



# Congress Symposia

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## Summary Reports



Special Edition



Dear Colleagues, dear Friends,

I am proud to present a new NEP initiative: a summary report collection of selected symposia held during the Berlin 2021 fully virtual ERA Congress.

The aim of this NEP Special Congress Edition is to highlight the content of our Congress, with great attention on sessions related to ANCA vasculitis or Nutritional targets in CKD patients, but also Diabetic Nephropathy and Hypertension.

New treatment to stop the CKD progression was a great session of the Congress and here you will find the results of the new studies presented.

COVID19 pandemic issues are also highlighted with a summary report of the symposium on the impact of Covid on haemodialyzed patients and infection control in dialysis units.

The acute kidney injury summary explores the cost effectiveness on the prevention of AKI as well as some possible treatment options.

Onconephrology and Lupus nephritis topic are summarized as well here as they were the topic of the entire LBTC symposia.

I am sure that in this edition of NEP you will find the most interesting Congress sessions, as well as practical suggestions for additional reading and much more for your clinical practice and research.

Enjoy the summary reports.

Davide Bolignano  
Nephrology Education Portal (NEP) Editor-in-Chief



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***Written by Jasna Trbojevic-Stankovic.  
All the speakers reviewed and approved the content.***

# Future scenarios for renal disease

## Climate changes in nephrology

*Richard J. Johnson, United States of America*



Mean temperatures have increased by 0.8°C since 1880, with two-thirds of this change occurring since 1975. According to scientists they are likely to increase by 3°C to 4°C by the end of the 21st century. Global warming is also responsible for 75% of moderate heat extremes throughout the globe.

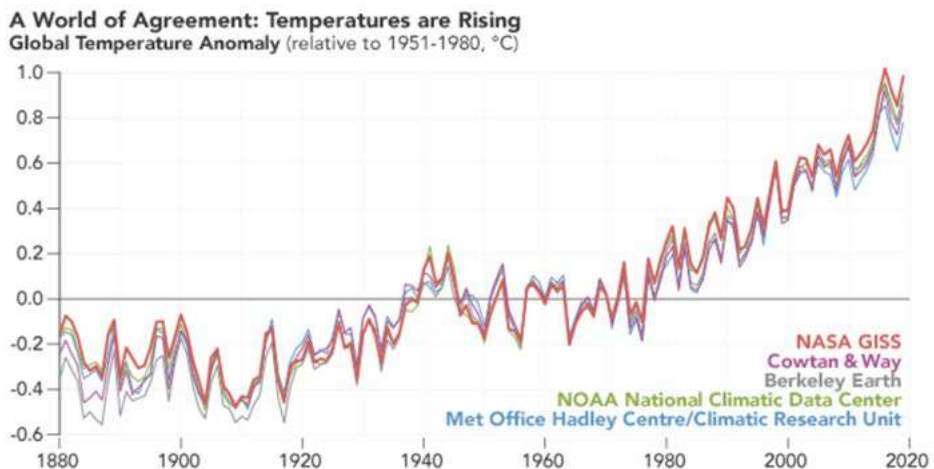


Figure 1. World Temperatures are Increasing.

One of the major health consequences of extreme heat is heatstroke. Heatstroke can occur during heat waves and also in association with exercise or labor in the heat. Electrolyte abnormalities, acute kidney injury (AKI), and chronic kidney disease (CKD) are common kidney manifestations of this condition. Heatstroke manifests with low serum potassium, sodium, phosphate, and magnesium, which are all associated with increased excretion of these electrolytes through sweat or urine. AKI can appear as classical rhabdomyolysis, often associated with hyperuricemia and signs of dehydration, or as acute interstitial nephritis, with leukocyturia and hematuria. Moreover, patients who suffered heatstroke have a 4-fold increased risk of CKD and a 9-fold increased risk of ESRD in later life.

## Future scenarios for renal disease

There are several arguments for the concept that climate change-associated heat stress causes CKD. Firstly, the CKD epidemic occurs most commonly in regions with frequent heat waves (e.g. Central America, India, etc.). Secondly, this epidemic correlates with rising temperatures. It mainly affects heavy physical workers in hot temperatures (e.g. sugar cane workers). The disease is less frequent in a cooler climate, such as in regions at high altitudes. Individuals who develop CKD often have acute presentations that resemble acute heat stroke (e.g. fever, vomiting, back pain, leukocytosis, AKI, etc.). CKD can be induced in mice by recurrent heat and dehydration. Lastly, hydration and shade have been shown to protect against heat stress caused by kidney injury.

Experimental studies show that the primary substance associated with heat stress might be uric acid, due to its increased generation following exercise-induced muscle damage and the urinary acidification that occurs during the concentrating process. Indeed, a study revealed that sugarcane workers exhibit a rise in serum uric acid and creatinine and a decrease in urine pH, thus leading to an increased risk for uric acid crystal formation.

As global warming continues, major efforts are required to assure adequate hydration and prevent overheating in vulnerable populations who are at risk for heatstroke. Heat warning systems, changes in occupational practices, and public health initiatives also are needed. Most importantly, scientific investigations should be directed at identifying how to slow, stop, and reverse global warming.

### Demographic changes in different parts of the world

*Hans Groth, Switzerland*



The Earth today is inhabited by 7.8 billion people of which 6.5 billion people live in less developed countries, whereas 1.3 billion people live in developed countries. Each year the world grows by 80 million people. About 3.4% of the global population live outside their countries of birth. The overall fertility rate has decreased all across the globe. It ranges from <1 child per woman in South Korea to 7 in Niger. The global infant mortality rate has declined since 1970 from 94 infant deaths per 1000 births to 29 deaths in 2020. Life expectancy at birth is higher than ever before with 71 years in less developed countries and 80 years in developed countries.



## Future scenarios for renal disease

Higher longevity, decreasing global fertility, and migration present challenges to the world and society that have to be acted upon to capture their potential for growth and sustainable development on the one hand, but also to prevent the emergence of major imbalances within and across nations. It is still unclear if a longer average life will equate to a healthy life for all equally. Thus, there is a rising concern that a higher long-run inequality of health is taking root in society.

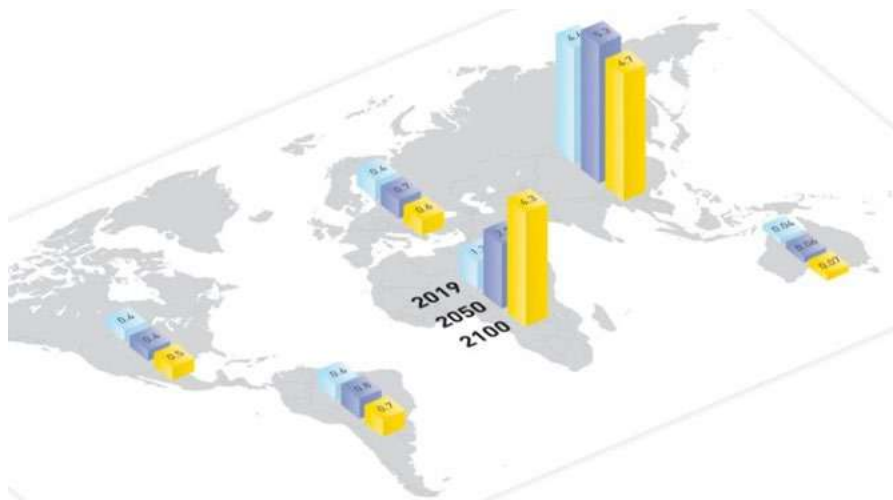


Figure 2. Our next world: Different qualities, different quantities

In Africa, the working-age population (15-64 years) will increase from 600 million to 2 billion by 2060, and 65+ cohorts will increase by at least 200 million. For instance, in Nigeria, the country's population is projected to increase to 263 million in 2030 and 401 million in 2050 when it will become the third most populous country in the world. In Asia, from 2040 on, its working-age populations will start to decrease. By 2060, 1.2 billion from the 65+ cohorts will live on this continent. In China, this dynamic has already started and is gaining momentum. India is set to surpass China as the world's most populous country by 2030.

