Nephro Update Europe 2018

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Keywords

Nephro Update Europe · Diabetic nephropathy · Peritoneal dialysis · Glomerulonephritis · Hepatitis C update · Hypertension update

About Nephro Update Europe

The annual Nephro Update Europe took place on October 4–5, 2018, with a house full of nephrologists from across Europe. Over 2 full days, European specialists summarized the most recent and relevant developments across the broad spectrum of nephrology.

The scientific program and speakers were determined by cochair, Kai-Uwe Eckardt from Charité Berlin, and Ton Rabelink from the Leiden University Medical Center in The Netherlands. The faculty was made up of returning experts, such as Patrick Murray (Ireland), Charles Pusey and Iain Macdougall (UK), and An De Vriese (Belgium), along with many others, presenting on topics from acute kidney injury, systemic autoimmune diseases, and renal anemia, to peritoneal dialysis and transplantation.

Below is a glimpse of some of the information presented on the topics of hepatitis C (Michel Jadoul), glomerulonephritis (Jack Wetzels), diabetic nephropathy (Hiddo Lambers Heerspink), and hypertension (Ton Rabelink).

The lectures are available to view on www.streamed-up.com. Registration is free. The presentations are also available to download for participants up to 1 year after the event.

Screening and Treating Hepatitis C in Chronic Kidney Disease: Michel Jadoul (France)

Michel Jadoul was cochair of the recent KDIGO guidelines update, and presenting this recently released information was the backbone of his lecture.

There have been dramatic developments in the treatment of hepatitis C; most recently with direct-acting antiviral agents (DAA), an interferon-free combination of at least 2 agents. With this treatment, the sustained virological response (SVR) rate now exceeds 90%.

Jadoul's presentation included summary updates on the following topics: screening for hepatitis C virus (HCV) in chronic kidney disease (CKD), treating HCV in CKD, preventing HCV transmission in hemodialysis, and managing HCV before and after kidney transplantation.

Meeting highlights of Nephro Update Europe 2018 (October 5–6, 2018, Budapest, Hungary).

Rationale for screening Chronic Kidney Disease (CKD)-non dialysis patients for Hepatitis C Virus (HCV)

- HCV may cause membranoproliferative glomerulonephritis
- Greater prevalence of HCV in late CKD stages than in general population
- Consistent association of
 - HCV+ with worse liver, kidney and cardiovascular outcomes
 - anti-HCV treatment with better outcomes (liver, kidney, cardiovascular)
- Low cost of single enzyme immunoassay for HCV
- Thus testing once for this modifiable risk factor is recommended

Nephro Update Europe 2018

Fig. 1. Rationale for screening CKD non-diabetic patients for HCV.

An important recommendation in the current guideline is that all patients be screened for HCV infection upon the initial evaluation of chronic kidney disease. Along with this, hemodialysis patients should be screened at the beginning of treatment but also rescreened every 6 months. As long as patients remain on hemodialysis they remain at risk [1] (Fig. 1).

There is a good rationale for screening patients for the HCV who have CKD and who are not on dialysis. Though HCV may cause membranoproliferative glomerulonephritis, and that is a significant reason for screening, the KDIGO working group recommends screening for hepatitis C upon the first diagnosis of CKD. There have been multiple recent studies showing a greater prevalence of hepatitis C and/or a consistent association of HCV with deteriorating liver, kidney, and cardiovascular outcomes, along with multiple studies coming at it from the opposite angle. Recent studies have shown that anti-hepatitis C treatment, such as DAA or interferon-based treatments, with long-term follow-up is associated with better outcomes regarding the liver, kidneys, and cardiovascular events. A mediator for this may be that patients who are hepatitis C infected have insulin resistance.

Numerous studies have associated hepatitis C positivity in multivariable adjusted analyses with the on-set of CKD, speed of progression, and various liver and cardiovascular outcomes. One example Jadoul cited [2] is an American study which merged an administrative claims

database and a Medicare database in order to glean all relevant information for the analysis. After adjustment for a number of risk factors, the onset of CKD was most frequent in patients with hepatitis C as opposed to those without the virus. This is especially true for younger people, even though it is significant across all age groups. There is also interesting data in this study about the association between antiviral treatment and the absence of worsening outcomes. It appears that antiviral treatment for hepatitis C patients is protective.

