cause many comorbidities. We need to acquire the full picture, not just concentrate on the small core of renal replacement therapy, as it is often the case. Nephrology has to move forward and also has to occupy and strengthen its more peripheral areas. By doing so, we can develop and intensify our productive collaboration with other disciplines. We are already involved in many interdisciplinary projects, and there are many joint sessions at our Congress. But there is still room for improvement. Nephrology is not only about substituting for renal function – we have to move forward and revive every facet of our fascinating, overarching specialty. This is what we had in mind when we combined the initial banner theme with “Moving forwards”.

“We were the first discipline that could replace an organ function over a period of many years – something that is still not possible with the lungs or the heart – and I am optimistic that we will be the first to regenerate organ function”

Which general challenges does European nephrology face? What are the solutions to these challenges?

One of the most important challenges is to reverse the trend of diminishing interest in nephrology among young doctors. Between the 1960s and the 1980s, when nephrology was a young discipline, there was enormous enthusiasm – and many doctors wanted to be trained as nephrologists. It was perceived to be a very attractive and innovative specialty characterized by a pioneering spirit and entrepreneurial ingenuity. Dialysis was progressing rapidly and technological progress attracted many young talents. In recent decades, however, no groundbreaking changes in dialysis techniques have been achieved – from the outside it might even appear that progress is stultified. That is not the case, of course, because many advancements have been made, but they are certainly not as awe-inspiring as new inventions and new technologies. It is therefore time to widen our focus, as I pointed out before. There is so much thrilling basic research going on – and I am sure that in 30 to 40 years’ time we will no longer be talking about renal replacement therapy, but might even be able to regenerate kidney function or “grow” kidneys. We were the first discipline that could replace organ function for a period of many years – which is still not possible with the lungs or the heart – and I am optimistic that we will be the first to regenerate organ function so that our patients will not have to rely on the support of machines. So nephrology is still the same innovative, exciting and pioneering specialty as it was 40 years ago – the problem is that we neglected to communicate this, and that both the public and students of medicine perceive nephrologists as merely being the providers of dialysis care. This is what we have to aim at. We have to move forward and present the merits of present-day nephrology to the world.
Moving forward!

Professor Cannata-Andía, the main overarching theme or banner of the Congress is “Moving forwards” – and the Congress CI is a picture of a Spanish contemporary artist showing a woman moving forwards. Why do you think nephrology has to move forwards?

Well, the first motto we had chosen for this Congress was “Nephrology is much more than kidney disease”. Chronic kidney disease (CKD) is strongly related to aging somehow, and is even synonymous with premature aging. Moreover, it often affects older people, so it is also associated with cardiovascular disease, bone disease, hyper-tension, diabetes or rheumatic disease. That explains why there are so many overlaps between nephrology and other specialties of inner medicine. In my opinion, nephrology has to move forward in terms of its self-conception: Nephrology is still mainly perceived of as an organ-centered specialty focusing on the kidneys only. But we European nephrologists need to understand our discipline as a more general one, dealing with a kind of systemic disease, because kidney diseases affect many other organ systems and cause many comorbidities. We need to acquire the full picture, not just concentrate on the small core of renal replacement therapy, as it is often the case. Nephrology has to move forward and also has to occupy and strengthen its more peripheral areas. By doing so, we can develop and intensify our productive collaboration with other disciplines. We are already involved in many interdisciplinary projects, and there are many joint sessions at our Congress. But there is still room for improvement. Nephrology is not only about substituting for renal function – we have to move forward and revive every facet of our fascinating, overarching specialty. This is what we had in mind when we combined the initial banner theme with “Moving forwards”.

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Is that the reason why this year’s plenary speakers will be delivering main lectures on basic research topics?

Yes, they will all be speaking about promising ideas and concepts on the horizon that will influence, if not totally change, nephrology. Juan Carlos Iztapala Belon, from the University of California, will talk about “New approaches towards kidney regeneration” – a topic I have already mentioned. Hiroki Ueda from Tokyo will talk about “Whole-body and whole-organ clearing and imaging”. Steven Benner from Alachua in Florida on “Re-creating life”. The title of the lecture by Miguel Hernan from Boston is “Comparative effectiveness research in nephrology: using electronic health records to emulate randomized trials”. This is of special importance to nephrology, because they fear they might not get a proper return on their investment, due to their relatively small number of patients compared to cancer patients, for example. So what can be done? Miguel Hernan will give an outline of how “big data” can be used, and how we might simulate clinical trials with databases containing the electronic health records of our patients. I am sure that “big data” will provide an enormous impetus to innovate our discipline in the near future.

Apart from the plenary lectures, what are the main highlights of the scientific program, in your personal opinion?

That’s impossible to say! We have a great program with more than 60 sessions – it would be unfair to name one or two only. The lectures will all be of high quality and everybody should choose his/her “personal Congress program” according to his or her particular interests. I, personally, am very interested in the topics of aging and CKD, the heart–cerebrovascular axis, and all the mechanisms related to it, in new biomarkers that can help us detect CKD progression early, and in glomerular diseases. All the sessions on diabetes will also be very exciting, I am sure, due to the new drugs that have been introduced. On top of that, I am very interested in the topic of “physical exercise in renal patients”. According to recent studies, patients’ morbidity and quality of life can be improved if patients do exercises during dialysis. This is an opportunity we have failed to exploit so far. I am also looking forward to the sessions on DOPPS and COSMOS. These observational studies deliver new data every year that help in the management of everyday practice.

What do you think makes Congress especially attractive for young nephrologists?

I believe one reason to attend the congress is its sheer wealth of content. The whole field of nephrology is covered – and the program offers news and reviews! On Saturday we have the educational symposia, and I think these CME courses should be of special interest to young colleagues. Let me highlight and invite to one special session which will be held on Saturday from 12 to 2 pm, namely the symposium on the future of nephrology. There we want to discuss with young doctors why they decided to become nephrologists – or why they decided not to do so. We started an online survey and received responses from more than 1,000 participants. The results will be presented and discussed.

In addition, I am very proud that we will be handing over the certificates for the “European Nephrology Exam” to all those who passed. The exam was held for the first time this year and will facilitate the physicians to work in other European countries. We initiated this project and therefore I am greatly committed to it – we nephrologists still believe in Europe!

To what extent does the scientific program reflect Spanish topics and speakers?

You know, in 1999, when I was Congress Secretary of the ERA-EDTA Congress in Madrid, only about 2% of the faculties were from Spain. Now, more than 12% of the faculties are Spanish colleagues, and that, I think, shows that Spanish nephrology is “healthy” and highly productive. I am happy to be part of this scientific community – muchas gracias a todos!

Speaking of Spain – what should participants from abroad who are in Madrid for the first time make sure they see or do apart from attending the Congress? What’s your insider’s advice?

First of all, I would like to mention the museums – the Prado, the Reina Sofia and many other museums of classical and contemporary art. Another highlight are the palaces. You should come and see the Royal Palace, at least, and stroll around the parks surrounding it. They have a very special atmosphere, especially in early summer evenings. And, of course, you must visit the old town, the Plaza Mayor, and the numerous tapas bars. You’ll love it! Bienvenidos a Madrid!

We’re happy that our article helped to spread the word!© ekaterina_belova, fotolia.com

In May 2016, the paper “Does pre-emptive transplantation versus post start of dialysis transplantation with a kidney from a living donor improve outcomes after transplantation? A systematic literature review and position statement by the Descartes Working Group and ERBP” was published in Nephrology Dialysis and Transplantation. The publication was the most popular article in the “Transplant Library” in 2016 and was read more than 700 times. “This is flattering, of course. But in my view, this success mainly reflects the efficient and praxis-oriented collaboration of the Descartes Working Group and ERBP (European Best Practice)”, explains Prof. Wim Van Biesten, ERBP chairman. “The fact that we – two organizations of high reputation under the roof of the ERA-EDTA – worked together has obviously enhanced the impact of the paper. Besides, we addressed a topic of high relevance.” The review showed that pre-emptive transplantation in patients with a living donor can improve patient and graft survival and reduces the risk of acute rejection. The authors therefore recommended pre-emptive transplantation when a living donor is available, but they also discussed the other side of the coin: too early transplantation. Patients should be prepared timely, so actual transplantation can take place at the moment kidney function reaches a level where otherwise dialysis would be started. Besides, the paper suggests to set up a quality registry with the aim to measure the outcomes of the transplanted patients and their donors. “This is important, because we have to evaluate and outweigh possible benefits for the recipient and possible donors’ risks”, concluded Van Biesten. “We are happy that our article helped to spread the word!”

In the moment, ERA-EDTA supports 8 scientific groups, all of which are very active. Find out about the working groups’ CME courses on the following pages!

Hypertension in Dialysis Patients – Joint Consensus Document by EURECA-m and ESH

In patients with end-stage renal disease (ESRD) treated with haemodialysis or peritoneal dialysis, hypertension is common and often poorly controlled. This is the reason why the European Renal and Cardiovascular Medicine (EURECA-m) working group of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) and the Hypertension in the Kidney Working Group of the European Society of Hypertension (ESH) prepared a joint position paper (leading author: Professor Pantelis Sarafidis, Greece) on the diagnosis and treatment of hypertension in dialysis patients, that was published in NDT – one of the two official journals of the ERA-EDTA. The following recommendations are given in the paper: For the diagnosis of hypertension in haemodialysis patients a 24h (even better 44 h) ambulatory blood pressure monitoring (ABPM) should be made during a mid-week day free of dialysis. The diagnosis should not be based on pre- or post-dialysis blood pressure. Alternatively, home blood pressure (BP) measurements can be used to diagnose hypertension. One of the main pathogenic mechanisms of hypertension in dialysis patients is volume (and sodium) overload. This is why targeting this is fundamental for BP reduction in this population. The main non-pharmacological measures to reduce volume and (sodium) overload in haemodialysis patients are reaching the individual patient’s dry weight, the minimization of inter- and intra-dialytic sodium gain (e.g. by restriction of sodium intake to 1.5 g of sodium or 4 g of sodium chloride per day), and avoidance of short (i.e. <4 h) dialysis sessions. “These non-pharmacological interventions should be carefully implemented before considering pharmacological treatment”, explains Professor Carmine Zoccali, NDT editor-in-chief. “This is a task for the patient – he has to comply with a sodium-reduced diet –, but for the nephrologist, too: he has to optimize the dialysis treatment.” If medication is necessary, the use of β-blockers followed by aldosterone antagonists should be considered, while the first-line use of ACEs and ARBs in this dialysis population is not supported by randomized trials. “Nevertheless, we have to keep in mind that the use of any antihypertensive agents is associated with improvement in cardiovascular outcomes – and might therefore be beneficial for the patients”, comments Professor Zoccali. As the authors of this position paper emphasize, properly designed epidemiology studies and clinical trials to define BP targets for treatment and evaluate treatment effects in this population are still needed.
Managing CKD, Diabetes & CVD: Is epigenetics a new way forward?

A new event format will be introduced at this year’s ERA-EDTA Congress, which takes place on June 3–6, 2017, in Madrid, Spain. In this interactive workshop, various techniques to improve the communication with the patients can be learnt. The innovative thing about this session: The knowledge is not transported in a “dry” lecture-style, but acted out right before your eyes, to enhance learning experience and content retention.

“We doctors always focus on medical aspects, but there are many other aspects that have a clear impact on how patients feel and also on their outcome.”

Two professional actors will play various scenarios, typical scenes of a nephrologist’s everyday-life, in which the patient-doctor-communication can be sub-optimal. After the negative example has been acted out, Professor Van Biesen will give a short analysis, in which the audience will be involved, why the communication was poor and what could be done to improve it. Then, the actors will give a positive example of the same situation, in which the communication is done in a more effective style. “The motto of our symposium is ‘experience & learn’ instead of ‘lecture & learn’, because learning through experience is the most effective way”, explains Van Biesen.

Being asked why it is important for nephrologists to further improve their communication skills the expert answers: “We doctors always focus on medical aspects, but there are many other aspects that have a clear impact on how patients feel and also on their outcome. This is often underestimated. Take adherence, for example. If you do not bring the patients perspective in when you make a certain therapeutic decision, the chances are high that the patient will not adhere to the therapy. This is why patient-doctor-interaction is extremely important.”

The interactive workshop is divided into two parts. The first session will focus on communication in general. “There are different archetypes of patients, e.g. the non-responder or the one who knows everything better, and the audience learns how to best deal with each type”, explains Van Biesen. The second session in the afternoon will focus on shared decision making, especially on how you can enable a patient to make a therapeutic decision. “Active patient participation is really important nowadays. We moved from the concept of compliance – which somehow means that the patient just has to obey – to that of adherence, which means that the patient understands, agrees to a certain therapy and is therefore willing to follow and stick to it.” But how can this aim be reached? The key to it is “empathic listening”. It is central to acknowledge the emotional state of a patient first (“I see that you are feeling upset” or “I see that you are worried”) and then to respond appropriately. “This is why our workshop is called ‘Patient-Doctor-Communication acted out: An innovative way to further improve your communication skills’”, explains Van Biesen.

“I am sure, it will be enlightening and fun!”

“Difficult patient or wrong communication?”, June 3, 10.45 – 11.45

“Shared Decision Making with patients: opportunities and pitfalls”. June 3, 11.45 – 12.15

Special Interactive Session
June 3, 13.45 – 14.45

MONDAY, JUNE 5 2017, 13:45 – 14:45 HRS • SALA RETIRO

patients: opportunities and pitfalls” Sala Retiro
Personalized treatment in ANCA-associated vasculitis

When reading recently published guidelines on the treatment of ANCA-associated vasculitis (AAV), one can get the impression that the same regimen should be offered to all patients. That one size fits all. However, when looking at the text more carefully it becomes evident that the therapy should be tailored according to a whole series of factors. Beyond the guidelines, there are data from observational studies, not supported by hard evidence, that can be taken into account when finalizing the prescription for the individual patient (Table 1).

Most drugs, like azathioprine (AZA), are adjusted by body surface area. Many drugs should be reduced in renal insufficiency, but the reduction is not always proportional to the decline in glomerular filtration rate (GFR).

This is, for instance, the case with cyclophosphamide (CYC). The dose of CYC is also lowered in elderly patients without renal failure due to presumed bone marrow sensitivity.

These crude dose adaptations could be refined with better knowledge of the individual pharmacokinetic profile of the patient. Measurement of trough levels is not easily available for most drugs used in AAV. For AZA, it is possible to measure gene variants leading to reduced activity of the main metabolizing enzyme (thiopurine methyltransferase) or directly measure the enzyme activity in vitro. For CYC, polymorphisms in metabolizing enzymes also affect drug efficacy and toxicity, but have not yet reached clinical practice.

The EUVAS study group, which has launched many of the pivotal studies in the field of AAV, has based their trial design on two assumptions. One is that disease severity should be taken into account and the other is that the disease phenotype should not be considered. The first assumption is supported by the Five Factor Score developed by the French Vasculitis Study Group. According to the FVSS, at least osmoprotic granulomatosis with polyangiitis (GPA) but maybe also microscopic polyangiitis (MPA) with a score of zero can be treated with steroids alone. On the other hand, EUVAS studies with mycophenolate and mycophenolate in non-severe AAV show that such induction therapy is associated with a very high relapse rate. At the other end of the spectrum, guidelines call for the addition of methylprednisolone and/or plasma exchange in life-threatening disease.

The lumping together of MPA and granulomatosis with polyangiitis (GPA) in treatment recommendations has been questioned. GPA has a much higher relapse rate than MPA, which has a bearing on the length and intensity of the maintenance therapy. Data from observational studies indicate that certain features, such as lung involvement or serology (PR3-ANCA, MPO-ANCA or ANCA-negative), may be even more important than the GPA/MPA dichotomy.

Persistence and recurrence of antineutrophil cytoplasmic antibody (ANCA) seem also to influence the risk of relapse, but the value of ANCA to guide therapy is debated. Views ranging from ‘useless’ to ‘very helpful’ can be heard. Recent data suggest that changes in ANCA levels are more informative in AAV with renal disease as compared to non-renal vasculitis. B-cell count has, along with ANCA, been suggested as a biomarker for predicting relapses after RTX. There are ongoing studies comparing preemptive re-treatment based on biomarkers with re-treatment at fixed intervals.

Exactly how previous treatment and previous response to therapy should be taken into account when deciding upon treatment is open for debate. The RAWE trial shows that RTX is superior to CYC in patients previously treated with CYC, and similarly the MAURITZAM trial shows that in patients induced by CYC, RTX maintenance therapy is superior to AZA. This does not necessarily mean that RTX is also superior as first-line induction therapy. Actually, data from the RAVE trial show (numerically but not statistically) better results in treatment-naive MPO-ANCA patients with CYC compared to RTX.

Atherosclerosis is very prevalent, accelerated and closely associated with cardiovascular events

The analysis also identified several CKD-related factors as independent factors associated with plaque presence. For instance, higher phosphate levels and lower 25(OH) vitamin D levels emerged as new variables that can explain at least part of the higher incidence and severity of atherosclerosis in CKD. In the case of phosphate, further analysis revealed that the blood levels associated with the presence of plaque are different in men and women. Although phosphate levels within the normal range are associated with the presence of atherosomatic plaque in men, this association is not found in women until phosphate reaches pathological levels. Due to this differential effect regarding sex, recommended serum phosphate levels could be different for male and for female CKD patients.

The study has also confirmed that low sTWEAK levels, which are associated with atherosclerosis in the general population, also show a strong association with subclinical atherosclerosis in CKD patients. In addition, angiotensin-converting enzyme 2 (ACE 2), an enzyme that converts angiotensin I to angiotensin 1 – 7 and angiotensin 1 – 9, has been identified as a new marker of silent atherosclerosis in CKD.