In Europe, working-age populations have already shrunk. By 2060, the working-age population will decrease by 120 million, while 65+ cohorts will increase by 60 million. In North America, both the working-age population and 65+ cohorts continue to increase, but the elderly increase more rapidly. In Latin America, from 2050 the working-age population will decrease by >100 million, while 65+ cohorts will increase by 180 million in this century. In Oceania, both the working-age population and elderlies will grow at a similar pace.

## Future scenarios for renal disease

From a nephrology perspective, it has been known for decades that eGFR declines in parallel with age. As life expectancy increases, the prevalence of CKD and other age-related kidney disorders will increase as well thus presenting a challenge to the healthcare systems and nephrology community.

### Planetary health and burden of lifestyle diseases – what saves the planet saves our health

*Peter Stenvinkel, Sweden*



Planet Earth has witnessed at least five major mass extinctions over the past 450 million years. Depressing evidence suggests that humans are responsible for the ongoing sixth major mass extinction (Anthropocene), which has led to a multitude of urgent external environmental problems, such as global warming, deforestation, habitat loss, pollution, and a shortage of clean water. In the 'Living Planet Report 2020', the World Wildlife Fund reported an alarming 68% decline in the animal population between 1970 and 2016. Progressive loss of biodiversity has catastrophic effects including an increase in the spreading of emerging and existing infective diseases, reduced opportunities for new drug development that comes from the natural world, decrease in animal pollinators, and reduction of gut microbial diversity.

Global health is rapidly being challenged by an aging population and epidemics of the burden of lifestyle diseases that accumulate with age, such as type-2 diabetes, obesity, arteriosclerosis, depression, CKD, cancer, etc. This rapidly growing group of chronic diseases is characterized by low-grade chronic inflammation, termed inflammageing, mitochondrial dysfunction, and oxidative stress that accompanies the aging process. These features are, in part, reflected by the repressed activity of a master regulator of hundreds of cytoprotective genes - the transcription factor Nrf2 that protects against inflammation and oxidative stress.

There are many examples in nature from which we can learn about mechanisms to escape one or several lifestyle diseases that bedevil humans. For example, hibernating bears, despite months of anuria and decreased renal function during winter sleep, do not develop osteoporosis, inflammation, muscle wasting, or atherosclerosis.

## Future scenarios for renal disease

Hibernating bears also provide a natural model of reversible, healthy obesity with favorable seasonal changes in insulin resistance. Another example is the giraffe, which is protected from kidney disease and stroke despite alarmingly high blood pressure. Elephants and naked mole rats are protected from cancer, whereas Malaysian pen-tailed tree shrews are protected against the toxic effects of chronic alcohol consumption from floral nectar.

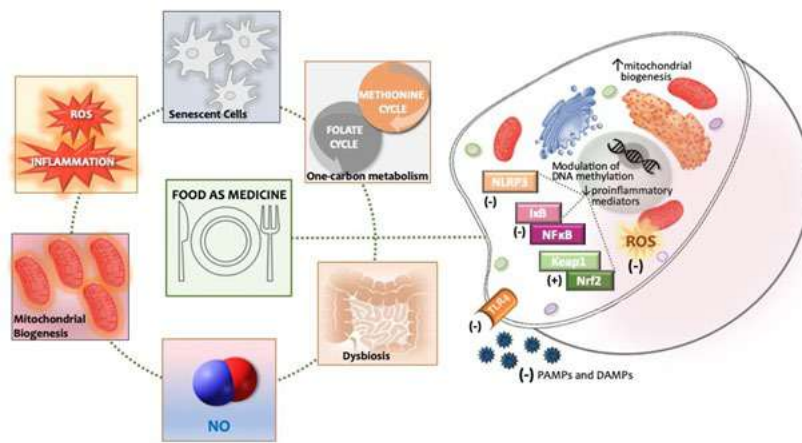


Figure 3. 'Food as medicine' concept benefits

In addition, unhealthy diets (e.g. high in sugar, salt, saturated fat, and ultra-processed foods) are a major risk factor for poor health outcomes causing gut dysbiosis, inflammation, oxidative stress, mitochondrial dysfunction, premature aging, and epigenetic changes – all of which are also common features of CKD. Hence, tailored, healthy diets that include bioactive nutrients could potentially be used to prevent and treat CKD and its complications.

# Future scenarios for renal disease

## Further reading

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# New treatment targets to halt CKD progression

## SGLT-2 inhibition – the new standard?

*Maria Jose Soler, Spain*



One of the major goals in nephrology is to prevent the progression of chronic kidney disease (CKD). Recent years have brought substantial advances in this field. Renin-angiotensin-aldosterone system (RAAS) blockade has long been the mainstay of antiproteinuric and renoprotective action directed to preserve renal function. A few years ago, SGLT2 inhibitors and GLP1 antagonists have emerged as possible alternatives to achieve cardiovascular (CV) and renal benefits in CKD patients. Even more recently, endothelin antagonist, a DPP4 inhibitor, and mineralocorticoid receptor antagonist (MRA) finerenone have also presented encouraging results, thus adding to the selection of available drugs to abate CKD progression.

Patients with CKD have traditionally been excluded from initial drug testing. Nevertheless, when the potential beneficial effect of SGLT2 inhibitors on renal function has been noted, later studies focused attentively on this particular patient group rendering astonishing results. SGLT2 inhibitors enhance renal glucose excretion by inhibiting renal glucose reabsorption in the renal proximal tubule. Consequently, they reduce plasma glucose in an insulin-independent manner and improve insulin resistance in diabetes. Beyond the hypoglycaemic and natriuretic effects, the most important mechanisms of SGLT2 cardiorenal protection include the reduction in the intraglomerular pressure, restoration of the tubuloglomerular feedback, the changes in the local and systemic degree of activation of RAAS, and a shift in renal fuel consumption towards more efficient energy substrates such as ketone bodies.