A 2017 study from the Hemodialysis DOPPS (Dialysis Outcomes and Practice Patterns Study), on which Jadoul was a coauthor, concentrated on the morbidity and mortality associated with hepatitis C positivity [3]. All-cause mortality was 12% greater in the group adjusted for hepatitis C+. As expected there was more liver-related mortality, but the trend for cardiovascular outcomes did not reach a significant level, showing similar results to the nondialysis population and suggesting that hepatitis C in the dialysis population might also increase to some extent the cardiovascular risk.

An important study from a few years ago showed that antiviral treatment for hepatitis C infection is associated with improved outcomes in diabetics [4]. The results showed that the treated cohort or the uninfected hepatitis C cohort had a better outcome than the untreated cohort.

Jadoul explained a few basics about the DAA regimen. Recently, there have been 3 classes of drugs available. The

suffix identifies the class; for example, a protease inhibitor will end with “-PREVIR” (such as grazoprevir), the NS5A inhibitor will end with “-ASVIR,” and the polymerase inhibitor will finish with “-BUVIR” (like sofosbuvir). The extent of elimination by the kidneys versus the liver is important. For late CKD or dialysis patients a drug eliminated by the liver is preferable so that the dosage does not need to be adapted. With a drug eliminated by the liver there is the possibility of causing drug-to-drug interactions, which is an important point when using DAA regimens. Also to be considered, there may be barriers to viral resistance resulting in the need to add ribavirin, which is poorly tolerated in late CKD or dialysis patients. Finally, like in many other antibiotic or antiviral therapies, such as for HIV, at least 2 drugs need to be used in all hepatitis C regimens to reduce the risk of hepatitis C resistance.

Studies are currently under way reporting that sofosbuvir-based regimens, which are cleared by the kidney, are safe and effective in late CKD patients, although the optimal dosage has not yet been determined. Alternatively, worsening of CKD progression during a sofosbuvir regimen is not to be excluded.

With the goal of giving a comprehensive update, Jadoul referenced the 3-year-old C-SURFER study [5]. Before those results came in, and the newer drugs were introduced, treating late-CKD or dialysis patients for hepatitis C was still difficult. The first randomized, controlled trial of an oral, interferon-free DAA regimen in CKD stage 4/5 patients used grazoprevir plus elbasvir. Both drugs are eliminated almost exclusively by the liver so there is no dose adjustment in CKD. Jadoul mentioned the study design, which he said was excellent, and which included a placebo phase, making it possible to assess the tolerability and not just the efficacy of the study drug versus the placebo. The results showed that regardless of the full analysis or the modified full analysis there were very few relapses among immediate and deferred treatment patients, with – 94 to 99% SVR12 (SVR = 12 weeks, meaning no detectable virus 12 weeks after stopping treatment), basically a cure of hepatitis C [6]. The conclusion was that interferon/peginterferon is the past, as now there is a treatment which is effective but also much better tolerated.

A year ago, an open-label trial with no placebo period produced more encouraging results. In a multicenter phase 3 study, patients with HCV were treated with glecaprevir and pibrentasvir [7]; 88% of the patients were on hemodialysis and 58% were treatment naive, with no previous hepatitis C therapy. The posttreatment results were

again in the 95–100% range, with impressively 37% of the patients already at week 1 having no HCV detectable in the blood.

Glomerulonephritis: Jack Wetzels (The Netherlands)

Membranous Nephropathy

A 2018 published comparison between cyclophosphamide and rituximab considered immunological remission [8]. The disappearance of antibody levels in cyclophosphamide-treated patients versus rituximab-treated patients who were positive for the antibody at the start of treatment was measured after 6 months. In more than 80% of the cyclophosphamide-treated patients the antibodies disappeared after 6 months, with no major difference between the baseline antibody levels. With regard to the rituximab-treated group, the higher the antibody levels were, the less effective rituximab was. The conclusion is that patients within the upper half of antibody levels have a lower chance of going into immunological remission. These results coincide with original data suggesting that in patients with high antibody levels rituximab is not effective, and this suggests that cyclophosphamide might still be effective in these patients.

C3 Glomerulopathy

A recent retrospective study from the USA [9] considered the effect of mycophenolate mofetil on 120 patients with C3 glomerulopathy (C3GN), 30 of whom were treated with a dose of 2g/day for a median duration of 24 months. In the study 20/30 responded to the treatment; a reasonable response for a disease which has been considered untreatable. Wetzels pointed out that it is also important to realize that in this study 50% of the patients had a rapid relapse after withdrawal making it clear that we cannot yet cure C3GN.

