques.
- Special newer methodologies may be required to demonstrate the MiG on renal biopsy.
- The course of MiG-associated renal disease is variable depending on the type of the renal disease.
- Treatment and prognosis are similarly variable, and depend on the type of renal disease and the underlying hematologic disease.

Due to the complexity of MiG associated renal diseases, it is imperative in their diagnosis and management that there should be close collaboration between the nephrologist, pathologist and hematologist-oncologist.

References


Lessons from the MYRE study
A role for extracorporeal treatments in myeloma cast nephropathy?

Acute kidney injury (AKI) is a common complication in multiple myeloma (MM). Its incidence at the diagnosis of MM is around 20% to 40%, and up to 10% of patients require hemodialysis. Cast nephropathy (CN) resulting from monoclonal light chain (LC) precipitation with uromodulin in the distal tubule is the main cause of AKI, always observed in the setting of high tumor mass MM. Urgent treatment is mandatory, since persistent renal dysfunction, particularly end-stage renal disease, induces higher morbidity and mortality, strongly affects quality of life and increases costs. Treatment relies on the correction of dehydration, hypercalcemia and other precipitating factors, with rapid introduction of high-dose steroids and chemotherapy to suppress the production of nephrotoxic LC. Even with novel anti-myeloma agents, including the proteasome inhibitor bortezomib, only 30% of patients requiring dialysis achieve renal recovery.

The use of adjunctive extracorporeal treatment to remove serum free light chains (FLCs) – i.e. plasmapheresis or high cutoff (HCO) hemodialysis using dialyzers with high permeability to proteins – is debated. In a study limited by the lack of histological confirmation of CN, in retrospective studies, extended HCO-hemodialysis with chemotherapy based on novel anti-myeloma agents produced dialysis-independence in 60% of patients with biopsy-proven CN. The MYRE study was designed to compare the hemodialysis-independence rate in newly diagnosed CN patients treated with hemodialysis using an HCO or a conventional high-flux dialyzer. This multicenter randomized clinical trial was conducted between 2011 and 2016, and included 98 patients with biopsy-proven myeloma CN still requiring hemodialysis after symptomatic measures including high-dose steroids. All participants received the same bortezomib-dexamethasone chemotherapy and an intensive hemodialysis (eight daily five-hour sessions over 10 days) with either HCO (n = 48) or conventional high-flux dialyzer (n = 48). The primary endpoint was dialysis independence at three months; sample size was set to detect an increase from 30% to 60% between control and HCO group, respectively.

Among 98 randomized patients, 94 (median age, 68.8 years) were included in the modified intent-to-treat analysis. Baseline characteristics in HCO and control groups were similar, including serum creatinine levels (median 6.4 [565.76 µmol/l] versus 7.3 mg/dl [645.32 µmol/l]), LC-only myeloma prevalence (50% versus 45.8%) and FLC levels (median 6,590 versus 5,230 mg/l). Hemodialysis-independence rates at three months were 41.3% and 33.3%, respectively (p = 0.42). At six months and 12 months, the respective rates were 56.5% versus 35% (p = 0.04), and 60.9% and 37.5% at 12 months (p = 0.02), respectively. Tolerance of hemodialysis and chemotherapy was similar. At 12 months, nine patients (HCO) and 10 (control group) had died.

Although no significant difference in dialysis independence rates was observed at three months, the MYRE study showed that intensive HCO-hemodialysis combined with bortezomib-based chemotherapy resulted in increased renal response rates at six and 12 months. These data indicate that HCO-he-
Post-transplantation diabetes mellitus
Insulin secretion and immunosuppression-related pathogenesis

In my presentation, I will focus mainly on ANCA-associated small vessel vasculitis (AAVs) Wegener granulomatosis – granulomatosis with polyangiitis (GPA) – microscopic polyangiitis (MPA) and polyarteritis nodosa (PAN), and finally newly described monogenic vasculitides, GPA, MPA and eosinophilic granulomatosis polyangiitis (EGPA) are life-threatening diseases that are more common in adults. However, the frequencies of Kawasaki disease (KD), Henoch Schonlein purpura (HSP) and polyarteritis nodosa (PAN) in children are markedly higher in children. The real incidence of AAV in children (cAAV) is uncertain; however, GPA seems the most frequent among cAAV, with the incidence ranging from 0.03 to 3.2 per 100,000 children/year. On the other hand, very few cEGPA cases have been reported.