# New treatment targets to halt CKD progression

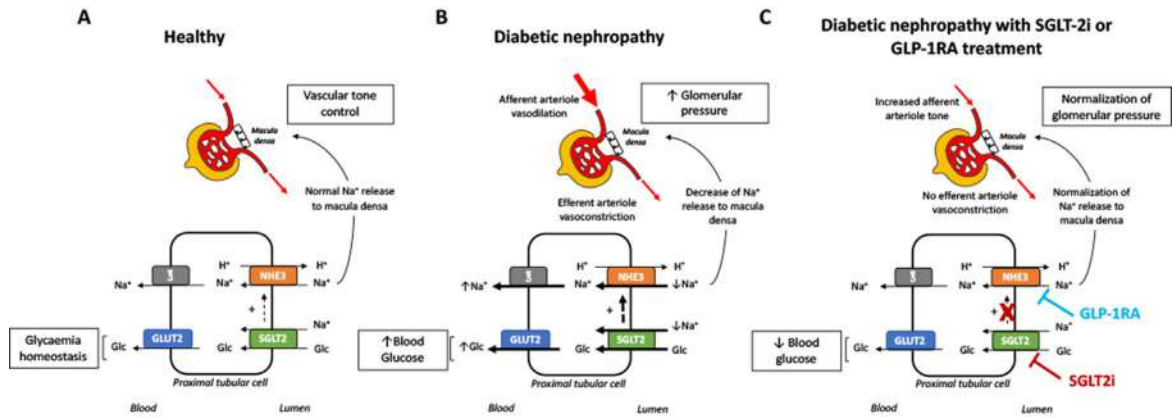


Figure 1. Mechanisms of SGLT2 cardiorenal protection

The recent randomized controlled trials, including CANVAS, CREDENCE, DECLARE, DAPA-HF, DAPA-CKD, EMPA-REG, and EMPEROR-reduced accumulated evidence on SGLT2 renoprotective effects in both diabetic and non-diabetic CKD patients making them the first-line therapy for CKD, independent from diabetic status. This has expanded the target populations in whom SGLT2 inhibitors can be used for their cardio- and nephroprotection to patients with type 2 diabetes with high CV risk, and diabetic and non-diabetic CKD and heart failure patients. No data are currently available regarding CV or kidney benefit in non-diabetic patients with CKD and an absence of heart failure. Furthermore, these trials, and especially the DAPA-CKD, have far-reaching implications for a series of traditional concepts in nephrology. As the DAPA-CKD trial included more patients with immunoglobulin A nephropathy (IgAN) than any of the previous IgAN-focused trials, dual renin-angiotensin/SGLT2 inhibition may become the new standard in this population. The same refers to patients with podocytopathy-related focal segmental glomerulosclerosis lesions. Future studies are expected to elucidate the possible beneficial role of SGLT2 inhibitors in the treatment of acute myocardial infarction, atrial fibrillation, hypertension, obesity, kidney transplant, and even COVID-19 patients.

# New treatment targets to halt CKD progression

## Non-steroidal MRA – an emerging option?

*Christian Rump, Germany*



The RAAS plays an important role in regulating blood volume and systemic vascular resistance, which together influence cardiac output and arterial pressure. Renin is a proteolytic enzyme that is released into the circulation by the kidneys in response to sympathetic nerve activation, renal hypoperfusion, and decreased sodium delivery to the distal tubules. Renin stimulates the formation of angiotensin I, which is subsequently converted to angiotensin II by the angiotensin-converting enzyme (ACE). Angiotensin II is a potent vasoconstrictive peptide that also stimulates the release of aldosterone from the adrenal cortex. Aldosterone in turn acts on the kidneys to increase sodium and fluid retention, thus contributing to volume preservation. The first approved aldosterone agonist to treat fluid retention due to heart failure, liver dysfunction or kidney disease was spironolactone, sold under the brand name Aldactone among others. Nevertheless, it took nearly four decades to notice aldosterone effects beyond sodium and water reabsorption and potassium excretion, namely the increase of cardiac sympathetic activity while reducing inflammation, fibrosis, oxidative stress, endothelial dysfunction, albuminuria, and cardiac remodelling and improving insulin resistance.

Nearly two decades ago it was observed that aldosterone causes nongenomic vasoconstriction of the glomerular circulation, predominantly the efferent arterioles, thus playing an important role in the pathophysiology and progression of renal diseases by elevating renal vascular resistance and glomerular capillary pressure. Furthermore, the discovery of its role in the secondary increase of albuminuria, termed “aldosterone escape”, occurring in patients treated with RAS blockers presented the rationale for blockade of the mineralocorticoid receptor in this event. Later studies confirmed the antiproteinuric effect of MRAs and their favourable influence on renal function and a remarkable sustained reduction in proteinuria.

# New treatment targets to halt CKD progression

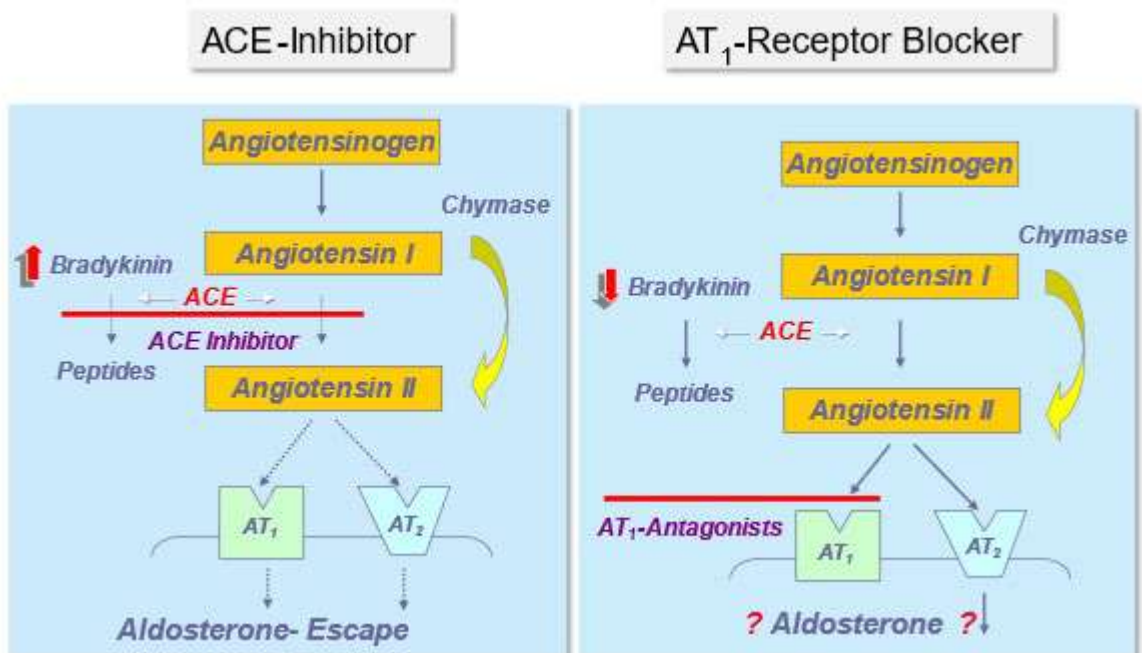


Figure 2. The mechanism of aldosterone escape

The high incidence of the most common side effects of long-term MRA therapy, gynecomastia, and hyperkalaemia, has inspired the search for better tolerated and more efficient agents. The recently developed nonsteroidal MRA finerenone has a unique pharmacodynamic profile based on its physicochemical properties, tissue distribution, mode of mineralocorticoid receptor inactivation, and differential regulation of downstream antihypertrophic gene expression. Aldosterone-dependent phosphorylation and degradation of mineralocorticoid receptors are inhibited by both spironolactone and finerenone, but finerenone delays aldosterone-induced nuclear accumulation of mineralocorticoid receptors more efficiently than spironolactone and is an inverse agonist of the mineralocorticoid receptors reducing cofactor recruitment. These different molecular properties translate into different in vivo properties with significant relevance for patients with CV and kidney diseases.

Several recent studies have investigated the beneficial effects of non-steroidal MRAs on reducing proteinuria and preserving renal function. A large prospective double-blind FIDELIO-DKD trial randomly assigned 5734 patients with CKD and type 2 diabetes to receive finerenone or placebo in a 1:1 ratio on top of maximum RAS blockade. The primary composite outcome was a sustained decrease of at least 40% in the eGFR from baseline or death from renal causes. The key secondary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. After a median follow-up of 2.6 years, the trial confirmed that treatment with finerenone delayed the progression of CKD and reduced the risk for CV among adults with type 2 diabetes, with an acceptable safety profile.