C3 glomerulopathy is a very difficult disease because competent pathology is needed, complements need to be considered, and deciding when to define the disease can pose problems. Iatropoulos, from Italy, and his team did a cluster analysis of patients with C3GN or immune complex MPGN [10]. The data revealed, after considering clinical parameters, such as complement gene/antibodies, electron microscopy and immunofluorescence, that out of four determined clusters, cluster 2 had C1gG and C1q staining of more than 1+, meaning that in the original definition of C3GN these patients would not have been included in the C3GN group. The conclusion should be that with a patient presenting a MPGN-like picture

C3-Nephropathy Take-Home Message

- Definition of C3GN: *presence of IgG or C1q does not exclude C3GN → expert pathologist!*
- C3GN: *paraprotein-associated in patients > 50 years*
- Idiopathic C3GN:
 - *Treatment: MMF + prednisone (outcome in studies biased)*
 - *Eculizumab: maybe effective in RPGN + crescents*
 - *New complement inhibitors are coming (factor D/C5aR)*
 - *→ refer patients for study*
- Paraprotein-associated C3GN:
 - *Haematological remission should be the goal*
 - *Not all patients need therapy (age/progression rate/risks)*

Nephro Update Europe 2018

Fig. 2. C3 nephropathy: take-home message.

with IgG or C1q on the biopsy but the staining of C3 is co-dominant or more than 1+, consider complement components. In the case of an abnormality in the complement one can use the definition C3GN, and that should affect the treatment decision (Fig. 2).

Wetzels summed the section up by explaining that if a patient presents C3GN one should measure the paraproteins, especially in patients older than 50 years. In patients with idiopathic C3GN there are some treatments, with the best one at the moment being mycophenolate mofetil together with prednisone. It is important to realize that there are now studies starting with new complement inhibitors that could significantly impact the field. In patients with paraprotein-associated C3GN, hematological remission should be the goal. It is important to keep elderly patients in mind, as well as patients with very slow progression, because due to the toxicity of the treatment not all patients should be given hematological treatment. Therefore, care should be taken when selecting patients.

Diabetic Nephropathy: Hiddo Lambers Heerspink (The Netherlands)

An observational study published in early 2018 analyzed the mortality burden associated with diabetes from among 35,000 randomly selected American households

and the specific cause of death over time [11]. The prevalence of kidney disease in patients with diabetes remains high, although historically cardiovascular disease accounts for the majority of deaths. Mortality rates due to cardiovascular death have been declining in America, potentially increasing the relative importance of other causes of death in diabetes.

About 25 out of 1,000 patients per year die in the diabetic population; this is twice as high as in the nondiabetic population, where approximately 11 out of 1,000 patients die per year. Vascular death has been declining over time, while nonvascular death increases proportionally over time; this holds true for diabetes and nondiabetes patients.

In the 10-year percentage change in death over time, essential hypertension or renal death is extremely high (66%) in diabetic patients, while in nondiabetics it is 36%.

This study shows that excess mortality among diabetics travels across multiple and diverse organ systems. This diversity of cause of death should have important implications for health policies, the prioritization of health budgets, and the further development of therapies.

A recent, similar study from Mexico assessed the effect of diabetes on cause-specific mortality [12]. In low- and middle-income countries the prevalence and complications resulting from diabetes are expected to increase, but in Mexico there is already a 4-fold increase in the mortality risk with a diabetes diagnosis. This was a large, pro-

What's new?

- Both studies support recent guidelines to consider metformin in moderate to severe CKD providing that the metformin dose is adjusted
- Suggested daily doses and guidance:
 - CKD stage 3A: 1500 mg (500mg morning / 1000 mg evening)
 - CKD stage 3B: 1000 mg (500 mg morning / evening)
 - Assess eGFR at least every 6 months
 - Withhold metformin in case of reduced circulating volume (fluid loss) or in patients likely to experience AKI

Nephro Update Europe 2018

Fig. 3. What's new: pharmacotherapy.

spective study with 133,662 individuals, among which 16,940 (13%) were diabetic and 6,541 (5%) had undiagnosed diabetes, resulting in a diabetes prevalence rate of 18% in Mexico. The authors compared the association of diabetes versus nondiabetes with death due to vascular disease, CKD, or infections. For all-cause mortality, 35% was attributable to diabetes, making diabetes a major player for all-cause mortality in this cohort. The rate of attributable diabetes-related renal death was 80%, showing that diabetes plays an extremely important role in renal death. The study confirmed that uncontrolled glycemic control is a strong contributor to renal death, along with vascular, renal, and infection-related death rates increasing drastically the longer one has diabetes and a deteriorating glycemic control. Lambers Heerspink reiterated the need for strategies to delay diabetes in order to improve outcomes in patients with a high prevalence of diabetes, since diabetes continues to increase in many regions of the world.