The rate of atherosclerosis progression has been also analyzed in the cohort. Data indicate that

Table 1: Patient factors influencing treatment decisions in ANCA associated vasculitides.

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<tr>
<th>Patient size and age</th>
<th>Renal and liver function</th>
<th>Comorbidities</th>
<th>Disease severity and phenotype</th>
<th>Response to treatment and previous responses to treatment</th>
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 Europeans Renal and Cardiovascular Medicine

Cardiovascular risk in CKD: novel insights from the NEFRONA study

Cardiovascular disease is the main cause of death in patients with chronic kidney disease (CKD), in whom cardiovascular death is a more likely outcome than progression to end-stage renal disease (ESRD). Although numerous studies show an association between decreased kidney function and cardiovascular disease and mortality, mechanisms underlying this association are incompletely understood. Thus, the contribution of atherosclerosis to the increased cardiovascular morbidity in CKD has been usually neglected, probably because the main cardiovascular events in ESRD seem to be related to electrolyte imbalance.

However, some of the events labeled as sudden death could be undiagnosed silent myocardial infarctions, as are often found in this population. In addition, atherothrombotic events are very prevalent in earlier stages of CKD. Furthermore, the JUPITER and SHARP trials demonstrated that treatments aimed to reduce lipid burden are effective in reducing cardiovascular events, mainly in early stages of CKD. Thus, the NEFRONA study was designed to determine the role of subclinical atherosclerosis on cardiovascular events of CKD patients.

The study recruited 3004 subjects (559 controls, 950 CKD stage 3, 807 CKD stage 4 – 5, 688 dialysis) in 81 hospitals of Spain with a median follow-up of 48 months. The cross-sectional analysis of the population showed that the prevalence of atherosclerosis increased progressively with more advanced CKD stages, suggesting that there is a close association between atherosclerosis and CKD. The multivariate logistic regression model identified CKD as an independent factor associated with the presence of plaque, with a higher odds ratio in more advanced stages.

Therapy must be tailored to the needs and preferences of each patient

Patient preference is naturally an important aspect of individualized therapy. A wish to preserve fertility is a common reason for choosing RTX instead of CYC, and intermittent intravenous CYC instead of daily oral dosing. Side effects and fear of relapse should influence length of maintenance therapy.

CME 1 – IWG
News in the pathogenesis and treatment of glomerular disease

Saturday, 08.30 – 11.45, Hall 10A

News in the pathogenesis and treatment of glomerular disease
Is there a role for iron beyond erythropoiesis in patients with chronic kidney disease?

Chair: Professor Danilo Fliser
Sunday 4 June 2017
13:30–15:00
Hall 10.B, IFEMA Feria de Madrid (North Congress Centre)

Objectives
- Discuss benefits of treating non-haematological effects of iron in nephrology
- Review clinical evidence from cardiology studies and interpret them from a nephrologist’s perspective

Programme
13:30 Lunchboxes will be provided
13:45 Chair’s welcome and introduction
Danilo Fliser (Saarland University Medical Centre, Homburg, Germany)

13:55 Interactive panel discussion
Open panel discussion based on expert experience and recommendations for treating iron deficiency
Danilo Fliser
Iain Macdougall (King’s College Hospital, London, UK)
Carlo Gaillard (University of Utrecht Medical Centre, Utrecht, The Netherlands)
Austin Slack (Health Research Institute, Limerick, Ireland)
Josep Corom-Çolet (Bellvitge University Hospital, Barcelona, Spain)
Darlington (Obi) Okonko (King’s College Hospital, London, UK)

Meeting close
www.era-edta2017.org

progression of atherosclerosis is strongly influenced by the presence of plaque at baseline. Thus, patients free from the disease remain mostly atherosclerosis-free during the next two years. These ‘protected’ patients are a very special subpopulation within the NEFRONA cohort, and are of high interest in order to identify possible protective factors.

Another interesting result showed that patients who exhibited progression of CKD were more likely to have progression of atherosclerosis, underscoring the close association between both pathologies. Furthermore, several CKD-related variables like phosphate, uric acid and 25(OH) vitamin D are predictors of subclinical atherosclerosis progression over two years. Finally, analysis of the cardiovascular events identified the presence of plaque as a very strong predictor of an event, confirming atherosclerosis as a factor influencing cardiovascular mortality in CKD.

In summary, atherosclerosis in CKD is very prevalent, accelerated and closely associated with cardiovascular events. Its determination by a simple method like ultrasound could be very useful in calculating cardiovascular risk in CKD patients.

Developing Education Science and Care for Renal Transplantation in European States

Before wait-listing: pre-transplant cardiac work-up

Optimal cardiovascular work-up for potential renal transplant recipients remains controversial. Cardiorenal disease (CRD) is the leading cause of death of patients with end-stage renal disease (ESRD), whether treated with dialysis or following successful renal transplantation. Moreover, CVD is a leading cause of death with a functioning kidney transplant, and therefore should be considered a major cause of premature kidney transplant failure. Furthermore, as well as improving life expectancy and quality of life, successful renal transplantation is associated with a dramatic reduction in cardiovascular risk compared to dialysis. Therefore, transplantation represents an intervention that reduces long-term risk of cardiovascular events in ESRD, albeit this is untested in a prospective randomized controlled trial.

So, what are the goals of cardiovascular work-up in patients going on the list for kidney transplantation? Importantly are there any benefits for an individual patient? Critically, patients whose perioperative risk of a cardiac event is unacceptably high, in whom safe anesthesia is contraindicated, should be identified. Reversible cardiovascular risk factors should be addressed or cardiovascular status should be optimized; e.g. patients with symptomatic critical coronary artery disease should undergo revascularization. Timing of cardiovascular work-up and intervention should be scheduled such that potential perioperative cardiovascular or bleeding risk is minimized, whilst avoiding undue delay to transplant listing.

Where availability of organs for transplantation is outweighed by the number of patients on the transplant list, some consideration of the utility of the transplanted organ compared to expected long-term survival of the recipient should be given, although using cardiovascular screening to ration organs should not be acceptable. If the patient’s cardiovascular status permits safe undertaking of the transplant operation, then those patients at higher cardiovascular risk also most likely experience relative benefit compared to staying on dialysis. Sadly however, some patients may always remain at such extreme high cardiovascular risk that transplantation cannot be undertaken. In these cases, objective cardiovascular testing may permit informed discussion with the patient about why the decision not to list them for a transplant has been taken.

For many patients with kidney failure, cardiovascular assessment is fraught with potential dilemmas. The prevalence of cardiovascular risk factors such as hypertension, diabetes, dyslipidemia and left-ventricular hypertrophy is high. Standard investigations for cardiovascular assessment such as ECG, echocardiography (often with dobutamine stress), myocardial perfusion scanning, or coronary CT scanning often reveal abnormalities that have prognostic significance, but may not lead to inventions such as coronary revascularization. These abnormalities may lead to some delay in transplant listing whilst consideration is given to whether they require specific therapy. Expert assessment by the multidisciplinary team (surgeons, nephrologists, cardio-

Uncertainties exist, but provide opportunities for patients and nephrologists

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gists and anesthetists) should lead to rapid resolution of these dilemmas to allow timely wait listing or further testing where required.

Whilst these uncertainties exist, cardiovascular assessment for kidney transplantation presents opportunities for both patients with kidney failure and their nephrologists. Cardiovascular assessment for transplantation should be personalized to be appropriate for that patient’s background risk. Discussing cardiovascular assessment permits dialogue between patient and clinician around the nature of cardiovascular disease in kidney failure and may lead to optimization of treatment to minimize future cardiovascular risk, not only for renal transplantation.

Consideration can be given to management post-transplantation to minimize cardiovascular risk, such avoidance of post-transplant diabetes, steroid avoidance or maintenance of a healthy lifestyle to address obesity and hypertension. Finally, although of less direct benefit for individual patients, over the years cardiovascular screening for transplantation has provided several insights into the nature of CVD in kidney failure and continues to provoke clinicians to optimize novel techniques for assessment of cardiovascular disease in this patient group.

The RKF provides effective and naturally continuous clearance of both small and middle molecules; it is associated with better patient survival and greater health-related quality of life, and plays a major role in effective phosphorus excretion, and endogenous vitamin D and erythropoietin production. [1] While the RKF and urine output do not measure the same physiologic quantities – the former is clearance while the latter is just a fluid volume – they are closely related, as documented by some of our own data (Figure 1). Preservation of the RKF requires a careful approach, including regular monitoring, avoidance of nephrotoxins, gentle control of blood pressure to avoid intradialytic hypotension, and an individualized dialysis prescription including consideration of incremental HD.

Although the regulatory agencies might consider the 3HD/wk regimen as ‘standard of care’ and ‘adequate requirement’, it is by no means perfect. The 3HD/wk regimen has been assumed, until recently, almost as a dogma in the dialysis community. Historically, however, HD started with two treatment sessions per week in the 1960s and 1970s, but by the early 80s HD frequency had increased to 3HD/wk. Incredibly, the 3HD/wk schedule has been widely accepted worldwide without ever undergoing any randomized controlled trial (RCT) to examine whether less frequent HD treatment would be inadequate or harmful.

Owing to this background, it is easy to understand why an HD frequency of less than 3HD/wk is rarely prescribed in Europe (currently in only 5.2% of all patients in Europe), and even much less so in the US and Canada (probably less than 1%). In contrast to Europe and the US, a recent study reported that 26% of the Chinese dialysis population are treated using a 2HD/wk schedule, which may be the result of socioeconomic conditions, including less access to dialysis therapy and inadequate resource availability. [1]

There is currently no standardized method of applying incremental HD in practice. Infrequent (once- to twice-weekly) HD regimens are often used arbitrarily, without identifying the patients who would benefit most from them or how to escalate the dialysis dose required as RKF declines over time. The recently heightened interest in incremental HD has been hindered by the current limitations of urea kinetic models (UKM), which tend to overestimate the dialysis dose in the presence of substantial RKF. This is due to an erroneous extrapolation of the equivalence between renal urea clearance (Kru) and dialyzable urea clearance (Kd), correctly assumed by the UKM, to the clinical domain. In this context, each ml/min of Kd clears the urea from the blood just as 1 ml/min of Kru does.

By no means should such kinetic equivalence imply that 1 ml/min of Kd is clinically equivalent to 1 ml/min of urea clearance provided by the native kidneys. [1] A recent paper by Casino and Basile suggested a variable target model (VTM), which gives more clinical weight to the RKF and allows less frequent HD treatments at lower RKF, as opposed to the fixed target model, based on the wrong concept of the clinical equivalence between Kru and Kd. [2] An RCT comparing incremental HD with the standard 3HD/wk in incident HD patients is urgently needed and should be planned to test the VTM hypothesis formulated by Casino and Basile. [2]

In conclusion, the potentially important clinical and financial implications of incremental HD render it highly promising and warrant RCTs. The UKM is the keystone for conducting such studies.
Due to the scarcity of deceased kidney donors, live-kidney donation is now widely implement-ed; however, ABO-incompatibility (ABOi) and/or HLA incompatibility (HLAi) are often problematic. HLAi refers to the presence, at pretransplant, of preformed donor-specific alloantibodies (DSAs). In the setting of ABOi, we have to deal with isoagglutinins (both IgG and IgM). If we want ABOi and/or HLAi kidney transplantation to succeed, isoagglutinin titers need to be lowered to < 1/16 and DSA levels to < 3,000 MFI (mean fluorescence intensi-tity) at pretransplant. This can be achieved by desensitization, which relies on immunosuppressive drugs, e.g., rituximab, tacrolimus, mycophenolic acid (MPA), which can prevent antibody synthe-sis, and on anaphylaxis (plasmapheresis, double-fil-tration plasmapheresis, immunoadsorption, both specific and semi-specific), which can remove the culprit antibodies (isoagglutinins or DSAs).

Desensitization has proven to be very effective at treating patients that are ABOi. The ABO Japa-nese registry showed that the long-term patient and graft survival rates of > 2,300 ABOi kidney transplant recipients were very similar to the data from ABOi-compatible kidney transplant patients. This is particularly striking as rituximab has now replaced plasmapheresis. In this registry, it was ob-served that isoagglutinin-mediated acute rejec-tion mainly occurred within the first 3 weeks post-transplant, irrespective of the isoagglutinin titer at the time of transplantation. Beyond three weeks posttransplant, there were almost no graft rejec-tions, because at this point accommodation has taken place. However, one of the concerns with re-gard to ABOi kidney transplantation is the high oc-currence of posttransplant DSA replication, which could be minimized by replacing at posttransplant MPA by everolimus.

HLAi kidney transplantation is much more chal-lenging, because depending on the pretransplant DSA level, it can be very difficult to decrease the threshold level to below 3,000 MFI. It has been recognized that when the DSA level at transplant is below 3,000, the risk of acute antibody-mediat-ed rejection is quite low. There are two scenarios: living-kidney or deceased-kidney transplantation. In case of living-kidney transplantation, desensiti-zation takes place pretransplant. In some instanc-es, this can be achieved with IVIg + rituximab, rit-uximab + IVIg + plasmapheresis, or with ritux-imab + semi-specific immunoadsorption (SSIA). In our experience, rituximab + SSIA (Gulati® col-umns) + membrane filtration, i.e., Monet®, is very efficient. However, at present, it is almost impos-sible to desensitize patients that have a DSA lev-el of > 15,000 MFI. In this situation, tocilizumab may be of value. A series of HLAi kidney patients at Cedars Sinai Hospital (LA, USA) that had failed de-sensitization with IVIg + rituximab were success-fully desensitized with tocilizumab, and had good outcomes after transplantation, without increas-ing the risk of opportunistic infections. In the USA, a retrospective study that included > 1,000 HLAi living-kidney transplant recipients that had un-derged pretransplant desensitization has shown that those who were HLA-desensitized had signifi-cantly better long-term patient survival rates com-pared to matched kidney patients that were on a waiting list, and who subsequently had a trans-plant from a deceased donor, or than those who remained on dialysis.

In case of HLAi deceased-kidney transplant desen-sitization takes place both at pre- and post-trans-plant. The first step is to have a negative cross-match by microlymphocytotoxicity, e.g. immedi-ately before transplantation, the patient is submit-ted to an apheresis session plus one injection of rituximab; posttransplant desensitization is pro-longed by apheresis sessions, IVIg, and rituximab. Immediately before transplantation, the patient is submitted to an apheresis session plus one injec-tion of rituximab; posttransplant desensitization is prolonged by apheresis sessions, IVIg, and ritux-imab. However, despite HLA desensitization re-gardless of the type of donors, these desensitized patients experience significantly higher rates of antibody-mediated rejection; nonetheless, this does not impair long-term allograft survival rates.

The use of Immunoglobulin G-degrading enzyme of Streptococcus pyogenes (IdeS) could soon change dramatically the way we envision pre- and post-transplant HLA desensitization.

Desensitization for ABO-incompatible and for HLA-incompatible kidney transplantation

High-volume hemodiafiltration: the new standard treatment

Convective renal replacement therapies, espe-cially online hemodiafiltration, raise an increas-ing scientific and clinical interest. The number of patients treated with online hemodiafiltration is growing, and the highest prevalence of end-stage kidney disease (ESRD) patients treated with this modality is found in Europe. The Euro-pean nephrology community has been leading in this field of renal replacement therapy for more than two decades.

Randomized controlled trials comparing the out-comes of ESRD patients treated either with on-line hemodiafiltration or with conventional he-modiafiltration have been concluded over the past few years. A recent meta-analysis of all individ-ual data from these available trials, which was performed with the financial help of EuDiAl, sug-gests improved clinical outcome in patients who are on online hemodiafiltration. This is especial-ly the case when convection volume is > 23L/ses-sion or more (which equals to approximately 70L/ week). [1, 2] The existence of this ‘minimum dos-age’ to fully obtain the benefits of online hemo-diafiltration has been confirmed by large obser-vational studies.

The actual achieved convection volume per treat-ment session may differ from the set target vol-ume. Main determinants of achieved volume are treatment time (4–33 %), blood flow rate through the extracorporeal circuit (minimum of 350–400mL/min) and set filtration fraction (ratio of ultrafiltration volume/blood flow rate through extracorporeal circuit: aim at 30–33 %). Studies suggest that when these factors are tak-en into account, the minimum convection volume of 23L/session can be achieved in the great ma-jority of patients.

Further analysis indicates that in particular the risk for mortality due to cardiac causes is re-duced. [3] To date, the mechanism(s) of this ben-eﬁcial effect is(are) not completely understood. These may include: improved hemodynamic sta-bility, enhanced clearance of uremic toxins, re-duced chronic inﬂammatory state, and others. Importantly, none of the trials has raised any safety concern about the large-scale use of on-line hemodiafiltration.

In this presentation, the question will be ad-dressed whether online hemodiafiltration is ready to be accepted as the new standard of treatment.

Still questions remain open. So, for the near fu-ture EuDiAl working group will remain focused not only on increasing the knowledge of this ﬁeld, but also on organizing CMEs and other ac-tivities to review and share the information with others. Future studies should focus on the mech-anism(s) of a beneﬁcial effect of online hemo-diaﬁltration. Further, little is known on the effects

References

CME 4 – EUDIAL
Imposing the outcome of dialysis
Saturday, 08.30 – 11.45, Hall N101 – 102
Hemodiafiltration has no (significant) advantage over high-flux HD

As often, this behavior mainly originates from the uncountable retrospective studies that almost consistently demonstrate a better survival and lower morbidity in prevalent HD patients allocated to HDF instead of low- or high-flux-HD. But sometimes, and sadly too often, we hear a story that is too good to be true. These studies repeatedly suffer from including bias (especially selection bias, informative bias, lead time bias and others). That is why randomized controlled trials (RCT) should do the trick.