# New treatment targets to halt CKD progression

## Targeting inflammation pathways – the future?

*Timotheus Speer, Germany*



Numerous epidemiological studies highlighted inflammation as a risk factor for CV disease. CKD patients often present an increased inflammatory state due to multiple mechanisms inherent to renal function loss: oxidative stress, uremic toxins, impaired calcium-phosphate metabolism, uremic dyslipidaemia, RAAS activation, and intestinal dysbiosis. Therefore, the identification of endogenous activators of inflammation is essential for the development of new anti-inflammatory treatment strategies.

Recent research specifically focused on the role of uremic dyslipidaemia in the development of CKD-associated inflammation and CV diseases. Uraemia leads to several modifications of the structure of both low-density LDL and high-density lipoproteins HDL, such as changes of the proteome and the lipidome, post-translational protein modifications, and accumulation of small-molecular substances within the lipoprotein moieties, which affect their functionality, eventually leading to endothelial dysfunction, hypertension, and impaired vascular regeneration. On the other hand, apolipoprotein C3 (ApoC3), which raises plasma triglycerides by stimulating very-low-density lipoproteins (VLDL) secretion, has been identified as an activator of NLRP3 inflammasome in human monocytes, thus impeding endothelial regeneration and promoting kidney injury and CV diseases. This effect of ApoC3 is restricted to human monocytes and was not observed in mice.

Recent work explored the association of genetic NLRP3 variants with CV disease and mortality in over half a million subjects concluding that the NLRP3 intronic variant rs10754555 was associated with increased systemic inflammation, inflammasome activation, prevalent coronary artery disease, and mortality. This study provided evidence for a significant role of genetically driven systemic inflammation in CV disease and highlighted the NLRP3 inflammasome as a potential therapeutic target. Recently published, is another research exploring the role of IL-1 $\alpha$  in inflammation, CKD, and myocardial infarction.

# New treatment targets to halt CKD progression

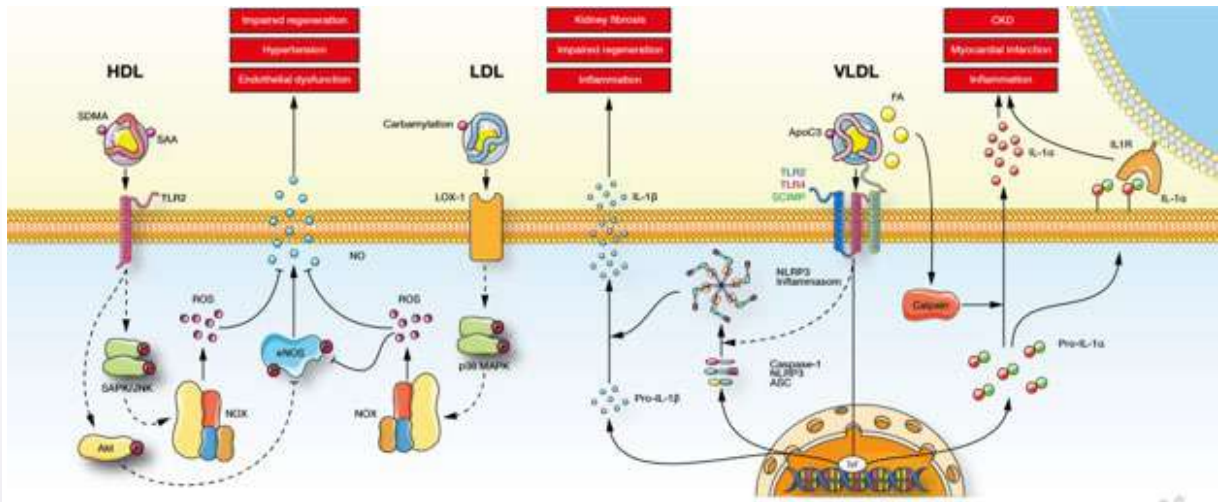


Figure 3. Lipoproteins and inflammation in CKD

Guided by these results, several trials have been undertaken to validate the effect of anti-inflammatory treatment strategies on reducing cardiovascular events. The breakthrough results from the CANTOS trial showed that directly reducing systemic inflammation with canakinumab, an IL-1 $\beta$  neutralizing monoclonal antibody, also reduced CV event rates, without affecting lipid levels. This effect was also observed among high-risk atherosclerosis patients with CKD, particularly among those with a robust anti-inflammatory response to initial treatment, thus suggesting that the effect of canakinumab was entirely independent of kidney function. This therapy was associated with a higher incidence of fatal infection, but also with a lower incidence of systemic inflammatory diseases, such as osteoarthritis or gout, and a lower risk for fatal cancers. Another randomized, double-blind trial – the COLCOT trial, recruited over 4,500 patients within 30 days after myocardial infarction to evaluate the effect of colchicine, a potent anti-inflammatory medication, on the occurrence of CV events. It concluded that a daily dose of 0.5 mg colchicine significantly reduced the risk of ischemic CV events compared to placebo, with an acceptable safety profile. A post-hoc analysis revealed that beneficial effects of colchicine were best achieved when the therapy was initiated within the first three days after the myocardial infarction. More recently, the LoDoCo2 trial confirmed the protective CV effect of low-dose colchicine in patients with chronic coronary disease. Nevertheless, neither of these investigations included patients with advanced CKD.

Finally, the results from a randomized, double-blind, phase 2 RESCUE clinical trial, published just weeks ago, found that ziltivekimab, a fully human monoclonal antibody directed against IL-6, markedly reduced biomarkers of inflammation and thrombosis relevant to atherosclerosis in adults with moderate to severe CKD. These data paved the way to a large-scale CV outcomes trial that will investigate the effect of ziltivekimab in patients with CKD, increased high-sensitivity CRP, and established CV disease – the ZEUS trial, scheduled to start this year.

# New treatment targets to halt CKD progression

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## New treatment targets to halt CKD progression

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## Late Breaking Clinical Trials

### Orally administered C5AR inhibitor Avacopan in a randomized, double-blind, placebo-controlled study (ACCOLADE) for treatment of C3 glomerulopathy



*Andrew Bomback, United States of America*

Complement 3 glomerulopathy (C3G) is a rare kidney disorder comprising C3 glomerulonephritis and dense deposit disease. The complement system plays a significant role within the pathological process of C3 glomerulopathy. The dysregulation of the alternative complement pathway leads to increased levels of terminal fragments of the C5 pathway including C5a, which exhibits a proinflammatory effect attracting and activating myeloid cells. Patients with C3G can present with proteinuria, haematuria, renal failure, and/or hypertension, and generally progress to end-stage renal disease (ESRD) within ten years after diagnosis. Avacopan is an orally administered highly potent antagonist of C5aR which selectively blocks C5a-induced cell activation and leaves the rest of the complement system intact and functioning, providing anti-inflammatory benefits while avoiding broad immunosuppression. It has already presented impressive results in the treatment of ANCA-associated vasculitis.

The Orally Administered C5aR Inhibitor Avacopan in a Randomized, Double-Blind, Placebo-Controlled (ACCOLADE) study aimed to evaluate the safety and efficacy of avacopan in patients with C3G. The study initially enrolled 22 patients with biopsy-proven C3G and C5b-9 level >244ng/mL to receive avacopan 30mg BID and a matching placebo cohort of 22, but later added another 22 biopsy-proven cases with C3G and C5b-9 level ≤244ng/mL as the second stratum in the intervention group and a matching placebo cohort of the same size.