Pharmacotherapy of Diabetic Kidney Disease

The field of diabetic kidney disease is evolving in the area of pharmacotherapy. After 15 years of no new interventions for diabetic kidney disease progress is finally being made.

Lambers Heerspink reviewed new studies on metformin, sodium glucose cotransporter 2 inhibitors, and

GLP-1 receptor agonists, all drugs targeting glycemic control in diabetic kidney disease.

Although guidelines discourage the use of metformin in patients with moderate to severe CKD, because of the fear of lactic acidosis attributed to metformin accumulation, the European Medicine Agency (EMA) guideline in 2016 allowed the use of metformin in patients with moderately reduced kidney function. Due to a lack of prospective studies, the EMA changed its guidelines.

In a prospective study, Lalau and his team performed 3 complimentary pharmacokinetic studies: a dose-finding study, a chronic metformin study, and a pharmacokinetic/pharmacodynamic study [13]. In all of the studies it was concluded that if you adjust the dose of metformin (lower doses at higher CKD stages) then there is no difference in the pharmacokinetics, indicating that you can use metformin in these patients.

Another study published in July 2018 looked at metformin use in a real-world setting [14]. It had a community-based cohort of 75,000 diabetic patients within the Geisinger Health System in the USA. The study concluded that, in comparison, the risk of lactate acidosis in patients with diabetes who receive metformin and those patients without diabetes, across different eGFR stages there is no increase in risk below an eGFR of 30, which is when the risk of lactate acidosis begins to increase. The authors had adjusted for everything, across all kinds of models,

What's new?

- SGLT2 inhibitors are promising agents to slow progression of DKD and to reduce the risks of cardiovascular events
- Hba1c lowering effect attenuated in people with DKD
- Cardio-renal benefits are independent of renal function
- CREDENCE trial will likely be the first trial in 15 years to deliver a new drug for patients with DKD
- Ongoing trials, like DAPA-CKD, test the effects of SGLT2 inhibitors in diabetic *as well as* non-diabetic CKD

Nephro Update Europe 2018

Fig. 4. What's new: SGLT2 inhibitors.

but all results were consistent, supporting the use of metformin in this population (Fig. 3).

Similar to metformin, SGLT2 inhibitors are not recommended in patients with diabetic kidney disease because, according to the guidelines, these drugs are less efficacious in patients with diabetic kidney disease. Recent studies seem to suggest otherwise.

A study published just a few weeks before this congress, demonstrated that the SGLT2 inhibitor dapagliflozin can be safely used in patients with CKD stage 3A [15]. There is an acute drop in the eGFR data which we know happens when the SGLT2 inhibitor is sustained, but when the drug is stopped the eGFR directly returns to baseline values, indicating that this drop is reversible and likely a hemodynamic effect.

There is more data, resulting from the CANVAS trial, about the use of SGLT2 inhibitors in patients with diabetic kidney disease [16]. This was a big program consisting of 2 trials involving 10,142 patients with type 2 diabetes and a regimen of canagliflozin. The trial reduced the risk of cardiovascular death and markedly reduced the risk of hospitalization for heart failure and renal endpoints.

The EMPAREG trial looked at the effects of empagliflozin [17]. When we look at cardiovascular death in people with or without prevalent kidney disease, and the endpoint for hospitalization for heart failure, the effects are consistent in both subgroups, regardless of the preva-

lence of kidney disease or not. Therefore, SGLT2 inhibitors can be used in this population.

The effects of SGLT2 inhibitors on kidney function decline in the CANVAS patients was also published last year [18]. Canagliflozin causes an immediate drop in eGFR, which then recovers, indicating that the drug is working and slowing down the long-term progression of kidney function decline. This is noticeable with SGLT2 inhibitors when compared to the placebo group, where the eGFR shows a continuous decline over time. Importantly, the study also measured eGFR values 30 days after drug discontinuation, which resulted in a direct increase in eGFR of a magnitude similar to that of the initial reduction in eGFR, again showing that the reduction in eGFR is completely reversible even after 2 years of treatment. When considering the clinically relevant endpoints, such as a 40% eGFR reduction, the doubling of creatin, or end-stage renal disease, it is clear that the point estimates favor the SGLT2 inhibitor, indicating that these drugs are very beneficial for diabetic kidney disease. Further evidence comes from the CREDENCE trial, a dedicated clinical trial looking at the effects of canagliflozin, which was stopped early due to positive efficacy findings. The results, which seem to be very positive, will be published in 2019 (Fig. 4).