Unfortunately, the majority of RCTs, of which three larger ones are dominating the current evidence, were characterized by a moderate- to high-risk of bias. Moreover, they principally failed to demonstrate a significant beneficial effect of HDF on overall mortality according to published meta-analyses that were not overly restrictive in their inclusion of trials (Figure 1). Also, effects on secondary or surrogate endpoints were often variable, negligible or even absent. In post hoc analyses, patients receiving the highest convective volume consistently and dose-dependent had a better outcome. Unfortunately, as those studies were not a prius designed to clarify this issue, we cannot exlude that the ability to reach a maximally attainable convective volume teaches us more about the health state of the patient (with vascular access as a proxy) or the dialysis center than of the utilized technique. Without adjustment for body surface and with variable and seemingly random thresholds, the external validity and the translation from this technical issue to the floor of the dialysis unit remain undefined.

So we have to ask ourselves what advantages online HDF can offer, apart from fewer hypotensive episodes during dialysis? According to a recent RCT, HDF was not associated with a shorter recovery time from dialysis, nor better quality of life according to standardized measurement tools. The field now gets more slippery and the question of whether we should prescribe this still more expensive and laborious technique to all HD patients cannot be answered entirely by the current evidence. Also, a bothering fact remains in the staggering melting pot of practices in the intervention (pre-, post- or mixed dilution), but especially the comparator groups (low-flux HD, high-flux HD or a mix of both), in both observational, interventionial and pharmaco-economic studies (Figure 1). We should choose our cards and design our studies accordingly. Ironically, high-flux HD should be considered a hybrid technique, as well incorporating low-volume convection of less than 10 L per session.

Finally, the actual evidence for the potential added value of convention should be accessible to all stakeholders, including patients and healthcare providers. Shared decision-making and a more patient-centered approach should definitely become a therapeutic target.

Can we use routine primary care data to estimate the number of people with CKD?

Using routine data from primary care to estimate the number of patients with chronic kidney disease (CKD) would enable big-data research on the burden of CKD, its risk factors, and outcomes. It would also enable better planning of local health services. There are a few issues that need to be considered when using big data, which are best understood if we contrast the best case scenario with what happens in reality – here I use the example of the UK system.

If we did a survey, we would want to measure a representative sample of the population at one point in time using blood and urine tests, using the same assays for everybody. This happened in the UK in 2009/10 as part of the Health Survey for England. If we want to use routine care data instead of doing a survey, we first need to understand the denominator data – i.e. who are the people seen in primary care? Is it everybody, or would we only see sections of the population depending on their income or other factors? What exactly is recorded in primary care data?

The UK has a gatekeeper system in which access to health care requires registration with a general practitioner (GP). GP practices have been computerized since the early 1990s, capturing clinical diagnoses using Read-codes, prescriptions, and laboratory test results. If appropriate ethical approvals are in place, anonymous data can be used for research for a fee. The Clinical Practice Research Datalink (CPRD) covers 7–8% of the UK population and is representative in terms of distribution of sex, age and ethnicity [1]. Hence, in theory, if we use CPRD we could assume that we have a snapshot of a percentage of the UK population.

Yes, but we need to overcome the challenges of using big data

A survey would test everybody with the same assay to find the people with biochemical evidence of CKD (numerator). In reality, not every patient undergoes testing for renal function in primary care – currently this is only advised in the UK for people who are considered at risk of CKD. Therefore, a large proportion of the registered practice population will not have a creatinine test on file,

Figure 1: The effect of convective therapy versus high/low flux hemodialysis on mortality: summary of published meta-analyses. © van Laecke

Figure 1: Prevalence of eGFR <60 ml/min/1.73 m² modified according to [1] © Nitsch

References


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Approximately two million people worldwide receive renal replacement therapy. The pandemic of obesity and diabetes will boost the prevalence of end-stage kidney disease (ESKD) in the future. This will obviously translate into incremental costs and imminent pressure on global health budgets. Luckily, the search for optimization of hemodialysis (HD) is still ongoing.

Online hemodiafiltration (HDF) is a safe technique that is increasingly being used in many, especially European, dialysis centers, because of its optimized clearance of larger uremic retention solutes, the so-called middle molecules. The increased clearance of these solutes, including cytokines and beta-2 microglobulin, is expected to improve overall survival and cardiovascular outcome. How can we now explain the seemingly exponential rise in utilization of this expensive technique with doubleable cost-efficiency when compared to low-flux HD?
When interpreting data over time it is also important to consider whether there are incentives for testing or diagnosing CKD. Not every patient with an abnormal creatinine test will necessarily be re-tested or recorded as having CKD. Indeed, this was one of the reasons why the National Health Service (NHS) commissioned the National CKD Audit [2]. The Audit shows that testing patterns vary by general practice and by type of risk factor, and testing for albuminuria is poor for anyone without diabetes.

The contrast between the perfect scenario and routine primary care data shows the challenges when using big data. However, we can learn from the Audit to make some assumptions. If we can assume that the majority of people with an estimated glomerular filtration rate (eGFR) <60 ml/ min/1.73 m² end up being tested by their GP within a defined time period, the prevalence of eGFR <60 ml/min/1.73 m² in the CPRD should mirror the prevalence in the Health Survey for England. This is indeed the case (figures) [3]. The CME talk discusses in more detail various sensitivity analyses in terms of using different eGFR formulae, the role of creatinine calibration, and varying time-periods for capturing cases of CKD.

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Reading a systematic review: a hands-on experience

What is a systematic review and what are they good for?
Systematic reviews are key to evidence-based medicine and are the cornerstone of trustworthy guideline development. Relevant research for daily practice is scattered throughout the medical literature, and with ever-increasing numbers of studies published, it has become impossible to stay up to date. Systematic reviews provide a summary of the available empirical evidence for a specific clinical question, and are thus a practical way to stay informed without having to search for and read through all primary research studies ourselves.

What’s so special about reading a systematic review?
Despite a clear argument for having systematic reviews, some are more trustworthy than others and, whether topics could be appropriately addressed by systematic review. A list of suitable topics was than analyzed in Delphi rounds between clinicians and patients. The final guideline scope covers four subgroups: catheter-related topics; peri-operative-related topics; peri-and postoperative topics; and topics related to surveillance/maintenance/follow-up. In each subgroup there were 7 to 11 questions to answer. All national nephrologic societies within the ERA-EDTA were asked to recommend experts to support the core group and the ERBP methodological team to do the data extraction and to draft statements. Every question was analyzed in duplicate by two experts. Thousands of papers were reviewed, data extracted, the grading of evidence checked and flowcharts drawn if appropriate. The progress within the different questions is displayed in the table. Next steps will be the draft of all statements, the draft of the guideline and an internal and external review.

We think that we can finalize this by the end of 2017.

ERBP Vascular Access Guideline – Work in progress and the next steps

In 2014, the European Renal Best Practice (ERBP) team decided to update parts of the current vascular access guideline, which was published in 2007. [1] It was the objective of the ERBP team to identify clinical topics regarding vascular access care in haemodialysis patients that are considered a high priority by clinicians and patients. By focusing on high-priority topics, ERBP aims to increase the relevance of the guideline for daily clinical practice.

The topics were selected after a survey including nephrologists, nurses and patients from Austria, Belgium, Spain, The Netherlands and the United Kingdom. We analyzed which topics were covered by other organizations and whether topics could be appropriately addressed by systematic review. A list of suitable topics was than analyzed in Delphi rounds between clinicians and patients. The final guideline scope covers four subgroups: catheter-related topics; peri-operative-related topics; peri-and postoperative topics; and topics related to surveillance/maintenance/follow-up. In each subgroup there were 7 to 11 questions to answer. All national nephrologic societies within the ERA-EDTA were asked to recommend experts to support the core group and the ERBP methodological team to do the data extraction and to draft statements. Every question was analyzed in duplicate by two experts. Thousands of papers were reviewed, data extracted, the grading of evidence checked and flowcharts drawn if appropriate. The progress within the different questions is displayed in the table. Next steps will be the draft of all statements, the draft of the guideline and an internal and external review. We think that we can finalize this by the end of 2017.

References
Using marginal structural models in clinical research in nephrology

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In some study designs, information on a treatment (or exposure) and an outcome are updated over time. Analyses including this ‘time-varying’ information are useful in obtaining estimates of the effects of a treatment on the outcome that address time-related changes of the treatment. For example, studying the effects of the change in use or dose of beta-blockers over time on mortality from myocardial infarction can provide different insights as compared to a study of mortality by baseline assignment to beta-blockers.

Confounding is a major problem with non-randomized studies, i.e., studies that do not ensure group comparability. A confounder is a variable that is unequally distributed between groups, and affects both the likelihood of treatment and the outcome. Controlling for confounding factors measured at baseline (age, smoking or history of hypertension or diabetes) is easily addressed both in studies that compare the effects of baseline assignment to an intervention and in studies of the effects of its changes over time.

Some longitudinal studies, however, collect information on time-varying changes in potential confounders, which are often affected by previous treatment. For example, changes in blood pressure values over time impact both the treatment and the outcome (blood pressure level is a confounder), but are also affected by previous treatment. When a time-varying confounder is affected by prior treatment, standard methods for controlling confounders are inappropriate, because over time the covariate plays both the role of confounder and mediator of the effect of treatment on outcome.

Marginal structural models have been designed and used to control for the effect of confounding variables that change over time, and are affected by previous treatment. A marginal structural model is a statistical procedure that involves several analytical steps. To address confounding, marginal structural models first calculate a weight to assign to each observation in the study. These weights reflect the extent to which observations with certain characteristics are over- or under-represented in the sample with respect to a target population in which these characteristics are balanced across treatment groups. Then, marginal structural models estimate the outcome of interest when accounting for these weights, therefore enhancing group comparability. Marginal structural models are a powerful method of confounding control in longitudinal study designs that collect time-varying information on treatment (or exposure), outcome and other covariates.

A powerful method of controlling confounding in longitudinal study designs

Marginal structural models were designed to control for the effect of confounding variables that change over time, and are affected by previous treatment. A marginal structural model is a statistical procedure that involves several analytical steps. To address confounding, marginal structural models first calculate a weight to assign to each observation in the study. These weights reflect the extent to which observations with certain characteristics are under- or over-represented in the sample with respect to a target population in which these characteristics are balanced across treatment groups. Then, marginal structural models estimate the outcome of interest when accounting for these weights, therefore enhancing group comparability. Marginal structural models are a powerful method of confounding control in longitudinal study designs that collect time-varying information on treatment (or exposure), outcome and other covariates.

Sample size calculations

The sample size is the number of patients or other experimental units included in a study and calculation of the sample size required to answer the research question is one of the first steps in setting up a study. Although most statistical textbooks describe techniques for sample size calculation – also known as power calculation – it is often difficult for investigators to decide which method to use. There are many formulas available which can be applied for different types of data and study designs. However, all of these formulas should be used with caution since they are sensitive to errors and small differences in selected parameters can lead to large differences in the sample size. For those reasons, the ERA-EDTA Registry published in 2010 a paper on sample size calculations in “Nephrology Dialysis Transplantation”[1]. According to the journal’s statistics, this paper is already for a long time listed in the top 5 of most read NDT papers, indicating that there is great interest in this topic. Therefore, it was decided to present the basic principles of sample size calculations, in this year’s session “Crosswalk in Renal Epidemiology”. In this talk, it will be explained why, when, how and by whom sample size calculations should be performed. In addition, examples of sample size calculations in different situations will be given. Below the most important messages of the talk are summarized.

Why – The primary aim of a sample size calculation is to determine the number of participants needed to detect a clinically relevant treatment effect. Usually, the number of patients in a study is restricted because of ethical, cost and time considerations. However, if the sample size is too small, one may not be able to detect an important existing effect, whereas samples that are too large may waste time, resources and money. It is therefore important to optimize the sample size. Moreover, calculating the sample size in the designing phase of the study is often a requirement when seeking ethical committee approval for a research project.

When – A sample size calculation should be the first step after formulating the research question and choosing the study design. Pre-study calculation of the required sample size is warranted in the majority of quantitative studies. They are particularly of interest in the design of randomized controlled trials (RCTs). In RCTs, a lot of money is invested, and it is therefore important to be sufficiently sure that enough patients are included in the study arms to find a difference that we assume there is in the population, as statistically significant.

How – To calculate the sample size, it is required to have some idea of the results expected in a study. In general, the greater the variability in the outcome variable, the larger the sample size required to assess whether an observed effect is a true effect. On the other hand, the more effective (or harmful) a tested treatment is, the smaller the sample size needed to detect this positive or negative effect.

The calculation of the sample size for a trial typically requires four basic components: the type I error (alpha), the power, the smallest effect of interest and the variability of the (primary) outcome. These components can be inserted in one of the formulas to calculate the sample size. Formulas for sample size calculation differ depending on the type of study design and the studies outcome(s).

Who – Many of the formulas available to calculate sample size are not straightforward, and we recommend to ask for the help of a statistician in all but the most basic studies.

References


CME 5 – ERA-EDTA REGISTRY
Cross-talk in Renal Epidemiology
Saturday, 08.30 – 11.45, Hall 10.B
Diabesity – Working Group researching on the nephrological impact in relation to diabetes and obesity

HD or PD for obese diabetic patients?

Obesity is closely linked to the development of hypertension, dyslipidemia and type 2 diabetes, which together constitute the metabolic syndrome. Together, they are well-established independent risk factors for cardiovascular (CV) disease and chronic kidney disease. Two leading causes of end-stage renal disease (ESRD) are type 2 diabetes and hypertension, which together account for more than 70% of patients with ESRD. Since the growing prevalence of obesity is a key driver for the continued increase in the prevalence of type 2 diabetes, it is hard to study the individual contribution of obesity, type 2 diabetes or hypertension to the development of ESRD.

The question of the optimal choice of dialysis modality — peritoneal dialysis (PD) or hemodialysis (HD) — remains a matter of debate, especially in diabetic patients with ESRD. In contrast to the general population, a higher body mass index (BMI) in HD patients is not associated with an increase in mortality risk. Studies have shown the presence of ‘reverse’ epidemiology, a seemingly paradoxical observation that the presence of hypercholesterolemia, hypertension and high BMI is associated with improved survival in patients on maintenance HD.

In PD patients, reverse epidemiology is less evident or even inverted; i.e., the so-called ‘paradox-in-paradox’ PD. The additional glucose load in PD could be a contributing factor to obesity in ESRD patients leading to adverse outcomes, which is not seen in HD patients. PD offers several advantages including better preservation of renal functions and lower mortality risk compared to HD.

The decision is not simple and choice should be individualized.
The latter usually have increased body water and the body contains approximately 70% of its total mass. Intestinal phosphate absorption depends on the nutrient intake and the P/protein ratio of nutrients (normally 1:3–4). This P is rapidly dissociated in gut acidity and is highly absorbed (70–100%) only accounts for 10–12% of the total. This is because of the variability in the estimation of P intake, the time of blood sampling, which often does not take into consideration physiologic circadian P cycling, and differences in P bioavailability from protein sources, food additives and dietary patterns. Likewise, foods that significantly lower the calcium-phosphate ratio (Ca:P) can also increase net intestinal P absorption.

The association between BMI and outcomes in the HD population has been studied more frequently and more intensively than in the PD population. BMI does not characterize excess of centrally distributed obesity, which is more consistently associated with adverse effects on metabolism. Central adiposity confers more CV risk than peripheral subcutaneous adiposity. The waist-to-hip ratio has a better discrimination power for atherosclerosis than BMI, and in future waist circumference may become a much more reliable tool than BMI for assessing metabolic risk and CV events.

No randomized controlled clinical trial comparing outcomes in PD or HD obese diabetic patients with ESRD has been published. Which dialysis modality should be advised in clinical practice to the obese diabetic patient? Taking all factors into consideration, the decision in an obese diabetic patient is not simple and should be individualized.

Based on the current data, obesity is not considered to be an absolute contraindication for PD treatment, and there is a priori no reason to advise obese patients to choose HD, especially if the desire for PD is present. Ultimately, we have to assess each patient individually, and if the Kt/V values are reduced or there are other clinical problems, such as hyperkalemia, then we have the possibility of earlier switching to HD treatment. According to the latest European Clinical Practice Guidelines, all the different renal replacement therapy modalities should be equally available for all patients, and we should allow free modality choice to patients.

References

Reducing weight to slow GFR decline

Obesity, especially if centrally located, and diabetes are both associated with renal dysfunction sustained by glomerular hyperfiltration, a risk factor for accelerated renal function loss, and onset and progression of nephropathy. Thus, glomerular hyperfiltration might be one of the possible pathogenic links between obesity and chronic kidney disease (CKD). Calorie restriction (CR) remains the principal method for inducing weight loss. We evaluated whether and to what extent measured glomerular filtration rate (GFR) (by the iohexol plasma clearance technique) could be affected by 25% CR in the context of a controlled, randomized clinical trial: Calorie Restriction in Subjects with abdominal Obesity and Type-2 diabetes at increased risk (C.RE.S.O.).

Data showed that in 70 type 2 diabetic patients with abdominal obesity, 25% CR for six months significantly decreased GFR compared to standard diet (SD). This effect was largely driven by GFR reduction in patients with a higher baseline GFR, and was associated with a reduction in waist circumference, body weight, body mass index (BMI), systolic and diastolic blood pressure (BP), blood glucose, serum LDL/HDL cholesterol levels, and amelioration of insulin sensitivity as assessed by euglycemic hyperinsulinemic clamps in all patients. Of interest, every 1 kg weight loss was associated with approximately 1 ml/min GFR reduction. Both CR and SD were well tolerated and no side effects possibly related to inadequate or unbalanced nutrient supply were observed throughout the study.