The avacopan therapy led to significant improvement of renal function measured by eGFR and a beneficial difference in the C3 histological index (C3HI) of disease activity after 26 weeks of follow-up. Improvement in GFR correlated with C3HI for disease chronicity which measures the progression of fibrosis and is currently accepted as the best predictor of time to ESRD. Furthermore, the urinary protein to creatinine ratio exhibited a significantly larger decline in patients treated with avacopan after 16 weeks of follow-up. No significant difference was observed in the incidence of adverse events between the groups and no drug-related safety signal has been identified so far.

# Late Breaking Clinical Trials

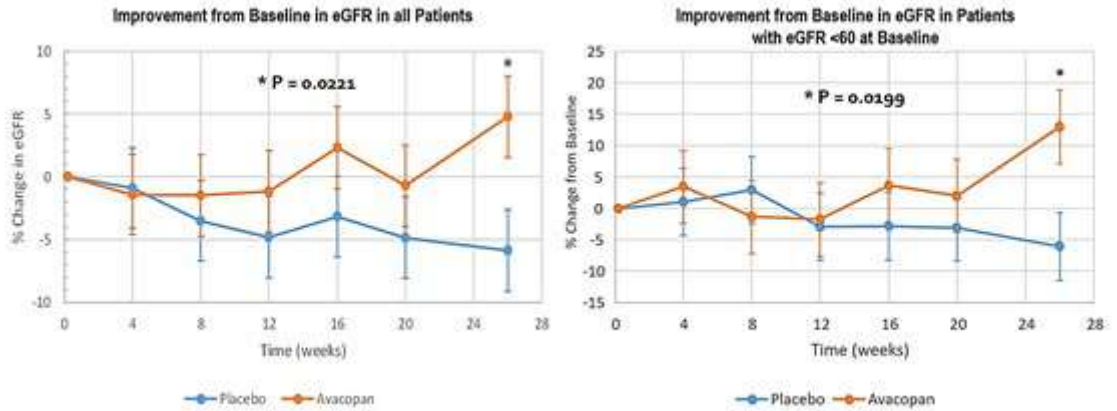


Figure 1. The effects of avacopan on renal function in patients with IgAN

The current data suggest that avacopan is effective in stabilizing the activity and preventing the progression of chronicity of the C3G disease with a favourable safety profile.

## Interim analysis of a phase 2 dose-ranging study to investigate the efficacy and safety of Iptacopan in primary IgA nephropathy



*Jonathan Barratt, United Kingdom*

IgA nephropathy (IgAN), also known as Berger's disease, is one of the most common causes of glomerulonephritis in the world. Pathologically, a spectrum of glomerular lesions can be seen, but the deposition of IgA-containing immune complexes in the glomerular mesangium is observed in almost all biopsies. The disease most often affects young adults and up to 50% of the patients eventually develop end-stage renal disease. There are currently no effective targeted therapies approved for IgAN that slow or prevent renal function decline. The current mainstay of treatment remains and optimized goal-directed supportive care with RAS acting agents.

This adaptive seamless randomized, double-blind, placebo-controlled, dose-ranging study, aimed to investigate the safety and efficacy of iptacopan, an attractive therapeutic to halt the progression of IgAN. Iptacopan is an oral, highly potent, safe, and well-tolerated selective inhibitor of factor B (FB) that binds to FB and its catalytically active fragment Bb to suppress the activity of the AP C3 convertase and activation of the amplification loop, and prevent a downstream generation of the alternative pathway (AP) C5 convertase complex.

## Late Breaking Clinical Trials

Forty-six patients with IgAN were initially randomized to receive three different doses of iptacopan or placebo for 90 days treatment period in Period 1. Guided by the Part 1 interim analysis (IA 1) results, an additional 66 patients were then randomized to four doses of iptacopan or placebo in Part 2 for a 180 days treatment period. The patients had an eGFR  $\geq 30$  mL/min, and proteinuria  $\geq 0.75$  g/24h at screening and at the end of the run period, and were receiving RAS-acting agents, antihypertensive therapy, or diuretics, but not immunosuppressive therapy  $\geq 90$  days before study treatment. Treatment groups were mostly balanced in terms of demographics and baseline characteristics.

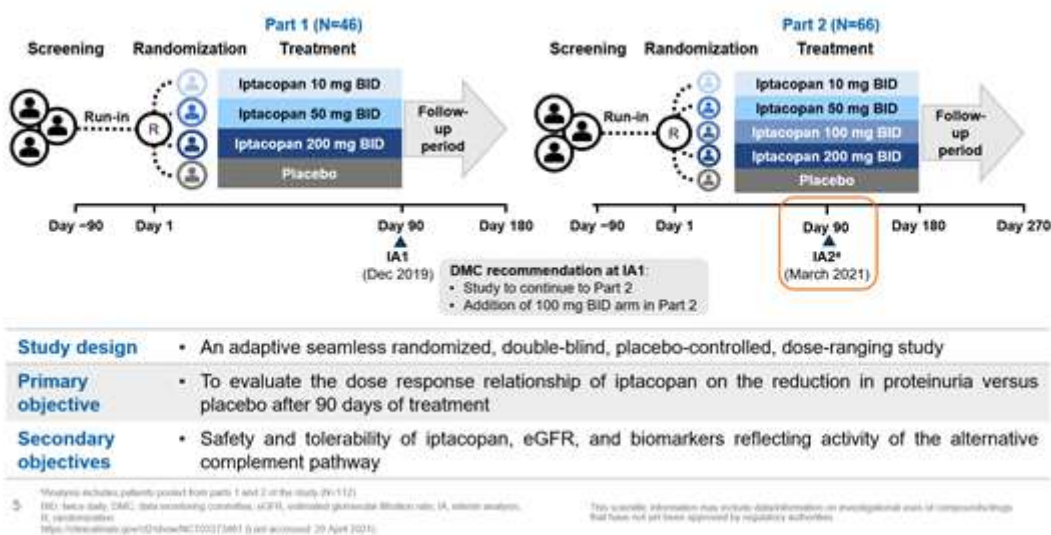


Figure 2. The design of the study investigating efficacy and safety of iptacopan in primary IgAN

As expected, iptacopan treatment resulted in inhibition of the AP with a marked decrease of the plasma levels of the Bb fragment. Near-complete inhibition of AP activation was observed with the dose of 200mg BID. Clinically, the iptacopan treatment resulted in a dose-dependent reduction in 24-hour proteinuria. Furthermore, treatment with all doses of iptacopan was associated with a trend towards stabilization of eGFR over the 90 days treatment period compared with a decline in eGFR observed in the placebo group. Lastly, and perhaps most pertinent to a kidney-specific effect of iptacopan in IgAN, a reduction in urinary soluble C5b-9, reflective of terminal pathway activation and formation of membrane attack complexes, was observed. There were no treatment-related serious adverse events or deaths, and no serious infections reported during the study, thus suggesting a favourable safety profile of this drug.

## Late Breaking Clinical Trials

### Effects of Dapagliflozin on major adverse kidney events in patients with focal segmental glomerulosclerosis: a prespecified analysis of the DAPA-CKD trial



*David C. Wheeler, United Kingdom*

Focal segmental glomerulosclerosis (FSGS) is an important cause of nephrotic syndrome progressing to ESRD in about two-thirds of the cases. Current therapeutic approaches to FSGS include RAS blockade and immunosuppression, although there is limited evidence to support these approaches. Recent evidence suggesting that sodium-glucose co-transporter-2 (SGLT2) inhibitors demonstrate nephroprotective effects in type 2 diabetes independent of blood glucose levels inspired the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial which assessed the effects this SGLT2 inhibitors in CKD patients with and without diabetes. Participants who were required to have an eGFR between 25 and 75 mL/min/1.73m<sup>2</sup>, a urine albumin to creatinine ratio between 200 and 5000 mg/g, and who were receiving a stable dose of RAS acting agents, were randomized to receive dapagliflozin or placebo. Compared to placebo, dapagliflozin reduced the risk of kidney and cardiovascular outcomes and prolonged survival regardless of diabetes status.