According to a French Vasculitis Study Group report of 2018 comparing 35 cAAV with 151 adults with AAV (aAAV), at baseline children had less frequent myalgias and peripher al neuropathy but more fever. Rates of renal involvement were comparable. Initial GPA-associated abdominal pain and nasal cartilage damage were more common in cAAV. During follow-up, children experienced more relapses, accrued more damage and needed longer maintenance treatment than aAAV. The incidence of PAN has been estimated at 2–9 per million in adults, but it is perhaps rare in children. In children there is no gender difference, while PAN in adults is seen more commonly in males. Constitutional manifestations such as malaise, fever, weight loss, and musculoskeletal features such as arthralgia and myalgia, as well as skin manifestations, are common presenting features in both children and adults. While the kidneys and the gastrointestinal tract are most prominently affected, the cardiac, neurologic and respiratory manifestations occur less frequently in children.

Monogenic diseases causing necrotizing vasculitides and mimicking PAN are DADA2 and SAVI. Among the monogenic diseases causing vasculitis, 1 should also mention FMF-associated necrotizing vasculitis (PAN) in regions where FMF/MEFV mutations are prevalent.

Deficiency of adenosine deaminase type 2 (DADA2) is an autosomal recessive disease resembling PAN, and is caused by homoygous or compound heterozygous mutations in the CECP1 gene. Positive family history, vivid racemose and hemorrhagic stroke are common in this form of the disease. Another monogenic PAN-mimicking disease, caused by mutations in the gene encoding stimulator of interferon genes (STING), results in a disease called SAVI (STING associated vasculitides of infancy). It presents early in life with a vasculitic rash affecting the cheeks, nose and peripheries with chronic ulceration, with progressive interstitial pulmonary fibrosis and associated pulmonary hypertension. AAV in general are less common in children than adults but associated with significant morbidity and mortality. The recently described monogenic diseases resulting in vasculopathy and necrotizing vasculitis in children will give more insight to pathogenesis of vasculitis and enable more specific treatment modalities.
Physicians have been trained as single-organ specialists, often neglecting a multidisciplinary approach to patients and diseases. A significant amount of cardiovascular complications are observed in patients with chronic kidney disease, and heart failure is one of the major determinants of kidney dysfunction. The nature of heart and kidney interaction is evident and becomes even more evident in acute illness.

It has been known for a while that acute heart decompensation may lead to acute kidney injury through a series of mechanisms that encompass in different proportions a low cardiac output state, arterial underfilling, renal hypoperfusion and a significant amount of congestion, further reducing the arterio-venous pressure gradient in the kidney that ensures adequate perfusion. Only recently, however, it has been demonstrated that patients with acute kidney injury may present a severe degree of inflammation and high levels of circulating mediators affecting cardiac function and myocyte apoptosis. These conditions represent a typical example of a bidirectional organ crosstalk with time windows of hours, days and even months or years. These conditions have been fully described in the modern definition and classification of Cardio Renal Syndrome. While the acute syndromes are more evident and rapidly devastating, the chronic ones are generally subclinical but equally dangerous and leading to unfavorable clinical outcomes.

A recent approach to multiple and combined organ dysfunction has further developed the concept of organ crosstalk, leading to a series of new clinical conditions that must be evaluated. It is well recognized that chronic renal replacement by dialysis can generate specific cardiovascular consequences due to hemodynamic stress and insufficient removal of uremia retention products. The same is true for acute renal replacement techniques. In fact, especially when the treatment is intermittent and aggressive, it may result in significant hemodynamic instability and arrhythmias, a condition of myocardial stunning or a manifest acute coronary syndrome. It is established that intermittent therapies and rapid fluid removal from patients suffering from acute kidney injury may also affect the timing and the quality of renal recovery, producing a detrimental effect on tissue regeneration and the healing process.

On another front, we might observe significant insults to the kidneys of patients undergoing venovenous extracorporeal membrane oxygenation (VV-ECMO) for respiratory problems or venoarterial ECMO (VA ECMO) for depressed myocardial contractility. Also in this case, one method of artificial organ support interferes with the function of a native organ. We finally have a further condition where different organ support systems interfere one to the other. This is the case of extracorporeal CO₂ removal interacting with the ventilator allowing modification of tidal volumes and performance of ultraprotective ventilation. It is also the case that continuous ultrafiltration may contribute to improve cardiac failure symptoms and congestion by optimizing fluid status and circulating volume in acutely decompensated patients treated with VA ECMO.

We may conclude that today we should consider in a multidisciplinary approach all possible interactions affecting the management of the critically ill patient. We must evaluate native organ interactions, artificial to native organ interaction and finally, artificial organ crosstalk. A new universe of physiological functions and pathophysiological interactions is born and the center of this universe is our patient.

Heart and kidney: from native organ to artificial organ crosstalk
A new universe of physiological functions and pathophysiological interactions

Physicians have been trained as single-organ specialists, often neglecting a multidisciplinary approach to patients and diseases. A significant amount of cardiovascular complications are observed in patients with chronic kidney disease, and heart failure is one of the major determinants of kidney dysfunction. The nature of heart and kidney interaction is evident and becomes even more evident in acute illness.

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Impressions of Day 2

Heart and kidney: from native crosstalk A new universe of physiological interactions

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