These findings could have clinical implications, since persistent hyperfiltration predicts a faster GFR decline and an excess risk of progression to micro- or macroalbuminuria in patients with type-1 [1] or type-2 diabetes. In contrast, amelioration of hyperfiltration is associated with a slower long-term GFR decline and nephroprotection. We previously found that in a large cohort of patients quite similar to the C.RE.S.O. cohort, a larger GFR reduction at six months strongly and independently predicted a slower long-term GFR decline. In particular, a 7.6% short-term GFR reduction similar to that achieved by CR predicted a mean (SEM) long-term GFR decline of 0.08 (0.13) ml/min/1.73 m² per month, whereas a 2.7% reduction similar to that observed in patients on SD predicted a long-term decline of 0.36 (0.07) ml/min/1.73 m² per month.

If the above findings are generalized to our C.RE.S.O. cohort, we can speculate that CR might reduce the rate of long-term GFR decline by approximately four- to fivefold as compared to SD. This renoprotective effect might translate into a rate of renal function loss similar to that observed in healthy adults with aging. Interestingly, the benefit of CR on glomerular dysfunction was more consistent and clinically relevant in those patients with the highest GFR at baseline. Thus, the renoprotective effect of CR is expected to be greater in those patients who, because of hyperfiltration, are at increased risk of accelerated renal function loss.

In conclusion, CR-induced negative energy balance results in substantial improvements of several major risk factors for the initiation and progression of CKD in diabetic patients with abdominal obesity and without evidence of renal involvement. In particular, CR and weight loss, along with amelioration of insulin resistance and other functional and metabolic abnormalities, achieved a significant short-term reduction in the GFR that conceivably reflected amelioration of glomerular hyperfiltration and that resembled the reduction observed following an invasive procedure such as bariatric surgery [2]. Long-term randomized clinical trials (C.RE.S.O.-2) are needed to assess whether calorie restriction may achieve clinically relevant protection against progressive renal function loss and development of nephropathy in the long-term, as well as reduce patients’ overall cardiovascular risk.

References

Can we achieve nephroprotection in patients with obesity and diabetes?

Figure 1: Renal and Systemic Effects of Calorie Restriction in Patients with Type 2 Diabetes with Abdominal Obesity: A Randomized Controlled Trial © Ruggenenti

Check out the benefits of being an ERA-EDTA member!
How can we modify nutrient habits toward a lower phosphate intake?

As renal insufficiency progresses, accumulation of phosphates increases. From an advanced stage of chronic kidney disease (CKD) to end-stage renal disease (ESRD) treated by hemodialysis or peritoneal dialysis, reducing dietary phosphate intake is recommended, even in the absence of hyperphosphatemia.

Nonadherence in the ESRD population ranges from 22 % to 74 % and affects all areas of phosphate management self-care. Hyperphosphatemia is a frequently asymptomatic complication. It requires regular treatment several times a day, adaptation of eating habits without signs of physical improvement apart from a better result on its blood tests in the long term.

Health behavior model [1,2]

The health behavior model may explain this frequent non-adherence. The model suggests that people’s beliefs about health problems, perceived benefits of action and barriers to action, and self-efficacy explain engagement (or lack of engagement) in health-promoting behavior.

Perceived susceptibility is a person’s belief about the likelihood of acquiring a disease or reaching a harmful state through a behavior. Phosphorus is not a well-known mineral, or is seen as positive because of its supposed benefits for memory or its connection with calcium.

To move on to the next step, we need to use open questions to allow the patient to express his or her knowledge, opinions, and beliefs.

Perceived severity is the main problem posed by the absence of symptoms of hyperphosphatemia. One educational strategy to promote perception of the gravity of a condition is to “create a symptom”. This consists of educating the patient to improve understanding of the results of blood tests. [3]

Absence of perceived benefits for the patient apart from the satisfaction of a good blood result represents another major difficulty. The educational strategy here is to promote awareness of the potential impact on future access to health interventions such as transplantation.

Perceived barriers to taking phosphate binders are common, and adherence is largely inadequate. It is well known that adherence improves when the patient has a choice of treatment. Collaboration between the patient and the health professional is another factor for success. For example, accept that the patient forgets to take the binders, and agree the action to take when this happens. Linking intake of phosphate binders to food consumption promotes self-adjustment and improves self-efficacy.

Phosphate additives

A new dietary strategy that targets phosphate additives is needed before reducing consumption of naturally phosphate-rich foods, in order to avoid malnutrition due to protein deficiency.

The first step is to target, evaluate and educate about the presence of additives in the patient’s food choices. Digital tools exist for both patients and caregivers to better identify these additives. Open Food Facts (https://world.openfoodfacts.org) is a collaborative website that is a database of food products from around the world. It allows the user to search for the brands of food consumed by the patient and to identify the presence of additives in the list of ingredients. It is also possible to list food brands according to search criteria, such as the presence of phosphate additives.

As a second step, it may be necessary to adjust the qualitative and quantitative consumption of food sources of organic phosphorus. Nutridial® is a digital application that allows patients to self-evaluate in real-time their food consumption and the achievement of their objectives.

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European Uremic Toxin

Lanthionine: a prospective novel uremic toxin

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Hydrogen sulfide (H2S) is the third gaseous vasodilator after nitric oxide and carbon monoxide [1]. Its beneficial effects on the cardiovascular and nervous systems have recently been re-evaluated [2]. In particular, it has been shown that lanthionine, a side product of H2S biosynthesis, which was initially used to monitor H2S production in vivo, was increased in the circulation by over two orders of magnitude in uremic patients, while H2S release was impaired [3]. These findings as a whole allowed us to conclude that lanthionine is not a marker of H2S production and to characterize lanthionine as a novel uremic toxin. The aim of our research is to define the mechanism(s) of lanthionine toxicity and to explore possible therapeutic approaches to reduce its negative effects. Acetyl-glutathione (AcGSH) is a promising molecule, itself devoid of toxicity, which could counteract lanthionine biochemical and developmentally, thus preventing its toxicity. We hypothesized that AcGSH may activate Cystathionine-β-Synthase (CBS), a main in vivo H2S-producing enzyme, through its glutathionylation. Moreover, AcGSH may influence H2S biosynthesis, showing long-lasting effect on its production, probably because of its increased intrinsic stability with respect to its natural analog.

We demonstrated that lanthionine hampers H2S increase in endothelial cells, and it is associated with a significant reduction in CBS levels. As an in vivo experimental model, we used zebrafish (D. rerio). Our data from zebrafish were highly consistent with results we obtained from cell cultures. We used a high-throughput monitoring of zebrafish embryogenesis (DanioVision tracking system) in order to identify all possible toxic effects of lanthionine. In particular, prolonged treatment of zebrafish with lanthionine tended to induce an increase of heart rate, provoked arrhythmia, and it induced behavioral alterations, which could be a consequence of nervous system impairment.

AcGSH showed the ability to partially hamper lanthionine toxic effects on zebrafish heart rate and its behavior. We could conclude that zebrafish is a very suitable animal model to monitor the effects of uremic toxins in vivo.

References

Collagen IV glomerulopathies: an underdiagnosed phenotypic chameleon?

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Collagen IV nephropathies comprise a genetically and phenotypically heterogeneous group of disorders, invariably presenting with familial microscopically hematuria since childhood that may or may not progress to severe kidney function decline. Depending on genetic background and environmental factors, allelic mutations in the COL4A3/A4/A5 genes behave as a phenotypically and environmentally heterogeneous group of disorders, invariably presenting with familial microscopic hematuria all the way to severe chronic kidney disease (CKD) and even end-stage renal disease (ESRD). Specifically, patients with heterozygous COL4A3/A4 mutations have been diagnosed as having inherited one or more of the following:

(a) Thin basement membrane nephropathy (TBMN), a purely histological description in the presence of microscopic hematuria, caused by heterozygous COL4A3 or COL4A4 mutations. This was formerly synonymous with familial benign hematuria, but most experts agree to abandon this term, as it is not always true and is a misnomer leading to the wrong impression. Perhaps a better term for a subset of patients is (b).

(b) Later-onset Alport-related nephropathy, for those patients who present with familial microscopic hematuria in childhood due to TBMN (and heterozygous COL4A4 mutations), but for yet largely unknown reasons, they develop serious CKD and even ESRD, usually after the fifth decade of life.

(c) Autosomal dominant Alport syndrome (AS), for those rare occasions where heterozygous COL4A4 mutations are associated with ultrastructural and extrarenal features pathognomonic of AS. The age at onset is usually at much later ages, compared to classical X-linked AS in males or autosomal recessive AS in patients of either gender.

(d) Focal and segmental glomerulosclerosis, another purely histological description.

Notwithstanding that most patients with heterozygous COL4A4 mutations will have a rather mild disease course, the truth of the matter is that clinical presentation can be complex. A key unanswered question is: why some patients follow a mild course, while others with the same or similar primary mutations develop progressive renal dysfunction? According to the chameleon hypothesis, the full phenotypic spectrum of this monogenic single disorder behaves as a multifactorial condition, implicating primary genes, modifier genes and environmental factors (Fig. 1). In previous work, we and others have reported on two candidate variants in the NPHS2 gene (podocin) and one in the NEPH3 gene (fitsrin), both expressed in the slit diaphragm of the glomerular filtration barrier. However, these variants explain only a small part of the heritable heterogeneity.

To address this chameleon hypothesis, we performed unbiased whole-exome-sequencing of 260 Hellenic people from Cyprus and Greece, harboring a limited number of pathogenic heterozygous COL4A3/A4 mutations. About half of the patients are classified as ‘mild’ or ‘severe’ based on set criteria. Initial examination of the data does not support the existence of common variants with substantial effects, although one such variant is under further evaluation. The holistic analysis of data suggests the presence of a large number of variants that, when co-inherited in different combinations, might confer a high risk of, or protect from, manifesting a ‘severe’ disease. The development of an algorithm to enable prediction is in progress. We anticipate that such an algorithm could also allow the prediction of a similar risk (continued on page 12).

Primary genes, modifier genes and environmental factors are all implicated
Alport syndrome: a treatable – but the diagnosis is often made too late

Patients with the hereditary disease Alport syndrome (AS) develop progressive renal fibrosis due to mutations in type IV collagen genes. If diagnosed early, AS has become treatable, renal failure can be delayed by years, and life expectancy can be improved. Unfortunately, the diagnosis is often made too late. Every nephrologist should check his/her Alport patients (including heterozygous patients) for proteinuria and other risk factors every year.

Timing and methods for diagnosis
Screening for microhematuria should start before elementary school. Any renal microhematuria should lead to early transfer to a Pediatric nephrologist. Every suspected case of AS, including heterozygous girls, should receive a complete workup including genetic testing. Early diagnosis is mandatory because it enables early therapy. Kidney biopsies must include electron microscopy, because light-microscopic changes can be misdiagnosed as focal segmental glomerulosclerosis (FSGS).

Mode and frequency of control investigations
Heterozygous patients with X-chromosomal or autosomal-recessive disease must be informed about their risk: up to 40% develop renal failure, up to 20% require dialysis. Timely RAAS-blockade can avoid dialysis in most heterozygous patients. Therefore, care for heterozygous patients must include – for life – annual follow-up. Adults with microalbuminuria must be treated by RAAS-blockade; therapy in heterozygous children should start with onset of proteinuria.

In all other patients with hemizygous, compound-heterozygous or homozygous mutations, the timespan until renal failure depends on start of RAAS-blockade and type of mutation. Therefore, care for all patients must include – for life – at least half-yearly follow-up by the nephrologist.

In daily practice for adult nephrologists, every patient with renal microalbuminuria should be informed about her/his potential risk of AS. If micro-albuminuria develops, immediate work-up by a nephrologist should exclude or confirm the diagnosis of AS. In children with microalbuminuria, especially those with a positive family history, early transfer to a Pediatric nephrologist should lead to clinical and genetic work-up.

Optimal start of therapy
Expert recommendations guide the nephrologist through off-label therapy, until prospective clinical trials further improve evidence. Every patient should be reported to a national or international registry.

Mode and frequency of control investigations
Heterozygous patients with X-chromosomal or autosomal-recessive disease must be informed about their risk: up to 40% develop renal failure, up to 20% require dialysis. Time-

Future therapeutic options
In 2017, new phase 2 and 3 interventional international studies with new medications can be offered to many patients worldwide (please refer to websites of HERA and CARDINAL Alport studies for further information).

Conflict of interest
The author’s employer, University of Goettingen, receives financial compensation for his consultancy activities for Reata Pharmaceuticals and Regula Therapeutics. Please contact the author for all literature cited.

(continued from page 11) to people of the general population by aging. This, in turn may pave the way for new personalized treatments.

Acknowledgements
Many thanks to all collaborators of the Molecular Medicine Research Center (MMRC) of University of Cyprus, clinicians and researchers. This work is funded partly by a grant from the European Renal Association-European Dialysis and Transplant Association.

Relevant selected literature
Deltas C, Savva I, Voskardes K et al. Nephron 2015; 130: 271 – 280
Environmental factors have been implicated in the etiopathogenesis of ANCA-associated vasculitis, including air pollution (i.e. silica exposure), drug exposure (cocaine, propylthiouracil, etc.) as well as infections (Staphylococcus aureus and granulomatosis with polyangiitis (GPA), as well as proposed molecular mimicry with Gram-negative bacteria and onset of ANCA-associated renal disease).

In 1994, the first study systematically investigated the impact of chronic S. aureus carriage and risk of relapse in GPA. A randomized, controlled trial, which assigned participants to either trimethoprim-sulfamethoxazole (2 tablets daily for 2 years), found a significant reduction in relapses during the follow-up period compared to the control group. Further studies published to date have found a S. aureus carriage rate of around 65–70%. This is three times higher than in the general population, and the question remains whether presence of S. aureus in GPA is disease-related or follows chronic damage due to active vasculitis. More recently, analysis of two early EUVAS (European Vasculitis Society) trials revealed that chronic carriage during initial diagnosis was comparable to that in the general population. Analysis of cases with GPA highlighted an association between higher relapse risk and chronic carriage in patients with ‘generalised’ GPA and a borderline significance for patients with ‘early systemic’ GPA. Prophylactic treatment with trimethoprim-sulfamethoxazole (three times a week 1 tablet) did not lower the relapse risk, but did reduce the number of patients with chronic nasal S. aureus carriage.

To further investigate microbial diversity in patients with GPA, we performed a cross-sectional study and recruited patients with either active disease or during remission. Patients with eosinophilic granulomatosis with polyangiitis (EGPA) or microscopic polyangiitis (MPA), and healthy volunteers served as controls. Our findings illustrate the diversity and the inter-individual differences in the nasal microbiome. Although numbers were low for the microbiome analysis study, disease or during remission. Patients with eosinophilic granulomatosis with polyangiitis (EGPA) or microscopic polyangiitis (MPA), and healthy volunteers served as controls. Our findings illustrate the diversity and the inter-individual differences in the nasal microbiome. Although numbers were low for the microbiome analysis study,
Autoinflammatory diseases – an update for nephrologists

The main autoinflammatory diseases are familial Mediterranean fever (FMF), the tumor-necrosis factor receptor-associated periodic syndrome (TRAPS), the cryopyrin-associated periodic syndrome (CAPS) and the hyper-IgD syndrome. In addition to general symptoms, there are wide ranges of systemic and organ involvement. AA-amyloidosis, especially renal amyloidosis, is the life-threatening long-term complication and so prognosis is mainly determined by the rate of progression of amyloidosis. In over 90% of patients the first sign of AA-amyloidosis onset is glomerular proteinuria. In the course of time the kidney damage progresses in an unpredictable manner and results in nephrotic syndrome, renal failure or even end-stage renal disease (ESRD). Therefore, a close monitoring of renal function is necessary.

In our clinic we have long-term experience in the diagnostic evaluation, care and treatment of patients with Muckle-Wells syndrome, one of three entities of CAPS. The general symptoms include recurrent episodes of fever, urticaria, myalgia and arthralgia, conjunctivitis, headache and fatigue syndrome. The long-term effects are progressive sensorineural hearing loss, social isolation due to fatigue syndrome and AA-amyloidosis, mostly resulting in renal amyloidosis. In our patients we observed various developments of renal function in biopsy proven AA-amyloidosis. In 2010 we successfully performed kidney transplantation in one of our female patients with ESRD due to AA amyloidosis in Muckle-Wells syndrome. Today, she has a stable kidney transplant function and no sign of recurring amyloidosis. The underlying Muckle-Wells syndrome is in very good remission under a specific anti-IL-1 inhibition. In future, we need more clinical studies to assess patients with these rare diseases.

CME 11 Rheumatology for nephrologists Saturday, 12.00 – 15.15, Hall 10.A

Antiphospholipid antibody syndrome: a catastrophic disease?

The descriptive adjective ‘catastrophic’ was added in 1992 to define an accelerated form of the antiphospholipid syndrome (APS) in order to highlight a new subset of this syndrome that results in multigorgan failure that is often fatal. Patients with catastrophic APS have in common:

(a) Clinical evidence of multiple organ involvement that develops over a very short period of time,
(b) Histopathological evidence of multiple small vessel occlusions, and
(c) Laboratory confirmation of the presence of antiphospholipid antibodies (aPL), usually in high titre. Fortunately, less than 1% of patients with the APS develop this complication, but its potentially lethal outcome emphasizes its importance in clinical medicine today.

Although it is still unclear why some patients develop recurrent thrombososes, mainly of large vessels (simple or classic APS), while others develop rapidly recurrent vascular occlusions, predominantly affecting small vessels (catastrophic APS), our knowledge on this severe variant has increased a great deal during the last 25 years of intensive research.

Due to the rarity of catastrophic APS, an international registry (the CAPS Registry) was created in 2000. This registry documents the entire clinical, laboratory and therapeutic data of all published cases with catastrophic APS, as well as of many additional patients whose data have been fully registered. The periodical analysis of this registry has allowed us to increase our knowledge of this condition.