Further analysis of a subgroup of 115 participants with FSGS participating in the DAPA-CKD trial Fifty three of these participants were randomized to Dapagliflozin and 62 to placebo. The groups were balanced in terms of demographic and clinical characteristics, except for the prevalence of diabetic patients which was higher in the placebo group.



## Late Breaking Clinical Trials

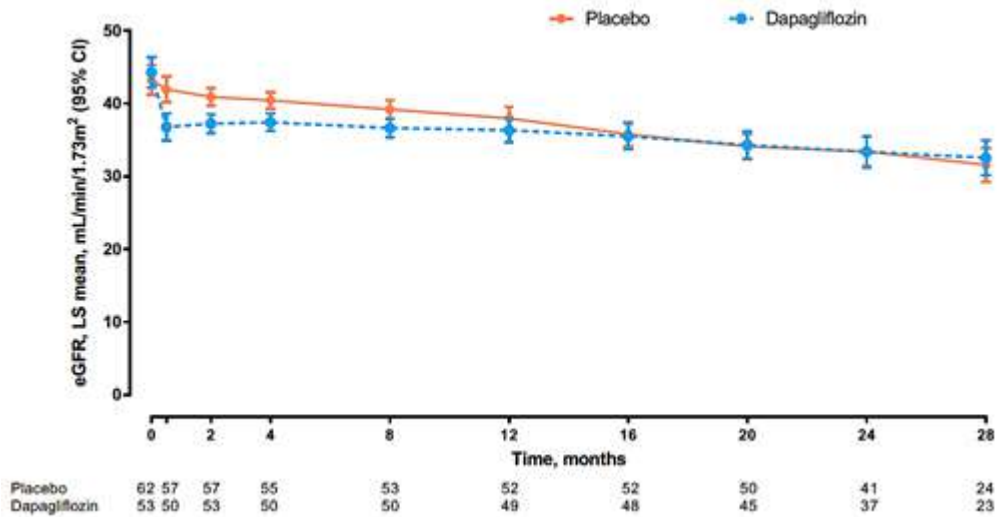


Figure 3. The effect of dapagliflozin vs placebo on eGFR in patients with FSGS

Dapagliflozin reduced the risk of major kidney and cardiovascular events in FSGS patients by approximately 50% and although the difference between the intervention and the placebo group was not statistically significant, it was consistent with the overall results from the DAPA-CKD trial. Furthermore, dapagliflozin tended to attenuate the decline in eGFR and reduced proteinuria during the two-year follow-up. The drug was well tolerated with no unexpected side effects in the FSGS subpopulation.

### A lung ultrasound-guided treatment strategy (LUST) in end-stage kidney disease patients at high cardiovascular risk: a randomized multicentre trial

*Claudia Torino, Italy*



Volume overload is a powerful risk factor for all-cause and cardiovascular mortality in End Stage Kidney Disease patients, especially in those with heart failure. There are several techniques for measuring extracellular volume, but they do not provide an insight into heart function parameters responsible for individual tolerance to volume excess and response to ultrafiltration. Extravascular lung water can be assessed by lung ultrasound (US) and quantified by the number of the recorded hyperechoic B-lines. B-lines have been associated with left ventricular filling pressure in patients with heart failure and are a powerful predictor of adverse clinical outcomes in haemodialysis (HD) patients. This technique reliably reflects lung congestion in these patients, thus suggesting its potential to guide volume removal in this population.

## Late Breaking Clinical Trials

The LUST study aimed to investigate whether a lung-US-guided treatment strategy improves survival and decreases the risk of death, decompensated heart failure and myocardial infarction compared to usual care in HD patients at high cardiovascular risk. It involved 363 HD patients with previous myocardial infarction, angina, coronary syndrome, or Heart Failure from 18 European nephrology centres. These patients were randomized to lung-US-guided ultrafiltration regimen or standard care with UF guided by clinical signs and symptoms. A cut-off of 15 B-lines was used to guide intensification of ultrafiltration by longer or additional dialyses in the active arm. The lung US was performed weekly, until the treatment target (<15 US-B lines) was achieved and once a month thereafter. The study arms were well balanced in terms of demographic and clinical characteristics.

During the follow-up period of 24 months, the average number of B-lines decreased from 15 to 9 in the active arm but increased from 16 to 30 in the control arm. Thus, a significantly higher number of patients achieved the targeted number of B-lines <15 in the active than in the control group. Also, the incidence rate of the adjustments of antihypertensive drug therapy was significantly higher in the active arm.

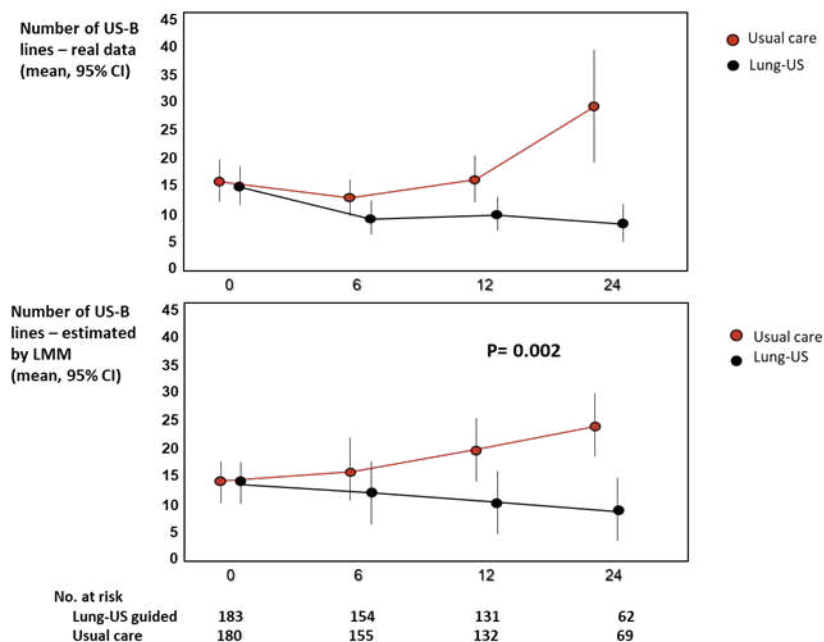


Fig. 4. Trend of the US-BL in the study arms.

Importantly, the intervention was safe because the incidence of dialysis hypotension across the trial was less in the active than in the control arm. No statistically significant difference was found in the combined outcome, all-cause hospitalizations, cardiovascular hospitalizations, or left ventricular ultrasonographic parameters between the groups. Nevertheless, a secondary post hoc analysis showed a higher incidence of recurrent episodes of decompensated heart failure and recurrent cardiovascular events in the usual care group.

## Late Breaking Clinical Trials

In conclusion, the treatment strategy guided by lung-US safely and effectively reduced lung congestion, a risk factor for pulmonary oedema, but was not superior to the usual care strategy in improving a composite endpoint including mortality, myocardial infarction and decompensated heart failure. A post-hoc analysis suggested that a lung US-guided treatment police may reduce the risk for decompensated heart failure. This hypothesis generating finding sets the stage for further studies focusing on prevention of decompensated heart failure in the haemodialysis population.