Hypertension: A. J. (Ton) Rabelink (The Netherlands)

A 2017 meta-analysis in the *Journal of the American Medical Association* [19] analyzed 9 million people and 157 studies, and it was concluded that in 2015 elevated systolic blood pressure was the single most important cause of cardiovascular disease. It caused approximately 10 million deaths, over 200 million disability-adjusted life years, and was a major contributor to ischemic heart disease and stroke. Hypertension is unfortunately poorly recognized; many people have a high blood pressure but are not aware of it, and if they do get treated they are often very poorly controlled [20].

The SPRINT study, a large 2015 examination of patients at a high risk for cardiovascular events, found that targeting a systolic blood pressure of 120 mm Hg results in a reduction of cardiovascular death and all-cause mortality, is cost effective, does not reduce the quality of life, and is safe for the elderly and for patients with mild cases of CKD [21].

Rabelink expressed concern that if blood pressure were driven to 120 mm Hg the diastolic blood pressure would not be too low at some stages. In a patient with a high pulse pressure, for example 150/70, when the pressure is driven to 120 mm Hg the result may be no diastolic pressure for cardiac perfusion.

A further analysis published in *Circulation* [22] in 2018 considered whether there was any effect of reducing diastolic pressure when targeting 120 mm Hg systolic. The results showed that when decreasing the baseline diastolic pressure a further reduction of blood pressure did cause an increase in mortality, but the mortality was still lower than with standard treatment. The opposite is true with CKD, because of an increase in renal failure, but the results were less death and less cardiovascular outcomes. The conclusion is that the risk reduction was maintained even over lower diastolic blood pressure levels.

In January 2017, the American Association of Family Physicians released their new guideline, which increased the drug treatment threshold to 150 mm Hg. The American Heart Association/American College of Cardiology introduced entirely new guidelines a few months afterwards, saying that based on the SPRINT study data hypertension is defined as a blood pressure level above 130/80 mm Hg. With patients at a higher risk, drug treatment should already commence at this level [23].

When considering the figures, the new guidelines are interesting. The analysis of Messerli et al. [24], published in the *European Heart Journal*, showed that in the American population the 2003 target (140 mm Hg) defined 72

million people as having hypertension – 41 million people based on the American Association of Family Physicians definition of hypertension at 150 mm Hg – and with the current American College of Cardiology proposal of 130 mm Hg 103 million people are now considered to have hypertension. This means that an extra 12 million people are now to be treated for hypertension. This poses the following question: are people now being treated for hypertension who are not at a high risk for having a cardiovascular event in the first place, and is this cost-effective?

A few weeks before the congress, the European Society of Hypertension and the European Society of Cardiology came up with their guidelines. They still consider hypertension in the office to be indicated by measurements above 140/90 mm Hg (home measurement of 135/85 mm Hg). Targets were also set for blood pressure, meaning that patients at a high risk should be treated below 140/90 mm Hg, but only if it is possible, and only at not too high a cost should the blood pressure be driven to 130/80 mm Hg [25]. The European break from the SPRINT data and the American guidelines may be a result of the omission of diabetic and stroke patients within the trial.

In an analysis comparing 2 studies, i.e., the SPRINT and ACCORD trials [26], incident CKD was defined as a 30% decrease in eGFR ending with eGFR below 60 mL/min. In the SPRINT data, this intensive treatment resulted in a slight increase in sustained kidney failure, but the same treatment in diabetics showed a significant increase in kidney failure (ACCORD trial). These intensive blood pressure treatments come at a cost. Rabelink noted that in neither trial was age taken into account, which he believes is an important factor and should be considered when making guidelines.

A meta-analysis by Chow et al. [27] of 354 trials considered the drug dosage. Results showed that half of the standard dose (the recommendation to reach blood pressure targets) achieved almost 80% of the blood pressure-lowering effect. This lowering effect of different classes of drugs is additive, meaning that it is much more useful to combine low-dose drugs right from the beginning than to titrate one drug up to its maximum curve and then add another. The reason for doing this is not only efficacy but also a reduction of the side effects of treatment.

Presentations and Content

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Nephro Update Europe 2019

Nephro Update Europe 2019 will be held on September 20–21, 2019, in Prague, Czech Republic. For more information, see www.nephro-update-europe.eu.

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