In the most recent analysis of the CAPS Registry including 500 patients, precipitating factors were identified in 65% of the episodes. The most frequent factors were infections (49% of episodes), mainly in the respiratory tract (33%), followed by the urinary tract (19%), and the skin (13%). The clinical picture was characterized by renal involvement (73%), with variable degree of renal failure, and lung involvement (60%) in the form of acute respiratory distress syndrome or pulmonary embolism (26%). Up to 56% of patients showed central nervous system manifestations because of stroke or encephalopathy. The heart was affected in half of the episodes, mainly due to myocardial infarction or valvulopathy. Lupus anticoagulant, IgG anticardiolipin and IgG anti-β2-glycoprotein antibodies were the most often implicated antiphospholipid antibodies (63%, 81% and 78%, respectively). Death occurred in 37% of episodes.

Management of the catastrophic APS is challenging. Early diagnosis and aggressive therapies are essential. In any APS patient, particular attention should be given to the following guidelines:

(1) Any infection should be energetically treated with the appropriate antibiotics;
(2) APS patients undergoing surgical procedures should all receive parenteral anticoagulation during the procedure instead of remaining on warfarin;
(3) The puerperium should be adequately covered for a minimum of 6 weeks with parenteral anticoagulants; and
(4) Severe systemic lupus erythematosus (SLE) flares should also be treated with parenteral anticoagulation.

Unfortunately, there is an absence of prospective and randomized therapeutic studies in catastrophic APS. In fact, the evidence-based information about current treatment also comes from the CAPS Registry:

(a) The higher recovery rate was achieved by the combination of anticoagulation (AC) plus glucocorticoids (GC) plus plasma exchange (PE) (77.8% versus 55.4%, p = 0.083), followed by AC plus GC plus PE and/or intravenous immunoglobuline (IVIg) (69% versus 54.4%, p = 0.083);
(b) Treatment with cyclophosphamide (CYC) did not demonstrate an additional benefit;
(c) Isolated use of GC was related to a lower rate of recovery (18.2% versus 58.1% of episodes not treated with GC; p = 0.01); and
(d) More interestingly, the mortality rate decreased from 53% in the patients diagnosed before 2000 to 33.3% in those diagnosed from 2001 to February 2005 (p = 0.005; odds ratio [OR], 2.25; 95% confidence interval [CI], 1.27 to 3.99). The main explanation for this significant reduction in mortality was the more frequent use of combined treatment with AC plus GC plus PE and/or IVIg. Additionally, there are few data on new therapeutic approaches, including rituximab and eculizumab.

CME 11 Rheumatology for nephrologists Saturday, 12.00 – 15.15, Hall 10.A
Position in CKD of novel compounds to treat bone disease

The clinical spectrum of Chronic Kidney Disease—Mineral and Bone Disorders (CKD-MBD) goes beyond bone lesions to include an increased burden of morbidity and mortality for any cause or for cardiovascular disease. Part of this increased morbidity and mortality has been recently referred to the high incidence and prevalence of bone fractures in Chronic Renal Failure (CRF). Not surprisingly, we are witnessing a renewed interest for bone histology in renal patients, aiming at recognizing not only the classical different types of renal osteodystrophy (ROD), but also the three bone parameters on which the new classification is focused: Turnover, Mineralization and Volume (so called TMV classification of ROD). The aim of this new classification is to highlight the mechanical and metabolic competences of bone rather than its morphologic aspects.

Cytotoxic drugs and their renal side effects

Cytotoxic drugs are widely used chemotherapeutics, and their use has resulted in increased survival rates in patients with different types of solid tumors. Cisplatin is the best-known platinum-based chemotherapy drug and is a cornerstone in the treatment of solid tumors such as ovarian and cervical cancer, testicular cancer, head and neck cancer including nasopharyngeal, and lung cancer. Although carboplatin and oxaliplatin, which are platinum derivates, have fewer side effects, cisplatin is still used more extensively as it is more potent and results in better outcomes.

The most notable and important cytotoxic side effect is nephrotoxicity. Cisplatin, ifosfamide, carboplatin, oxaliplatin and pemetrexed have all been associated with acute kidney injury (AKI) [3]. Besides acute kidney injury, cytotoxic drugs have also been associated with chronic kidney disease (CKD) and other renal symptoms such as hemolytic uremic syndrome and ifosfamide-induced nephrotoxicity associated with cisplatin is dose dependent [17]. In contrast, ifosfamide-induced nephrotoxicity could not be predicted based on cumulative dose or age at the time of treatment [18].

With improved survival, it has become evident that cytotoxic chemotherapeutics are also associated with the development of CKD. In childhood cancer it has been established that loss of tumor suppressor genes has been associated with reduced glomerular filtration rate (GFR) [2,3]. However, it is not possible to completely prevent cisplatin-induced nephrotoxicity. Based on the limited available evidence, clinical practice guidelines have been developed to prevent cisplatin-induced kidney injury [14].

References

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A further awareness of recent years is that an increased rate of fractures, similarly responsible for morbidity and mortality, is evident in CRF patients not on dialysis. This widens the population potentially affected by ROD, deserving evaluation and, possibly, preventive therapeutics. Irrevocably, searching for bone fractures in early stages of CKD means dealing with aged people at risk of osteoporosis (OP), the other metabolic condition responsible for increased fracture and morbidity/mortality in the general non-renal population. A practical consequence is that distinguishing between OP and ROD in early stages of CKD, is becoming a frequent issue in the daily practice. Another consequence is that nephrologists are ever more required to decide on the use of drugs developed for OP but in patients with CRF.
Multidisciplinary vascular access (VA) care is gaining importance due to an increase in difficult VAs as the epidemiology of the dialysis population is changing (age, obesity, diabetes etc.). Duplex ultrasound (DU) can be used by all the members of the VA team (dialysis nurse, nephrologist, vascular surgeon and interventional radiologist) as an additional way to further optimize the care of their patient’s lifetime.

To perform VA ultrasonography, one needs a (portable) ultrasound machine combining B Mode with Doppler Mode (Color Flow, Pulsed Wave and Power Doppler), a linear transducer, gel as a coupling agent, a tourniquet and sufficient training (theory and practice). Duplex ultrasound of VA is useful before, during and after VA creation. Preoperative mapping of the vascular structures of the upper limbs should be performed in all patients in need for a VA, especially difficult access. Mapping leads to the creation of more native arteriovenous (AV) fistulas and fewer AV grafts, a lower rate of negative exploration, an increased proportion of patients dialyzed with an AV fistula, and improved fistula adequacy. During the procedure, there is a selection of the most appropriate dialysis access modality, anatomical site and vessels. According to the European Best Practice Guidelines on VA (2007), dialysis catheter placement should be performed under ultrasound guidance, as this method is superior to and safer than the blind, landmark technique.

- Absent/diminished thrill
- As per protocol (surveillance)
- Dialysis VA-related problems: cannulation difficulties and other problems, including elevated venous pressures, low Kt/V and high recirculation, low access flow, aspiration of blood clots, local pain on cannulation, prolonged bleeding after cannulation.
- Arm swelling (local versus generalized)
- Arm pain (ischemia).

Although no pathologic lesion is found in up to 36% of angiography procedures performed because of cannulation difficulties, stenosis is the most frequent underlying problem. Borderline and significant stenoses are both characterized by a > 50% lumen diameter reduction and a peak systolic velocity (PSV) ratio > 2, whereas a VA with a significant stenosis has at least one of the following additional criteria: a residual diameter < 2 mm, flow reduction > 25% and/or an actual flow volume < 800 ml/min. Other problems besides stenosis include incorrect needle position, venous side branches, a too deep or too tor-
Most targeted cancer therapies have a degree of nephrotoxicity

Renal function may be compromised by different drugs used in the diagnosis and treatment of patients with malignancies, including chemotherapy, bisphosphonates, or contrast agents. Targeted treatment aims to inhibit the specific molecules participating in tumor growth, progression, and dissemination. Targeted signaling pathways are often involved in the regulation of cell division or inhibition of apoptosis, which both play an important role in many processes in the healthy organism, so their inhibition may be associated with many adverse events.

The clinical trials IRMA-1 and IRMA-2 demonstrated that more than 50% of patients with cancer may have at least slightly decreased renal function (glomerular filtration rate [GFR] <90 ml/min/1.73 m²), and the prevalence of chronic kidney disease (CKD) stage 3–5 (excluding patients on dialysis) was about 12%. On the other hand, CKD is often associated with a higher incidence of cancer (not only in patients with end-stage renal disease). Targeted treatment is more often used in these types of cancer, as breast, colorectal, kidney, and cervical cancer occur more frequently in patients with CKD. Antiangiogenic targeted treatment with monoclonal antibodies (bevacizumab, or ramucirumab), or tyrosine kinase inhibitors (TKI) (e.g. sunitinib, sorafenib, axitinib, regorafenib or nitedanib and afibreccept) inhibit either vascular endothelial growth factor (VEGF), or its receptor (VEGFR)-mediated signaling. Local production of VEGF in the kidney (namely by podocytes) plays an important role in the preservation of normal glomerular function, normal morphology of the glomerular endothelium, mesangial cells and podocytes and overall integrity of the glomerular filtration barrier. Toxicity of antiangiogenic treatment usually presents clinically with hypertension, proteinuria, reduced glomerular filtration rate, or even thrombotic microangiopathy.

Appropriate dose reduction and careful monitoring of renal function are essential

Drugs aimed at epidermal growth factor (EGF), the monoclonal antibodies cetuximab and panitumumab, and TKIs blocking downstream activation mediated through the EGF receptor (e.g. erlotinib, gefitinib and afatinib) interfere with tubular reabsorption of magnesium in the distal nephron, resulting in hypomagnesemia that may require magnesium supplementation.

Anti-HER2 therapy with trastuzumab or lapatinib (usually, but not exclusively used in breast cancer) is not directly associated with impairment of kidney function, but the putative cardiotoxicity of this treatment is more pronounced in patients with CKD. Pertuzumab (which inhibits the dimerization of HER2 and HER3) is, however, without renal toxicity.

Drugs used in patients with metastatic melanoma with BRAF mutation, such as vemurafenib and dabrafenib, are not highly nephrotoxic. However, case reports of renal failure have been reported in patients with diabetes and hypertension treated with vemurafenib.

Crizotinib, which is used in patients with non-small cell lung cancer with ALK mutation, may cause hypophosphatemia and, rarely, induce the formation of renal cysts. Severe nephrotoxicity may be associated with the use of the multi-kinase inhibitor vandetanib, which interferes with renal transporters MATE1 and MATE2K. The re-absorption of magnesium in the distal nephron.

The results are disorders of mineral metabolism (including hypocalcemia, hypercalcemia and hypophosphatemia), renal toxicity (hypertension, proteinuria, renal failure), and also micturition problems, including dysuria and pollakiuria).

On the other hand, PDL-1 (programmed cell death protein 1) inhibitors are not believed to be nephrotoxic, but there have been rare reports of hypophosphatemia and proteinuria. Safety of immunotherapy is now the subject of many studies.

Treatment targeted on RANKL, used in patients with bone metastases, is supposed to be relatively safe. This contrasts with bisphosphonates, which are associated with significant renal toxicity.

Oncologists also use mTOR inhibitors with well-established, but different nephrotoxicity. Temsirolimus seems to be the least nephrotoxic, with occasional reports of hypophosphatemia. Everolimus is more toxic, with reported hypertension, proteinuria, elevation of serum creatinine and renal failure, and also hypophosphatemia and hypomagnesemia.

Most drugs used in the targeted treatment of malignancies have a certain degree of nephrotoxicity. Fortunately, it is usually less severe. Nephrotoxicity of targeted treatment may be further enhanced if it is combined with chemotherapy. Appropriate dose reduction and careful monitoring of renal function in patients treated for cancer are the best prevention of progressive damage to the kidney.

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Check out the benefits of being an ERA-EDTA member!

Leading European Nephrology
From ‘primary’ amyloidosis to the ‘monoclonal gammopathy of renal significance’

1889: Kahler described a patient with plasma cells in the ribs and vertebrae, and BLP in the urine; Weber claimed that bone marrow was the site of production of the BLP.
1899: Ellinger supposed that the blood of patients with MM contains abnormal protein, similar to urinary BLP.
1909: von Decastello showed an association between MM and tubular plugging by an amorphous substance, later named ‘myeloma kidney’ or ‘cast nephropathy’.

1956: Wilks described kidney and other organ amyloidosis unrelated to known associated conditions, later referred to as ‘primary amyloidosis’.
1967: Weber reported a case of mollitis ossium with renal amyloidosis.
1970: Wintrobe and Buell recognized cryoprecipitation and discriminated pathologic serum proteins in MM from all normal proteins.
1976: Lerner and Watson introduced the term LC deposition with the name ‘light chain deposition’.
1981: Porush and Churg reported paraproteinemia and cryoglobulinemia associated with atypical gammopathy (GN). The Nomenclature Committee proposed to replace the terms primary amyloidosis and myeloma-related amyloidosis by the term ‘AL amyloidosis’.

1984: Aucoututier described heavy chain deposition with the name ‘light chain deposition disease’. Since then non-amylodigenic monoclonal LC are called ‘Randall-type’.

von Rustizky introduced the term ‘monoclonal gammopathy’ (MM) to describe tumors of bone marrow.
Lerner and Watson introduced the term ‘Bence Jones cryoglobulinemia’.
Korngold and Lipari identified two classes of BLP, designated in their honor as immunoglobulins LC kappa and lambda.

1993: Aucoututier reported bone marrow amyloidosis in patients with Waldenström’s macroglobulinemia.
1999: Porush and Churg reported paraproteinemia and cryoglobulinemia associated with atypical gammopathy (GN). The term ‘monoclonal gammopathy of renal significance’ (MGRS) to stress the pathologic nature of these diseases.

2015, arrival: The International Kidney and Monoclonal Gammopathy Research Group (IKMGRG) synthesized the data concerning renal consequences of low-grade paraproteinemias, and proposed the term ‘monoclonal gammopathy of renal significance’ (MGRS) to stress the pathologic nature of these diseases.

1845, departure: Bence Jones explained the unusual properties of urine in a patient with multiple myeloma, which was already described but not yet named) and edema by the presence of ‘hydrated deutoxide of albumin’.
1849: Dalrymple found replacement of bones by a ‘gelatin-form substance of a blood-red color and unctuous feel’, and round nucleated cells in the bones, when examining a patient’s autopsy material.
1854: Virchow proposed the term ‘amyloid’ instead of ‘lardaceous’ or ‘waxy’.
1856: Weber claimed that bone marrow was the site of production of the BLP.

1875: Short and Crawford confirmed the presence of ‘cast nephropathy’.
1876: Edelman and Gally confirmed identical properties of serum LC and urinary BLP from the same patient.
1879: Kobernik and Whiteside reported non-amylodigenic gammopathy-associated focal and segmental glomerulosclerosis.
1880: Hall N101–102

1993: Aucoututier reported bone marrow amyloidosis in patients with Waldenström’s macroglobulinemia.
1999: Porush and Churg reported paraproteinemia and cryoglobulinemia associated with atypical gammopathy (GN). The Nomenclature Committee proposed to replace the terms primary amyloidosis and myeloma-related amyloidosis by the term ‘AL amyloidosis’.
Randall reported systemic non-amyloid LC deposition with the name ‘light chain deposition disease’. Since then non-amylodigenic monoclonal LC are called ‘Randall-type’.

1993: Aucoututier described light chain tubulopathy.
1999: Porush and Churg reported paraproteinemia and cryoglobulinemia associated with atypical gammopathy (GN).
1999: Aucoututier described heavy chain deposition with the name ‘light chain deposition disease’.

2004: Naar published a description of proliferative GN with monoclonal immunoglobulin deposition.
2005: Dingly and Kyle reported monoclonal gammopathy-associated focal and segmental glomerulosclerosis.
2012: The International Kidney and Monoclonal Gammopathy Research Group (IKMGRG) synthesized the data concerning renal consequences of low-grade paraproteinemias, and proposed the term ‘monoclonal gammopathy of renal significance’ (MGRS) to stress the pathologic nature of these diseases.
2015, arrival: The IKMGRG postulated that MGRS encompasses all renal disorders caused by monoclonal immunoglobulins, secreted by nonmalignant B-cell clones.

**Dialysis and malignancy – a growing problem**

End-stage renal disease (ESRD) has long been linked to malignancy and patients with ESRD are more likely than the general population to die from cancer. In recent years the number of dialysis patients receiving a diagnosis of cancer has been shown to increase, but how ‘big is the problem’? Is it really the case that patients receiving dialysis are ‘developing’ more cancer? Or have the methods in which we screen, diagnose and manage patients with cancer on dialysis changed? What is the mortality rate of patients with cancer on dialysis and how different is this from that of the general population?

During the talk titled “Dialysis and malignancy–a growing problem” I will start with a brief description of the potential mechanisms between patients receiving dialysis and malignancy. I will then, using data from renal registry studies and individual studies attempt to quantify ‘how big the problem is’ by describing the current incidence and prevalence of cancer in patients receiving dialysis and recent trends. However quantifying ‘how big the problem is’, is not very straightforward and during this talk I will also explain why this is difficult to quantify and any biases that may be influencing the findings. Finally I will show the survival outcomes of patients receiving dialysis with cancer and how these compare to the general population.
The downside of ultrasound is its operator dependency and substantial learning curve, while training is often neglected in the curriculum of nephrologists, surgeons and dialysis nurses. Hansonecho.com is a useful online resource for the beginner ultrasonographer in the field of dialysis VA.

References

Vascular access stenosis: what do the guidelines say?

The current clinical guidelines on vascular access underline that hemodialysis units must have protocolized programs for follow-up of arteriovenous access, whether native fistula or graft, with multidisciplinary participation. [1] These programs should include screening methods for the early detection of stenosis, and location of its origin, as well as the performance of elective treatment before thrombosis. [2] According to these recommendations, we can highlight four steps in the diagnosis and management of arteriovenous access stenosis.