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# Hypertension treatment in special populations

## Hypertension management in transition from CKD to ESRD

*Aldo Peixoto, United States of America*



The Kidney Disease: Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease (CKD) for non-dialyzed patients has recently presented an update to the KDIGO 2012 guideline on this topic. New recommendations are based on systematic reviews of relevant studies and appraisal of the quality of the evidence. The scope includes proper blood pressure (BP) measurement, optimal BP targets, lifestyle interventions, and choice of medications for specific patient groups. The proposed target systolic BP for most non-dialyzed CKD patients is less than 120 mmHg using standardized office reading. Renin-angiotensin system (RAS) blockers represent the recommended cornerstone of therapeutic intervention regardless of the level of eGFR, presence of diabetes, or albuminuria.



KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease  
KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease  
Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group



### CKD Not on Dialysis

#### • BP Measurement

- R: Standardized measurement (1B)
- S: ABPM or Home BP to complement management (2B)

#### • Lifestyle interventions

- S: Na <90 mmol/day (2C)
- S: Moderate intensity physical activity, 150 min/week (2C)

#### • BP Targets

- S: SBP <120 mmHg (2B)

#### • Drug Choices

- R: ACE or ARB for non-DM CKD G1-4, A3
- S: ACE or ARB for non-DM CKD G1-4, A2
- R: ACE or ARB for DM CKD G1-4, A2 or A3

R = Recommendation, S = Suggestion

Figure 1. Summary of recommendations from the 2021 KDIGO Clinical Practice Guidelines for the Management of Blood Pressure in CKD

# Hypertension treatment in special populations

Earlier guidelines on this subject, such as those from the American College of Cardiology/American Heart Association (ACC/AHA) from 2017 and European Society of Cardiology / European Society of Hypertension (ESC/ESH) from 2018, suggested somewhat higher target BP levels. The targets defined in the KDIGO 2021 are primarily based on the results from the Systolic Blood Pressure Intervention Trial (SPRINT) published in 2017. This trial reported that targeting systolic BP <120mmHg compared with <140mmHg reduced rates of major cardiovascular events and overall mortality in non-diabetic CKD patients without deleterious effect on main kidney outcome. Nevertheless, there is still a lack of relevant data on the optimum BP targets in patients with advanced CKD and those on renal replacement therapies, mainly because of an altered benefit-risk balance associated with BP reduction in these patients.

ACC/AHA 2017 and ESC/ESH 2018 Previous suggested the use of calcium channel blockers and thiazide diuretics along with RAS blockers as first-line therapy. Recommendations for the treatment approach to hypertension in CKD patients in the KDIGO 2021 guidelines rely on the latest studies reporting that RAS blockers reduce the risk of kidney failure, cardiovascular events, and all-cause mortality in CKD patients. In practice, however, a notable decline of RAS blocker use is observed in advanced CKD, and data on the benefits from RAS blockage in this population of patients is still limited. The latest studies have also highlighted the promising results of the novel nonsteroidal, selective mineralocorticoid receptor antagonist (MAR) finerenone in reducing cardiovascular and renal events among patients with diabetic kidney disease. Nevertheless, both RAS blockers and MAR use may be associated with decreased eGFR and hyperkalaemia thus requiring close follow-up of volume status, adequate dietary adjustments, and adding non-potassium sparing diuretic or potassium binder.

## Hypertension in patients with renal transplantation: current concepts and future directions

*Jean-Michel Halimi, France*



The prevalence of hypertension remains high in transplant recipients, ranging from 60% five years after liver transplant, to as high as 95% five years after heart and kidney transplant. Hypertension is associated with significant adverse kidney and cardiovascular outcomes and reduced one-year graft survival in kidney transplant recipients (KTR).

# Hypertension treatment in special populations

There are three groups of factors contributing to hypertension in KTR: the pre-existing, the issues related to the transplant procedure, and the circumstances appearing after the procedure. Increased sympathetic afferent renal nerve signalling from native kidneys causes increased contractility and heart rate, RAS activation, and expansion of effective circulating volume. Procedure-related factors encompass fluid overload during dialysis, increased body weight, high donor age and familial history of hypertension, parenteral fluid administration, and delayed graft function. A multitude of hypertension-contributing factors may also appear following the procedure, such as acute and chronic rejection, calcineurin inhibitors associated with nephrotoxicity, graft artery stenosis or chronic neuropathy, sodium retention due to high dose glucocorticoids, and thrombotic microangiopathy.

The current transplant guidelines recommend only office BP assessments for risk stratification in KTR, even though it has been reported that nearly half of these patients require a change in treatment after ambulatory blood pressure monitoring. The latest consensus statement of the 'hypertension and the kidney' working group of the European Society of Hypertension calls for a reconsideration of such practice, given the prevalence of white-coat hypertension and masked hypertension, the hypertension misclassification, and the better prediction of adverse outcomes by 24-h ambulatory BP monitoring as indicated in recent systematic reviews.

Available guidelines are insufficient and inconsistent concerning recommendations for BP goals in KTR. While anticipating the results of randomized controlled trials which shall define optimal BP targets in this population, it seems reasonable to suggest relying on those employed in the wider CKD population, i.e. <130/80 mmHg.

Guide line	Office SBP/DBP (mmHg)	24h ABPM/HBPM (mmHg)	Specific mention of kidney transplant patients?
KDIGO 2012 (ref 84)	≤140 and ≤90 if UACR <30 mg/g ≤130 and ≤80 if UACR ≥30 mg/g	No formal targets	<130/80 mmHg
ERBP 2014 comment on KDIGO 2012 (ref 83)	Caution required in patients with isolated systolic hypertension and coronary artery disease Target should refer to resting conditions most of the time	No specific comment	Questions whether KDIGO 2012 target is realistic and whether 'one size fits all'
AHA 2017 (ref 81)	<130/80 mmHg**	No formal targets. See table 2 for correspondence	<130/80 mmHg
ESC-ESH 2018 (ref 80)	130-139/70-79*	No formal targets. See table 2 for correspondence	No
KDIGO 2019 (ref 82)	Careful review needed	Evidence should be explored	Concern about SBP <120 mmHg
KDIGO 2021 (ref 8)	SBP <120 mmHg (standardized office BP)**	No formal targets	SBP <130/80 mmHg for most patients

Figure 2. Blood pressure goals in current guidelines in CKD and KTR

# Hypertension treatment in special populations

Conflicting results are also present related to the choice of optimal antihypertensive therapeutics in KTR, as no clear benefit is documented for RAS blockers use over conventional treatment in the current literature. Current evidence suggests calcium channel blockers could be the preferred first-step antihypertensive agents in this group of patients, as they improve graft function and reduce graft loss. The new consensus statement from the „hypertension and the kidney“ working group of the European Society of Hypertension which is currently in press shall address all the major issue regarding hypertension in KTR.

## Hypertension in children and adolescents in CKD

*Stella Stabouli, Greece*



Hypertension is largely present in the paediatric population with renal disease. Over half of the children with non-dialysis CKD and over two-thirds of those on renal replacement therapy are hypertensive. Even though neither of the currently published guidelines for the management of high BP in the paediatric population differentiates BP diagnostic thresholds for children with CKD from those in the general paediatric population, they do propose different BP targets for hypertension treatment in this specific population. This is based on the data suggesting that elevated BP is associated with significantly faster renal function deterioration in children and adolescents with both glomerular and non glomerular kidney disease.