**STEP 1: early diagnosis of stenosis by applying monitoring and/or surveillance screening techniques**

We can classify these methods in two groups: first- and second-generation techniques. The first-generation methods are: clinical monitoring (physical examination, problems during hemodialysis session, DB stress test); pressure of vascular access (dynamic venous pressure, static intra-access pressure); recirculation; and inexplicable drop in dose of dialysis (RT and kt/v index, urea reduction ratio). The second-generation techniques allow the direct (by Doppler ultrasound) or indirect (by dilutional screening methods like ultrasound dilution or Delta-H or thermodilution) estimation of blood flow rate (QA). The surveillance techniques (determination of static intra-access pressure, Doppler ultrasound and dilutional screening methods) involve special instrumentation [3]; the remaining techniques are monitoring methods. All these techniques are not exclusive but complementary.

**STEP 2: diagnosis of significant stenosis or stenosis at high risk of thrombosis.**

It has been shown that some arteriovenous access stenoses remain stable without changing QA or degree of stenosis over time. Preventive intervention on these stenoses at low risk of thrombosis represents an unnecessary procedure with notable cost and it can lead accelerated restenosis. Therefore, according the Spanish Clinical Guidelines, the indication for elective intervention should be established only for stenosis at high risk of thrombosis — that is, significant arteriovenous access stenosis – if it meets the two main criteria mentioned above and, at least, one additional morphological (residual diameter <2 mm or functional QA (ml/min) <500 (AVF)-600 (AVG)) or QA reduction >25 % or QA <1000 ml/min) criterion on Doppler ultrasound. [1]

**STEP 3: diagnosis of significant stenosis by applying an imaging exploration (Doppler ultrasound/ fistulography) to confirm suspected stenosis.**

Any repeated alteration of monitoring and/or surveillance parameter should be a criterion to perform an imaging exploration of the arteriovenous access under suspicion of pathology. Although it cannot replace fistulography as gold standard, Doppler ultrasound is a method of imaging diagnosis that is noninvasive, harmless to the patient, and has greater availability (it can be used ‘in situ’ in the hemodialysis room). It also provides high sensitivity and specificity for the diagnosis of stenosis, and valuable additional functional information, with a favorable cost-effectiveness profile. The new Spanish Clinical Guidelines on vascular access for hemodialysis recommend performing a Doppler ultrasound as the initial imaging exploration if there is any suspicion of stenosis reserving fistulography for cases where there is a negative ultrasound result and a persistent suspicion of stenosis. [1] The diagnosis of stenosis can be established by the simultaneous presence of two main ultrasound criteria: vascular lumen reduction >50 % associated with peak systolic velocity ratio >2.

**STEP 4: elective intervention before thrombosis.**

The Spanish Clinical Guidelines recommend that, because of the high risk of thrombosis, elective intervention with angioplasty and/or surgery should be performed only when the diagnosis of significant arteriovenous access stenosis has been established. [1]
Care management is key

Vascular access is a fundamental part of renal replacement therapy with hemodialysis. Support for its role is based on two main characteristics: it is needed, firstly, to make optimum use of the technology required in hemodialysis, and secondly, to reduce the morbidity related to access complications.

For this reason, it is essential to establish strategies aimed at increasing the incidence and prevalence of native vascular access, and to avoid the use of grafts, and especially catheters, as much as possible. When they are necessary, catheters require optimum management to minimize complications, as most vascular access-related pathology is associated with their use.

How to prevent and treat vascular access complications

In arteriovenous fistulas, preventive measures must be designed to prevent early failure and improve long-term patency with the lowest possible number of complications. There are several phases that have to be systematically monitored. These are preparation for the creation of the arteriovenous fistula, its care and follow-up, treatment of complications, and at the same time, associated measures to manage catheter care.

For this reason, it is important to bear in mind procedures needed prior to vascular access creation. From the moment the decision is taken to create the access to the surgery itself, through the search for the best vascular bed using mapping, and including the prevention of complications such as ischemia. Care management plays an increasingly fundamental role in the prevention of complications, and nursing staff are a vital part of this care, which involves maturation, aseptic methods and needling.

Follow-up or surveillance is probably one of the aspects that has sparked most controversy relating to its necessity and, particularly, to its function. Available evidence, albeit scarce, is beginning to indicate the probable need to perform systematic surveillance and, more importantly, to implement diagnostic criteria for stenosis based on both hemodynamic and clinical features.

There are different types of treatment for complications in native arteriovenous fistulas and grafts. These depend on different specialists who, in addition, use different techniques. Complications essentially include stenosis and thrombosis, but those related to infections, ischemia, aneurysms and pseudoaneurysms, and those derived from high flow are also relevant. As there are no standardized treatment indications for many of these complications, treatment is not efficacious. However, evidence review is now beginning to allow us to recommend indications for some of these pathologies, especially stenosis.

Central venous catheters are undoubtedly the main source of complications, especially mortality. It is important not only to avoid use of catheters as far as possible, but also to prevent both infectious and functional complications. And when these complications occur, they should be treated appropriately. There are similarly important limitations here to the evidence. But there is no doubt that intervention protocols can be established to reduce associated morbidity.

Finally, a factor that usually does not appear in vascular access management protocols, but which will become the cornerstone of optimization, is management of quality indicators. This is the only way in which the different specialties involved in care management, and especially administrators and managers, will become aware of the issue as results begin to improve.

Central venous catheters in HD

Although nephrologists aim to obtain arteriovenous access for hemodialysis whenever possible, the use of central venous catheters (CVCs) is increasing in most countries. CVCs are therefore essential in the management of hemodialysis patients, but they also carry unintended negative consequences, in particular thrombosis and infection, adversely affecting patient morbidity and mortality. In other words, although CVCs may increase the risk of death (and therefore they should be avoided whenever possible), they may on the other hand also be lifesaving.

CVC management is a crucial issue in hemodialysis. If CVC dysfunction occurs, the clinical performance of dialysis may be also impaired, affecting the efficiency of depuration. Dr Maurizio Gallieni, nephrologist from the University of Milan, Italy, who is also a past-president of the Vascular Access Society (www.vascularaccesssociety.com), is addressing the issue of how to improve performance of CVCs in hemodialysis patients during the CME course ‘Practical issues in vascular access care’ on Saturday, June 3rd.

The design of the catheter is important in determining its performance. Better materials, larger diameters and innovative tip design have allowed blood flow rates to up to 500 ml/min, although CVC flow rates of less than 300 ml/min may provide adequate hemodialysis, if duration of the dialysis session is adapted to the patient’s needs. Symmetric-tip CVC have been recently introduced, enabling low access recirculation and ease of catheter tip positioning in the right atrium. A step-tip CVC in conjunction with reversed lines induces blood recirculation and reduces the adequacy of hemodialysis treatment, especially when the recirculation rate exceeds 10%.

A better CVC performance can be achieved by avoiding dysfunction, which may be divided into early or late, based on the time of occurrence after catheter placement. The causes of early dysfunction are generally technical, and the CVC shows blood flow impairment immediately (in the procedure room) or at its first use due to incorrect tip positioning, catheter damage or kinking. Using ultrasound guidance and fluoroscopy during the tunneled CVC insertion is of great help in avoiding early dysfunction.

If correctly managed, they can last for years with few complications

Late CVC dysfunction and poor performance are mainly related to thrombosis, which can be classified as either intrinsic or extrinsic. Thrombus formation, as well as the development of fibrous connective tissue sheath (commonly fibrin sheath), play a central role in establishing CVC dysfunction. Right atrial or mural thrombus may also determine blood-flow impairment.

Prevention and treatment of thrombosis-related CVC dysfunction can improve catheter performance and increase its duration in time. Prevention of intrinsic CVC thrombosis with anticoagulant locks is commonly used. When prevention fails, thrombolysis with urokinase or rTPA can be undertaken in the dialysis unit, restoring adequate blood flow in most patients, preserving the existing catheter, and avoiding vein abandonment or costly interventional procedures.

However, if thrombotic agents fail, a timely interventional procedure is indicated. To resolve dysfunction due to the presence of the fibrous connective tissue sheath, catheter exchange with fibrin sheath disruption may be successful and preserve the venous access site. In case of central vein thrombosis, relocating the catheter to a new vein may be successful in the short term, but vein abandonment increases the risk of future vein exhaustion and poor dialysis performance. Recently, techniques for catheterization of thrombosed veins have become available, such as the inside-out puncturing of the right internal jugular vein from a right femoral vein approach. If correctly managed, CVCs can last for years with low complication rates.
Correcting and avoiding vascular access malposition

A suitable and well-functioning vascular access is an ongoing challenge in hemodialysis. Despite international recommendations advocating an arteriovenous fistula as the hemodialysis access of choice, for several reasons the use of central venous catheters (CVCs) remains widespread among both incident and prevalent hemodialysis patients. [1]

Vascular access dysfunction is a major cause of morbidity. Early dysfunction usually happens as a result of mechanical issues. Malposition is one of the most common causes of dysfunction and is mainly associated with dialysis catheters.

The optimal site for placement of tunneled venous catheters is the right internal jugular vein (RIJV). [1] The correct location of a catheter depends on two main steps: the correct vessel insertion and the final tip position. According to published data, 29% of catheters placed without imaging guidance have a malpositioned catheter tip. [2]

Regarding the insertion procedure, ultrasound-guided puncture avoids the incorrect vessel because it reduces complications like arterial or small vein puncture. Even after an ultrasound-guided correct vein puncture, if the guide wire is inserted without imaging control, it can go through the wrong vein due to tip–wire angle and anatomical variations or pathology (Figure 1). Malposition in a small-caliber vessel can result in low blood flow and high recirculation rate. Reinsertion of a misplaced catheter is not without potential complications and there is also the possibility of repeating the malposition if imaging is not used.

After insertion of the catheter, the ideal position is yet to be determined. Clinical studies have demonstrated that there is significant movement of the catheter tip when the patient changes position. Additionally, the direction and degree of catheter tip movement is dependent on several variables, including the type of catheter, insertion site, and body habitus of the patient. For example, when the patient has a CVC in the RIJV and changes from a supine to an upright or sitting position, the catheter tip moves upward on average 2–3 cm. [2]

A tunneled catheter tip that is initially positioned in the right atrium will often retract upward into the lower superior vena cava (SVC), which can limit its ability to achieve a high level of performance because the tip may ‘suck’ against the adjacent vascular wall when aspiration is applied. On the other hand, positioning the tip too deeply into the upper right atrium can cause arrhythmias and may also ‘suck’ against the atrial wall. So, the ideal position advocated by most authors is the SVC/right atrial junction, which will rarely evoke a clinically significant arrhythmia or blood flow problems.

The assessment of tip location should be ideally made by fluoroscopy, because it allows the visualization of all endovascular manipulations during the catheter insertion procedure and the exact confirmation of the tip position. However, due to resource limitations, external anatomical landmarks and chest X-rays, which are often imprecise, are still used to confirm catheter location in many centers. Many authors state that the most reliable radiographic landmark to define the borders of the SVC is the right tracheobronchial angle, which is located at a median distance of 5 cm to the SVC/atrial junction. [3] This means that a catheter tip positioned 3 cm below the right tracheobronchial angle would always be within the SVC.

Although malposition is mostly a catheter problem, the outflow tract of fistulas or grafts can be located in less accessible areas, mainly too deep, which may compromise cannulation and be associated with several complications such as hematomas (Figure 2). Ultrasound mapping is a powerful tool to precisely locate outflow tract and to guide cannulation.

In conclusion, there are several factors to take into account to avoid catheter malposition. The best position for its tip requires an understanding of numerous clinical variables, including catheter type, insertion site, and the patient’s body habitus or movements, among others. Insertion procedure should always be guided by ultrasound and final tip position should be assessed by fluoroscopy. If fluoroscopy is not available, knowledge of radiographic landmarks is essential to estimate tip location, while bearing in mind its lack of precision. Repositioning of CVCs should always be done with fluoroscopy to avoid additional complications.

References

CME 15
Practical issues in vascular access care
Saturday, 12.00–14.00, Sala Retiro
Don’t forget to vote for your candidates for the ERA-EDTA Council!

**The Candidates – and what they hope to achieve as Council Members**

**ALEXANDER RODENKOULAZ**

**TALIA WEINSTEIN**

**PETER J. BLANKESTIJN**

**ANNETTE BRUCHFIELD**

**DIMITRIOS GOUMENOS**

**HANS-PETER MARTI**

"I would focus on three aspects:
1. Patients: Since we have successfully implemented a screening program for CKD in Austria, I would focus on a European-wide concerted effort for implementing a screening program.
2. Young Academics: We are starting to face a tremendous shortage of nephrologists in Europe. I would like to organize a European-wide effort to attract young doctors to the field of nephrology.
3. Compliance rules of the industry: In recent years companies have installed new compliance rules which regulate the interactions between physicians and industries. This leads to uncertainties how to handle invitations for congresses, and undersigning complicit legal contracts. I would establish a plan with clear rules in close cooperation with the industry for all ERA-EDTA members, which should lead to a more transparent way of providing education to our members."

"I would aim to promote nephrology training throughout Europe, and work together to plan strategies that would help recruit the best nephrology fellows."

"Most importantly, to strengthen the relatively weak links between Norway (plus some parts of Scandinavia) and ERA-EDTA. Intention to participate in the organisation of an annual ERA-EDTA congress in 2021, 2022 or 2023, as congress president (see below). Support of young nephrologists by increasing exchange programs with personalized career plans. Increase funding for kidney research through already established industry contacts. Defend the idea of European unity based on insights from my professional activities in Norway (Bergen), France (Paris), USA (San Francisco), New Zealand (Dunedin, Christchurch, Auckland) and Switzerland (Bern, Zurich), which is further facilitated by my dual Swiss-Italian background. Strengthen the role of ERA-EDTA as a prime forum for kidney diseases also beyond Europe with help of my leadership experience."

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The voting station, located next to the ERA-EDTA membership desk, in the registration area, will be open on 3–4 June 2017 during the opening hours of the registration desks. On 5 June 2017 the voting station will close at 09.00. Voting will also be possible immediately before the start of the General Assembly, which will take place from 09.30–10.45, 5 June 2017, Room N117–118, Level 1, IFEMA North Congress Center.

If a full member has lost his/her voting credentials (i.e. a passport or national identity card) will be required in order to receive them again. Voting by proxy is NOT possible. A short curriculum for each candidate will be on display at the voting station as well as on the ERA-EDTA website.
Worldwide renal registries report on the trends of the primary renal disease (PRD) of end-stage renal disease (ESRD) patients starting renal replacement therapy (RRT) in annual reports and/or scientific papers. The United States Renal Data System (USRDS) provides an international comparison of trends in the treatment of RRT, currently including data from 60 countries or regions. In addition, USRDS specifically reports the trends of incident patients on RRT with diabetes mellitus (DM) as the primary cause of ESRD. Also, the ERA-EDTA Registry reports on the trends of DM as PRD. Several papers published on other PRDs like glomerulonephritis (15 out of 25 papers) and ADPKD (13 out of 25 papers). Moreover, in addition to calculating the unadjusted trends, we standardized the numbers per million population by the European Union 2005 population. Following standardization, the age distribution at the start of RRT was similar across all years (2005–2014). This means that, although the mean age at the start of RRT may change over time, due to standardization the effect of age at start of RRT on the trends in PRD was eliminated.

Finally, we will pay special attention to Europe, as we were able to analyze the European data in more detail using the ERA-EDTA Registry database. The ERA-EDTA Registry database contains data on dialysis and transplant patients from 35 European countries. We will, among other results, illustrate differences in the trends of PRD in patients starting RRT across European countries.

Additionally, we will show the results of a systematic review focusing on papers published in scientific journals reporting on at least five-year trends on one or more of PRDs of patients starting RRT for ESRD. The vast majority of the published papers (24 out of 25 papers) reported on the trend of DM as PRD. Several papers published on other PRDs like glomerulonephritis (15 out of 25 papers) and ADPKD (13 out of 25 papers).

Finally, we will pay special attention to the trend of DM as PRD. Several papers published on other PRDs like glomerulonephritis, hypertension and renal vascular disease in patients starting RRT. [1]

This presentation on “The changing pattern of kidney disease at dialysis onset” will provide an overview of the trends of PRDs of patients starting renal replacement therapy (RRT) worldwide.

We will first provide an overview of renal registries worldwide (of which European countries are covered by the ERA-EDTA Registry) reporting on one or more PRDs in patients starting RRT in the period from 2005–2014. For the worldwide comparison, the following PRDs were considered to be comparable across renal registries: diabetes mellitus (type 1 and 2 as one group), glomerulonephritis, autosomal dominant polycystic kidney disease (ADPKD), renal vascular disease and hypertension (as one group), miscellaneous, and unknown and missing PRD (as one group).

The question “Can we really slow progression of renal/CV disease” is to be answered with a “yes… but”. The “yes” is related to the fact that we have shown that we can slow progression of the disease to some degree. The “but” is related to the fact that we have still a huge unmet need that can only be addressed if we are able to align our efforts to unravel the reasons for variation in response to current successful therapies.

A more important development for halting progression of renal/CV function loss is the recognition that our interventions are effective only in a select group of patients at risk. Although trials and guidelines suggest that we should adhere to the concept “one drug fits all”, recent analysis of trials and cohorts show clearly that only a relatively small proportion of patients respond well to the therapies. This variation in response will have to guide us in the very near future if we really want to combat renal/CV disease progression with success. New study designs that enrich for responders, and the investigation of alternatives for the non-responders/bad-responders are currently being tested in many disease areas. Nephrology is following, albeit slowly.

Finally, the most promising avenue for improving our personalized individual care is provided by the opportunities to measure and detect other and better biomarkers and/or surrogates for disease progression, as well as response to intervention. System biology that integrates genomics, proteomics and metabolomics will give us a better view on the individual patient’s risk, and more importantly also a better view of the effectiveness of an intervention in an individual patient. Large European Consortia such as Sys-Kid and BEAT-DKD are progressing this field in nephrology/diabetes.

The results may provide valuable information to determine which patients could benefit from a new or existing treatment, assess the effectiveness of treatment modalities — for example identify effective preventive measures — and ultimately stimulate improvements in healthcare quality. ◆

Can we really slow progression of renal/cardiovascular function loss in CKD?

The changing pattern of kidney diseases at dialysis onset

Worldwide renal registries report on the trends of the primary renal disease (PRD) of end-stage renal disease (ESRD) patients starting renal replacement therapy (RRT) in annual reports and/or scientific papers. The United States Renal Data System (USRDS) provides an international comparison of trends in the treatment of RRT, currently including data from 60 countries or regions. In addition, USRDS specifically reports the trends of incident patients on RRT with diabetes mellitus (DM) as the primary cause of ESRD. Also, the ERA-EDTA Registry reports on the trends of DM as PRD. Several papers published on other PRDs like glomerulonephritis (15 out of 25 papers) and ADPKD (13 out of 25 papers).

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Moreover, in addition to calculating the unadjusted trends, we standardized the numbers per million population by the European Union 2005 population. Following standardization, the age distribution at the start of RRT was similar across all years (2005–2014). This means that, although the mean age at the start of RRT may change over time, due to standardization the effect of age at start of RRT on the trends in PRD was eliminated.

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The answer at present must be: “Yes…but…”

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References
Identifying subjects with CKD using KDIGO guidelines

In 2006, Eriksen et al published the results of patient and renal survival in the population of Tromsø, Norway. Over a 10-year period, 17.9% had an eGFR < 60 mL/min/1.73 m². Considering only patients for whom a second measurement was available, 40.7% of subjects with a first eGFR < 60 mL/min/1.73 m² were not confirmed as being CKD on the second estimation. These authors also illustrated that the prevalence of CKD is further lowered by prolonging the period of time used for the chronicity criterion.

In 2015, Inker et al published a study with longitudinal creatinine measurements (and eGFR by the CKD-EPI equation) of 3888 residents aged between 31–59 years in Reykjavik, Iceland, with a mean follow-up of 25 ± 10 years and baseline eGFR > 60 mL/min/1.73 m². He used several modalities for proof of chronicity, in all analyses (men/woman, different ages and different follow-up), the CKD lifetime risk was systematically the highest when defined by a single eGFR result.

Confirmation of albuminuria (or proteinuria) found at first screening is another essential condition of the KDIGO guidelines before classifying an individual as having CKD, or not. Many factors may influence albumin excretion, including obesity, age, sex, distant inflammation, high blood pressure, infection, and drug use resulting in wide fluctuations—hence the false positivity of albuminuria. Several authors found a high percentage (≥50%) of false-positive albuminuria at low values (urinary AUCR: 30–50 mg/m²/m², dipstick proteinuria (+)), less at higher values or dipstick ++ and +++.

Together with the absence of proof of low eGFR chronicity, this non-confirmation of albuminuria (or proteinuria) in almost all epidemiological studies of the last 15 years, results in an important false positivity of CKD prevalence of at least 50% or more.

It was found that when an arbitrary single threshold of eGFR rate (<60 mL/min/1.73 m²) is used to classify CKD3,4,5, it leads to a substantial ‘overdiagnosis’ (false positives) in the elderly (>55 years of age), particularly in those without proteinuria, hematuria or hypertension. It also results in a significant ‘undiagnosis’ (false negatives) in younger individuals with an eGFR > 60 mL/min/1.73 m² (no proteinuria) and below the 3rd percentile of their age/sex category. The use of 3rd percentile eGFR rate level as cut-off based on age/sex-specific reference values of eGFR allows the detection of these false positives and negatives.

There is an urgent need for additional quality studies of the prevalence of CKD, using the recent KDIGO guidelines in the correct way, in order to avoid a 50% or more overestimation of the true disease state of CKD, with potential dramaticic consequences.

What is the pathology of mesoamerican nephropathy?

In 2002, it was reported that a high proportion of patients who started dialysis in El Salvador had kidney failure of unknown etiology. Since then, a number of reports have been published showing high prevalence of endemic renal failure due to unclear cause in several countries in Central America, the disease, called mesoamerican nephropathy (MeN), mainly affects male agricultural and, in particular, sugar-cane workers. The affected patients often lack traditional risk factors for chronic renal failure such as hypertension or diabetes mellitus. [1] In some areas, 20% of men of working age are affected, and in many cases, the disease progresses to terminal renal failure—a devastating diagnosis for people living in Central America, where dialysis resources are limited and no functioning kidney transplant programs are available.

The clinical picture in MeN patients is characterized by reduced glomerular filtration rate (eGFR), but no hematuria and no or low proteinuria. Patients often exhibit low Na, K and Mg levels, and sometimes hyperkalemia. The cause of the disease has not yet been fully understood, but strenuous physical work in a hot climate with the risk of repeated dehydration and salt deficiency is one of the leading hypotheses. [1] Intake of NSAIDs and rhabdomyolysis may also contribute to the renal damage, while no support has been found for several other suggested factors, including inorganic arsenic, aristolochic acid, mycotoxins, pesticides or alcoholic beverages.

Only a few biopsy studies have been conducted in this region. In 2012 our research team in collaboration with nephrologists in El Salvador, performed the first study of kidney biopsies in patients suffering from MeN. Eight sugar-cane workers were included in the study and we showed a unique renal morphology, with damage in both the glomerular and tubulointerstitial compartments. Widespread glomerulosclerosis, glomerular hyper trophy, signs of glomerular ischemia and mild to moderate tubulointerstitial damage were observed. Electrolyte disturbances, with low levels of potassium and sodium in plasma were seen in many patients. By immunofluorescence and electron microscopy, immune complex disease could be excluded and signs of podocyte injury could be identified.

Our research team has subsequently conducted a second study of 19 sugar-cane workers with values of eGFR > 30 mL/min/1.73 m². The results, in a similar morphological picture in the kidney biopsies and similar electrolyte imbalances, we have also followed up the biopsy patients in El Salvador and Nicaragua and then seen that the progression rate in MeN patients varies and that salt deficiency and some morphological findings were correlated with poor outcome. [2]

Epidemics of chronic kidney disease of unknown origin (CKDu) have also been reported in rural areas of other countries with a hot climate; e.g. Sri Lanka and India. Different causes of the CKDu in Sri Lanka have been suggested, mainly focusing on environmental toxins like heavy metals and agrochemicals in drinking water, but no definite causes have been found. A few biopsy studies have been performed but they are not directly comparable as the inclusion and exclusion criteria have been different. Our group is therefore, in collaboration with local researchers, currently finalizing a third biopsy study in Sri Lanka where similar criteria will be used.

In summary, MeN is a common cause of end-stage renal disease among agricultural workers in Central America. The epidemics in Sri Lanka and India show many similarities with MeN in their clinical and epidemiological presentations, but it is not yet clear if they represent similar diagnostic entities. More biopsy studies are needed where morphological and biochemical studies are combined with protein- and gene expression analysis to confirm the suggested pathogenesis of MeN and to clarify if it represents a disease of different continents.

References

The prevalence of chronic kidney disease (CKD) is increased in the elderly (usually defined as >65 years) and is reported to be as high as 20–47%, varying according to age and the definition of CKD. Frailty, comorbidity and polypharmacy (defined as more than five drugs or more drugs than needed) are frequently associated with old age and CKD. The number of drugs increases with declining glomerular filtration rate (GFR) due to the complex nature of renal disease and frequent comorbidity. Polypharmacy increases the risk of side effects, interactions, non-adherence, drug accumulation and health-care costs. Pharmacokinetic changes develop with increasing age and with the severity of CKD. Accurate estimation of kidney function is challenging in the frail elderly population due to low muscle mass and altered nutritional state, and estimated GFR (eGFR) using serum creatinine (CKD-EPI or MDRD) may often overestimate their kidney function. Including albuminuria in the definition of CKD identifies more patients than eGFR alone. Estimated GFR using cystatin C or creatinine clearance may be superior to eGFR using creatinine in the elderly [1]. An accurate measure of GFR is especially important when dosing drugs with a narrow therapeutic window and for drugs with mainly renal excretion. Deprescribing tools may reduce the high pill burden of CKD patients.

References

How to reduce the pill burden in elderly CKD patients? Relevance in clinical practice

The concept that the disease may be mediated by recurrent heat stress is consistent with climate maps that typically show that the regions affected are associated with high solar radiation and areas commonly associated with heat waves. Indeed, our group has suggested that the reported increase in CKD in these regions may be due in part to climate change with an increase in extreme temperatures (heat waves).

Insights into the role of inadequate hydration and heat stress as risk factors for CKD also may be relevant to classical forms of CKD. There is increasing evidence that CKD due to diabetes and other causes may also be influenced by hydration status, circulating vasopressin (co-penetration levels), and heat. Clinical trials to determine if increasing hydration can slow the progression of CKD are being conducted. Such simple and inexpensive new therapies for CKD would be welcome.

Epidemics of chronic kidney disease (CKD) have recently been recognized in rural regions of Central America, Mexico, India, and Sri Lanka. Unlike the CKD commonly observed in urban areas, this type of CKD is typically not associated with diabetes, hypertension, glomerulonephritis, or polycystic kidney disease. The primary groups affected are individuals performing manual work outside in typically hot environments. Onset of CKD typically begins the 20s, and many subjects often die from kidney failure, as dialysis is not always available. To date, there have been more than 50,000 deaths attributable to kidney disease from these areas. There are some striking similarities in the clinical presentation and historical findings among the various places where the epidemics have been reported. Most subjects are men, and they present with low-grade proteinuria with asymptomatic elevations in serum creatinine. Some have hypertension, hypokalemia and hyperuricemia. Some have dysuria in the absence of urinary tract infection, likely from crystalluria. Biopsies tend to show chronic tubulointerstitial nephritis with variable presence of glomerulosclerosis. While this is the chronic presentation, there is some evidence that subjects may be suffering bouts of acute kidney injury, as noted by elevated biomarkers, sometimes with fever or leukocyturia.

A wide variety of etiologies have been considered, including exposure to heavy metals, insecticides, agrochemicals, and infectious diseases (hanta and leptospirosis). However, the common denominator appears to be heat stress. Recently recurrent heat stress has been shown to cause CKD in laboratory animals. A variety of mechanisms have been implicated, including injury induced by hyperosmolality (such as from chronic activation of the vasopresin and polyol-fructose pathways), from subclinical rhodomyelitis, from urate crystalluria, and from volume depletion/low blood pressure, and from increased body temperature. Indeed, it is known that heat stroke can lead to an acute kidney injury as well as chronic kidney disease.

E-ISSUE
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Pathology of mesoamerican nephropathy
ANNIKA WERNERSON Stockholm, Sweden

Drug abuse and renal disease
Abuse of illicit drugs is common, it is often complicated with a variety of medical problems with high morbidity and mortality and is an important contributor to the global burden of disease. Opioid and amphetamine dependence are the two most common forms of illicit drug dependence worldwide. A multitude of renal diseases are associated with drug abuse including rhodomyelitis, interstitial nephritis and glomerulonephritis. Additionally, viral infections like hepatitis-B and -C and HIV are highly prevalent in drug abusers and renal disease associated with those infections has increased. Hepatitis-C related membranoproliferative glomerulonephritis has emerged as the most prevalent kidney disease in drug abusers worldwide. The last decade, the incidence of AA-amyloidosis as a cause of chronic renal disease in intravenous drug abusers has increased and is now the most common cause of renal failure in that patient population in Norway. This is thought to reflect the increased longevity of drug users and the concomitant long-standing bacterial and viral infections. The prognosis is poor.

Longstanding treatment of chronic kidney disease, including dialysis in chronic users of illicit drugs with variable adherence to recommended treatment is costly and can be challenging and raise many ethical questions. The prevalence of illicit drug dependence is increasing in developed countries. The global burden of renal disease related to abuse of illicit drugs might therefore be expected to increase in the years to come. Efficient strategies to reduce the burden of drug abuse are needed.
Infection in PD: from bench to bedside

Infection is a key potential complication of peritoneal dialysis (PD) – although it is important to observe that it is also a major risk for people treated with hemodialysis. The consequences of PD-related peritonitis include technique failure, hospitalization, morbidity, mortality, and loss of residual renal function. In the early days of PD, patients experienced peritonitis every few months, however improvements in technical aspects of treatment, combined with approaches in prevention, diagnosis and treatment, have resulted in rates of infection every 3 to 4 years of patient treatment at many centers. This raises a couple of key issues. Firstly, that the improvement in infection rates has leveled off since the millennium and, secondly, that there remains considerable variation between centers. Central to the management of PD-related peritonitis is diagnosis, which should be prompt and urgent attention, which is the focus of initiatives that summarizes the best evidence and recommendations for healthcare teams (TEACH-PD). Guiding patients and staff couched in robust quality improvement initiatives that have resulted in reduced infection rates. The ANZDATA registry has demonstrated progress on peritonitis rates over the last few years, which would not have been achieved if that registry had not been collecting the appropriate information. It is essential, therefore, that registries around the world include infection among their data fields. The SCOPE collaborative from North America recently reported that compliance with catheter care bundles is associated with a reduction in the individual risk of PD-related infection. [3]

Ultimately, peritoneal infection is a key issue where resolution depends on high quality training of staff and patients. This includes: appropriate placement of PD catheters to countries such as India, Philippines, Indonesia, Japan, Thailand… and many more. So the disease cannot be the stigma that defines me as a person. We depend on a machine to survive, but people do. I love traveling worldwide, and even I often think about myself in terms of my disease, and of course, I am a patient. However, I only feel I am a kidney patient during my hemodialysis (HD) sessions at the hospital, which I have been attending since 1995. When I finish my Anti-microbial resistance (AMR) is a major emerging concern that presents challenges for the whole medical community, with specific issues for PD. [2] The first Gram-positive resistance has been a fact of life for 20 years – steps to reduce impact have had some success in at least controlling the impact of methicillin-resistant Staphylococcus aureus (MRSA). There is much greater concern in relation to the more virulent Gram-negative enteric bacteria that produce extended spectrum β-lactamases and carbapenemases, a situation that is compounded by a very limited pipeline of new antibiotics. There are several international examples of quality improvement initiatives that have resulted in reduced infection rates. The SOCPer collaborative from North America recently reported that compliance with catheter care bundles is associated with a reduction in the individual risk of PD-related infection. [3]

References

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Starting a patient on PD: troubleshooting the first 3 months

MIGUEL PEREZ FONTAN
La Coruña, Spain

CME 21 State of the art in Peritoneal Dialysis in 2017
Saturday, 14.15 – 16.15, Sala Colon

Being a ‘renal person’ – The patient’s perspective on quality of life

I often think about myself in terms of my disease, and of course, I am a patient. However, I only feel I am a kidney patient during my hemodialysis (HD) sessions at the hospital, which I have been attending since 1995. When I finish my treatment, I am a person with dreams and hobbies, and try to have a fulfilling life, as healthy people do. I love traveling worldwide, and even when undergoing HD treatment, I have traveled to countries such as India, Philippines, Indonesia, Japan, Thailand… and many more. So the disease cannot be the stigma that defines me as a person. We depend on a machine to survive, but this machine is available worldwide (if you can afford it…). During 21 years of renal replacement therapy, I have seen remarkable changes, especially those approaches that tackle the problems that matter to patients. The technical changes in dialysis machines have improved the quality of the treatment, which has led to better adaptation to the burden of dialysis every two days. In addition, medicines such as calcimimetics and phosphatase inhibitors have been a revolution in improving mineral bone disorders.

However, psychological and emotional disorders must be addressed in chronic kidney disease (CKD). Sleeplessness, thirst, sexuality, dietary restrictions… we must tackle CKD as a global issue. Our society celebrates everything by eating and drinking, as we need resources and tools to manage everyday situations.

“When I finish my treatment, I try to have a fulfilling life, as healthy people do.”

DANIEL GALLEGO- AZUARO
Torronté Hospital, Spain

CME 22 Quality of life in people with kidney disease
Saturday, 14.15 – 16.15, Sala Neptuno

Internet: www.era-edta.org

ERA-EDTA NEWS / ISSUE 1 / JUNE 3rd, 2017 / page 20
The last decades have seen a marked improvement in the survival rates of patients treated with peritoneal dialysis (PD). Despite this advance, mortality remains high among these patients. On the other hand, progress in terms of PD technique failure has been less satisfactory, and this outcome represents a major concern in the day-to-day practice of PD nephrologists.

The first months on PD constitute a critical phase in the clinical course of the PD patient. Mortality is particularly high during this period. Preexisting comorbidity is a main determinant of this adverse outcome, demanding interventions oriented to improve modifiable risk factors. In addition, adequate selection of patients, timely initiation of PD with a functioning peritoneal catheter, and prompt and efficient attention to early complications (including volume overload and infections) may help to reduce mortality during this period. The first months on PD also represent the right time to implement measures oriented to sustain residual kidney function, prevent PD-related metabolic complications and preserve the peritoneal membrane, which will all likely improve later survival of these patients.

Improving outcome of patients on peritoneal dialysis

while other causes of technique failure, including inadequacy and ultrafiltration failure, are less frequently observed than in the later phases of therapy. This is relevant, because the main factors leading to early technique failure may be largely preventable, provided well-designed interventions are applied. Timely initiation of PD, correct catheter insertion and care, systematic training and close clinical surveillance (with an emphasis on preventing infections), and prompt attention to abdominal and technical complications are advisable measures that will likely improve early technique survival. In addition, the prescription must fit the lifestyle of the patient, and automated PD provides a useful tool for this purpose. Again, preserving residual kidney function and protecting the peritoneal membrane should be kept in mind from the start of PD, to ensure long-term PD technique survival.

Early technique failure is frequently a consequence of an inadequate selection for PD. Unfortunately, preventing this kind of error is not easy in clinical practice. Many studies have attempted to define predictive patterns for success or failure of PD, and an array of demographic and clinical factors have been claimed to portend these outcomes. Overall, and aside from some unquantifiable medical and social contraindications for PD, it may be hard to predict how an individual patient will get along with this therapy. Timely, complete and understandable information, and implementation of shared decision-making approaches may help to minimize wrong decisions. Once PD is initiated, early detection of new (or previously occult) barriers is essential. Assisted PD has proven to be of great value in this setting, particularly for the management of older patients and in non-optimal social environments.

To summarize, the first months on PD represent a risky period, demanding organized strategies oriented to reduce mortality and ensure technique survival. Should these measures be insufficient to sustain successful PD, do not neglect a well-planned transfer to hemodialysis, including timely creation of a permanent vascular access.

MIGUEL PÉREZ FONTÁN
La Coruña, Spain

CME 21
State of the art in Peritoneal Dialysis in 2017
Saturday, 14.15–16.15, Sala Colon

Check out the benefits of being an ERA-EDTA member!
ERA-EDTA was definitely the key to my career success

Kitty Jager is professor of medical informatics and kidney epidemiology at the University of Amsterdam’s Faculty of Medicine (AMC-UvA). In 2000 as an epidemiologist she became the managing director of the ERA-EDTA Registry – and with this, a success story started for both, the Registry and Kitty. Thanks to her firm commitment and hard work as well as that of her team the ERA-EDTA Registry became a scientific registry of highest international reputation, often consulted by developing renal registries and set as an example for modern kidney epidemiological research. The Registry is now staffed by 7 persons, among them medical doctors, epidemiologists and IT-staff. The list of publications by the Registry is impressive. In 2016, for examples, 28 articles were published in highly cited papers, among them, The Lancet, JASN, and NDT. In addition to this, the Registry publishes a comprehensive annual report. “But this can only be done because all the renal registries in Europe that kindly send us their invaluable data for free each and every year, provide a solid basis for our collaborative kidney epidemiology research network.” Kitty remarks. It is undeniable that Kitty Jager has been a gain for the ERA-EDTA Registry. And vice versa, as she emphasizes. “I have been given the fantastic opportunity to work with some great European nephrology researchers of my time, like Professor Carmine Zoccali (Reggio Calabria/Italy), Prof. Christoph Wanner (Würzburg/Germany) or Prof. Ziad Massy (Paris/France). Besides, all the collaboration with the ERA-EDTA under the umbrella of the Registry has provided me with lots of opportunities”. As instances she quotes the idea by Professor Zoccali, former ERA-EDTA Registry Chairman, of organizing epidemiology courses, writing educational articles, which have also added immensely to Kitty’s scientific reputation – and might have helped her to be appointed as full professor at the AMC-UvA. Other examples are the invitations to present data of the Registry at various international conferences or to build an international network with the aid of the ERA-EDTA Fellowship programs for young nephrologists or nephrology researchers or the countless workshops and courses run by the ERA-EDTA and/or the Registry. For example, the Registry office has established the fruitful ‘ERA-EDTA Registry Clinical Epidemiology Learning and Research Centre’ hosting visiting researchers from all across Europe and even Latin America, cross-fertilizing international clinical knowledge and research skills. “ERA-EDTA was definitely the key to my career success, but it also opened up promising opportunities for many other people. I think, ERA-EDTA has set a great example of how professional associations can serve their members by providing education and research opportunities. I am extremely proud to be part of this association and I would advise my younger colleagues to make use of all opportunities that ERA-EDTA has to offer.”

ERA-EDTA Registry

CARMINE ZOCCALI

Kitty Jager

Amsterdam: The Netherlands

References


Survival of Children receiving dialysis varies widely

All European Union Member States have made commitments towards reducing inequalities in access to health care and in health outcomes. But substantial differences in mortality rates persist in the paediatric renal replacement therapy population across Europe. This is the sad result of a study published in The Lancet [1]. The authors extracted and carefully analyzed patients’ data from the European Society for Paediatric Nephrology/European Renal Association-European Dialysis and Transplant Association (ESPN/ERA-EDTA) Registry from 32 European countries. In summary, the analysis showed that public health expenditure was inversely associated with mortality risk and explained 67% of the variation in renal replacement therapy mortality rates between countries. Moreover, differences between countries in their ability to treat the youngest patients, who are typically the most complex and costly to treat, were an important driver for poor outcomes. “We hope that this study is a huge wake-up call for policy makers in Europe”, explains Professor Kitty J. Jager, Managing Director of the ERA-EDTA Registry. Throughout Europe there are vast inequalities in access to renal care. Especially Eastern European countries remain burdened by stringent austerity measures and limited health-care budgets, which results in higher mortality rates. “In some countries children are still dying, because renal care does not meet the European standards. This is something we are not willing to accept any longer. Measures for improvement have to be taken!” But what measures would be promising? The study observed a positive trend between the number of paediatric nephrologists in a country and the time patients spent in nephrological care before starting renal replacement therapy. “This makes an early referral a key factor for a better survival of pediatric dialysis patients and underlines the value of specialist care as it has already been shown for adult patients”, comments Professor Dr Andrzej Więcek, president of the ERA-EDTA. “Nephrology is a key subspecialty of internal medicine which has to be strengthened within the healthcare systems.”

BAXTER

ERA-EDTA SYMPOSIA 2017

Join us for 3 symposia that will highlight current unmet needs in dialysis and help uncover the potential in what comes next.

SYMPOSIUM
Advancing Renal Therapies Through HDx (Expanded Hemodialysis)

4 JUNE
13:30 - 15:00
Hall 10.A

BAXTER

SYMPOSIUM
Long-term Dialysis Dependence after Acute Kidney Injury (AKI): the Health-Economic Impact

4 JUNE
18:45 - 19:45
Hall N107-108

SYMPOSIUM
Remote Patient Management (RPM) in Home Dialysis: Changing the Paradigm of Care

5 JUNE
13:30 - 15:00
Hall N103-104

VISIT US AT
BOOTH 5.005
The EDITH project

Good news: The European Union has taken a vital interest in evaluating the treatment modalities for patients with end stage renal disease (ESRD) in respect of effectiveness and costs – and initiated a new program: On 1 January of this year the EDITH project started, which is funded by the 3rd Health Programme of the European Union. The acronym stands for “The Effect of Differing kidney disease treatment modalities, organ donation and transplant practices on health expenditure and patient outcomes.”

“The EDITH program is long-overdue”, explains EDITH project manager at the ERA-EDTA registry, Amsterdam/The Netherlands, epidemiologist Doctor Vianda Stel. “In the moment, the overall management of ESRD as well as access to dialysis and kidney transplantation varies a lot across Europe, and nobody really knows which treatment strategy is best for patients and most efficient for the health systems.” The results of the EDITH project might therefore impact future treatment choices by patients and will also be a valuable source of information for health care policy and reimbursement authorities.

The EDITH consortium is led by the Deutsche Stiftung Organtransplantation (DSO) from Germany, and consists of 10 partners from all over Europe together with collaborating stakeholders including renal registries, the ERA-EDTA, the European Kidney Patients Federation (EKPF), the European Kidney Health Alliance (EKHA), the French Agence de la Biomédecine and national kidney foundations. The project consists of various work packages.

The ERA-EDTA Registry participates in the one that will address the epidemiology and costs of different treatment modalities for ESKD. This includes the assessment of 1) the frequency of the various treatment modalities for ESKD, 2) factors that influence the choice of those treatment modalities by patients and doctors, and 3) the impact of treatment modality choice on health outcomes as patient survival and quality of life as well as on health care budgets. The analyses on health care budgets will be performed by the Italian National Transplant Center (CINT–ISS). The other work packages will set up a European Living Donor Registry and a European Kidney Transplant Registry for the follow-up of living donors and transplant recipients.

The project duration will be three years. “For sure, we will gain important insights in 2020 and I am optimistic that the project is a big step towards better treatment choices in ESRD. Besides, the initiation of the program shows that renal care has been brought into the focus of European policy makers. I believe this is a direct result of the continuously ongoing lobbying activity of EKHA, which is supported in its work by the EDITH.” More information about the EDITH project can be found on www.edith-project.eu.

Addressing scientific issues related to clinical development

European medicines regulators have had several recent experiences in precompetitive and product-specific interactions with the academic nephrology community. These interactions can be productive in coping with uncertainties during scientific and regulatory assessment of medicines in the European Union (EU). This is valid for both authorization/development plans (such as scientific advice, protocol assistance, innovation task force debates, and classification and certification procedures), and for more general discussions on study designs (such as preparing guidance documents for product development in a particular disease area or biomarker qualification).

Very interesting lessons were learned during discussions with academia and R&D representatives from both sites of Atlantic. These included the AD-PKD foundation, the Critical Path Institute (C-Path), the Innovative Medicines Initiative (IMI), the FNIH Biomarkers Consortium Kidney Safety Biomarker Project Team and the C-Path’s Predictive Safety Testing Consortium Nephrotoxicity Working Group (FNIH BC/PSTC NWG), SAFE-T, the International Society of Nephrology (ISN), and KDIGO.

Fortunately, we can learn from the examples of diverse interpretations of study results by scientific regulatory and academic experts. These examples highlight the different values put on academic studies and studies for regulatory decision-making purposes (see Table). We should be more active in learning from these different approaches to interpreting the same study results. Now we see that several scientific issues that are being discussed under the umbrella of “How to speed up R&D in nephrology?” There is a living list of unresolved issues that deserves more intensive dialog among regulatory, academic/consortia and industry experts, such as: can 30% decrease in glomerular filtration rate serve as an early surrogate for hard clinical endpoints?; can 25% or 30% decrease in albuminuria serve as a surrogate for functional clinical endpoints?; what is the definition of a valid ‘early’ endpoint/biomarker? These types of question highlight the need for more comprehensive and constant platforms to address these and other emerging issues in a timely manner. Regulators also see the need to draw upon more EU academic expertise in this respect.

Table: CT for drug approval vs patient care

<table>
<thead>
<tr>
<th>R&amp;D</th>
<th>Patient Care</th>
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<tbody>
<tr>
<td>Efficacy</td>
<td>Focused on responder analysis are mean values measuring by clinically meaningful endpoints</td>
</tr>
<tr>
<td>Safety</td>
<td>Risk should be clearly specified and manageable</td>
</tr>
<tr>
<td>B/R (+)</td>
<td>Guided by targeted product profile during R&amp;D should be (+) at the time of Marketing Authorization</td>
</tr>
<tr>
<td></td>
<td>Usually more than just binary decision</td>
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Differentiation in clinical development is necessary when moving from R&D to patient care, and observing that both are subject to different regulatory requirements.

Symposium of the ERA-EDTA & Japanese Society of Nephrology (JSN)

Chairs: Motoko Yano & Andréj Wieczek

Endothelial Dysfunction: a common mechanism underlying diabetic kidney disease
Naoaki Kashihara, Kurashiki, Japan (President of JSN)

AGEs-RAGE system as a promising therapeutic target for diabetic kidney disease
Ko Fukami, Kurume City, Japan (Member of the Global Liaison Committee)

What do cohort studies tell us about CKD and diabetes?
Christian Combe, Bordeaux, France

Genetic and epigenetic factors associated with diabetic kidney disease
A. Peter Maxwell, Belfast, UK
As a member, you will become part of one of the most influential European Medical Associations! Check out all benefits:

- NDT (Nephrology Dialysis Transplantation) subscription, including exclusive access to the archives.
- Exclusive live streaming sessions during ERA-EDTA Annual Congress.
- Unlimited access to ERA-EDTA Congress E-materials, to all ERA-EDTA members who participate at the Congress.
- Exclusive access to special content on ENP (i.e., CME courses slides, ERA-EDTA Dialogue).
- Possibility to organize ERA-EDTA sponsored CME courses.
- Active participation in the decision making policies of the Association.
- Special discounted congress membership fees at the annual congress.
- Special discounts (35%) on the purchase fees of Oxford University Press (OUP) books.
- Participation in the Young Nephrologists’ Platform (YNP), if you are less than 40 years old.
- Take advantage of special membership fees for low income countries.
- Exclusive free access to EuroPD videos.
As a science-driven organization, the European Medicines Agency (EMA) has developed a framework to formalize, structure and further develop interactions with the academic community in the context of the European medicines regulatory network. The framework and an action plan for the next three years were adopted by EMA’s Management Board at its March 2017 meeting.

The framework’s overall objectives are:

- Raising awareness of the mandate and work of the European medicines regulatory network to increase academia’s trust in and engagement with the regulatory system
- Fostering the translation of academic research into novel methodologies and medicines that meet regulatory standards and address the needs of public and animal health
- Ensuring that the best scientific expertise and academic research are available on time to support effective evidence generation, regulatory advice and guidance, as well as decision-making in regulatory processes
- Working with academia to develop regulatory science that embraces scientific progress in medicines development without compromising patient safety, such as, for example, the use of novel endpoints or novel methodologies.

The framework builds on EMA’s experience in interacting with stakeholder associations representing patients and consumers, healthcare professionals and the pharmaceutical industry, which is based on the fundamental principles of transparency, independence and integrity, accountability, and broad representation.

Along with the framework, EMA has developed an action plan that includes, among other activities, initiatives for mutual education and training, staff exchange programs to promote mutual learning, a strategic research agenda for regulatory science and the creation of an EMA entry point for academia to receive information on available support within the EU Regulatory Network.

The session ‘ERA-EDTA & EMA’ is an excellent opportunity to deliver on the first objective of the framework. My presentation will elaborate further on the way EMA interacts with academia, building upon other EMA presentations focusing on how medicines are developed and authorized in the EU and on specific scientific issues related to clinical development in nephrology.

For further details please refer to the EMA dedicated webpages on academia www.ema.europa.eu/ema.

**Introducing a new framework for collaboration**

**The EMA and medicines evaluation in the European Union**

- It develops and publishes guidelines on the requirements for the quality, safety and efficacy of medicines
- It provides special assistance to micro, small and medium-sized enterprises (SMEs) through its SME office
- It issues opinions on orphan designation for medicines for rare diseases
- It manages the Innovation Task Force, a group that provides a forum for early dialogue with applicants, and others.

Involvement of EMA in the kidney and renal disease management will be highlighted, such as authorization of medicinal products for treatment of related conditions, development of scientific guidelines, role of the scientific advice, etc. Transparent interaction with all stakeholders, including health care professionals, patient organizations, learned societies and academia in general, are among the priorities in order to use state-of-art knowledge and expertise in the clinical field. The opportunities for further expansion of EMA/ERA-EDTA collaboration are welcome.

**New medicine evaluation after licensing**

**Professor Jonathan Fox**

Glasgow, United Kingdom

Professor Jonathan Fox will give a lecture entitled ‘New medicines evaluation after licensing – benefits versus costs’ in a special session on the topic: Development of therapies for kidney diseases – a framework of regulatory agencies, academia and industry organized by ERA-EDTA and the European Medicines Agency (EMA).

Professor Fox said: “It is a pleasure to be able to give this talk, which covers a topic that has received insufficient attention in nephrology, namely the post-licensing evaluation of clinical and cost effectiveness of medicines, in order to decide whether or not they should be introduced into clinical practice. This is becoming increasingly important given the rising costs of new medicines, some of which offer only marginal benefit over existing therapies.” He continued: “Licensing bodies such as the EMA and the Food and Drug Administration (FDA) of the USA do vital work to ensure that all new medicines satisfy standards of quality, safety and efficacy, but they do not assess comparative clinical effectiveness or cost effectiveness. This is the job of the increasing number of health technology assessment (HTA) agencies around the world, such as the National Institute for Health and Care Excellence (NICE) in England, the Scottish Medicines Consortium (SMC) in Scotland, the Gemeinsamer Bundesausschuss (G-BA) in Germany and the Haute Autorité de Santé (HAS) in France.

As well as working as a National Health Service (NHS) Consultant Nephrologist in the Glasgow Renal & Transplant Unit, I have been involved with the assessment of medicines for many years,” he added. Most recently this has been as the Chairman of the SMC, which evaluates the clinical and cost effectiveness of all new medicines and significant new indications for existing medicines. Acceptance by the SMC is necessary before any new medicine can be routinely prescribed in the NHS in Scotland. In common with other HTA bodies, SMC is a multidisciplinary organization that includes clinicians (doctors, pharmacists, nurses), health economists and NHS managers, but also has public partners and representatives of the pharmaceutical industry as full voting members.

“My talk in this very interesting and innovative symposium organized by Professor Markus Ketteler will cover key concepts in HTA, including opportunity cost (in this context, what could be gained if the funds needed for a new medicine were spent on other healthcare strategies or, to put it another way, the benefit that would be lost elsewhere by funding a new therapy), and the quality adjusted life year (QALY) and its use in assessing comparative cost effectiveness. It is the cost effectiveness, or value for money, of a treatment that is important, not simply the price – there are many expensive medicines that are cost effective, and cheap medicines that are not.”

Professor Fox concluded: “HTA may be seen to be particularly relevant to publicly funded healthcare systems, such as the NHS in the United Kingdom, but it is also important for any system where there is a limit to funding – at some level, this surely includes all healthcare systems in the modern era, if arbitrary and inequitable decisions about funding new therapies are to be avoided. There is a moral dimension to HTA if therapies that do not offer value for money are funded, then patients requiring other therapies may lose out.”

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**Introducing a new framework for collaboration**

**The EMA and medicines evaluation in the European Union**
Benefits versus costs and the role of health technology assessment

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