Previous studies have shown that intensified BP control targeting 24-hour BP levels in the low range of normal, confers a substantial benefit for renal function among children with CKD. The findings from the European Effect of Strict Blood Pressure Control and ACE Inhibition on Progression of Chronic Renal Failure in Paediatric Patients (ESCAPE) trial that the aggressive BP treatment to 24h MAP < 50th percentile, provide a greater renal survival benefit in children with CKD remains the gold standard in clinical practice. This BP treatment target has also been adopted in the latest KDIGO Clinical Practice Guideline for the management of BP in children with CKD, despite raised concerns about the potential risks for adverse events from intense BP lowering, which may vary depending on the underlying cause of CKD, risk of dehydration, hypotension, and acute kidney injury.

Ambulatory BP monitoring remains the gold-standard method for diagnosing hypertension in children with CKD. Nevertheless, in children, it may represent a challenge, due to the limited availability of resources and lack of normative values in children younger than 5 years old or with a height < 120 cm. Thus, it has been suggested that in clinical settings with limited availability of ambulatory BP monitoring in children with mild to moderate CKD decisions could be made based on BP obtained during a clinic visit.

# Hypertension treatment in special populations

There are currently no head-to-head randomized controlled trials comparing antihypertensive drug classes in children with and without CKD. Furthermore, there is no evidence of a consistent dose-response relationship for escalating doses of RAS blockers or calcium channel blockers. RAS inhibitors remain the cornerstone of antihypertensive treatment in children, but dose reduction or drug cessation could be considered in case of uncontrolled hyperkalaemia or hypotension, or if GFR decline >30%. The most used second-line medications are calcium channel blockers, but have been associated with higher levels of proteinuria and less efficient BP control in the pediatric population with CKD without concurrent RAS inhibitor treatment. Mineralocorticoid receptor antagonists exhibited promising results in controlling hypertension in adults and could be used to treat resistant hypertension in the pediatric CKD population, with caution on possible side effects. Pharmacological measures should always be supported by lifestyle changes, limited salt intake, adequate diet, and increased physical activity, especially in children with CKD and presence of obesity or metabolic syndrome.

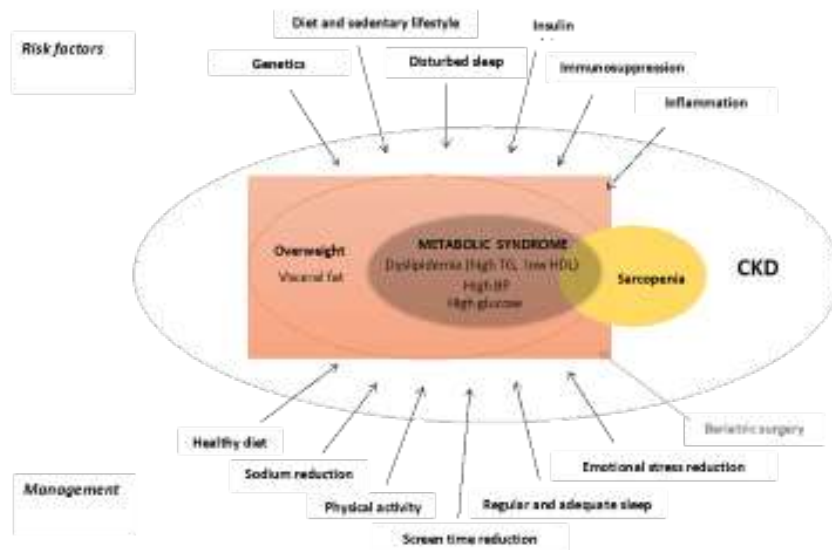


Figure 3. Assessment and management of obesity and metabolic syndrome in children with CKD stages II-V and on renal replacement therapy (clinical practice recommendations from the Paediatric Renal Nutrition Taskforce, Paediatric Nephrology 2021, in press)

Despite the publication of guidelines for BP control in patients with CKD, it appears that hypertension remains undertreated and under-recognized in children with CKD and is associated with left ventricular hypertrophy in this population. Large multicentre normative data are still needed on this topic.



# Hypertension treatment in special populations

## Further reading

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# New nutritional targets in CKD

## Are low or very low-protein diets still useful and attractive treatment in CKD?

Denis Fouque, France



The nutritional status of patients with chronic kidney disease (CKD) is generally compromised and requires adjustments of dietary protein, energy, and micronutrient intake. High protein intake in CKD patients may lead to increased intraglomerular pressure and glomerular hyperfiltration, causing glomerular injury and aggravating CKD. For this reason, reducing protein intake is recommended in this population.

The latest update of the KDOQI Clinical Practice Guideline for Nutrition in CKD (2020) recommends a low protein diet of 0.55–0.60 g/kg/day or a very low-protein diet providing 0.28–0.43 g/kg/day with additional keto acid/amino acid analogues to meet protein requirements in all CKD patients not on dialysis and without diabetes. In adults with CKD stages 3-5 and diabetes, it is reasonable to prescribe, under close clinical supervision, a dietary protein intake of 0.6-0.8 g/kg/day to maintain a stable nutritional status and optimize glycaemic control.

Stage	eGFR (mL/min/1.73 m <sup>2</sup> )	Considered daily protein supply	
1	≥ 90	Normal protein intake (RDA: 0.8 g protein/kg/day)	<ul style="list-style-type: none"> <li>• Low-normal protein, low sodium</li> <li>• Low phosphate, normal energy</li> <li>• Improve CKD-MBD, BP, proteinuria</li> <li>= <b>Slow renal progression</b></li> </ul>
2	60–89	Normal protein intake (RDA: 0.8 g protein/kg/day)	
3	30–59 (a) 45–59 (b) 30–44	Normal protein intake (RDA: 0.8 g protein/kg/day) Protein restriction 0.6 g protein/kg/day	
4	15–29	Protein restriction (1) 0.6 g protein/kg/day (2) 0.3–0.4 g protein/kg/day*	<ul style="list-style-type: none"> <li>• Low protein, low sodium, low phosphate</li> <li>• Low acids, increase energy</li> <li>• Reduce uremic toxicity</li> <li>• Improve uremic symptoms</li> <li>• Reduce protein–energy wasting</li> <li>= <b>Delay ESRD</b></li> </ul>
5	< 10–15	Protein restriction (1) 0.6 g protein/kg/day (2) 0.3–0.4 g protein/kg/day*	

eGFR = estimated glomerular filtration rate    CKD-MBD = chronic kidney disease – mineral and bone disease  
RDA = recommended daily allowance    BP = blood pressure  
\*should be supplemented with amino acids/ketoanalogues

Figure 1. Beneficial effects of an optimal renal diet at different CKD stages (Fouque *et al.*, *NDT* 2020)

## New nutritional targets in CKD

A very low protein diet is both effective and safe in CKD patients. The lower the baseline dietary protein intake, the slower the progression toward end-stage kidney disease (ESKD) and better survival. For instance, a Cochrane systematic review of 17 studies involving 2996 CKD patients found that very low protein intake reduced the risk of CKD progression to ESKD by 36% compared with low or normal protein intakes. Side effects of very low protein diets such as weight loss, protein-energy wasting, and malnutrition are uncommon. Such a diet can also improve the quality of life (QoL) in CKD patients. One study found that the protein-restricted group of CKD patients had significantly higher QoL scores for general health and physical status compared with the maintenance dialysis group.

The clinical benefits of low protein diets include better digestion, postprandial lightness, less constipation, less salt intake, better sleep quality, less need for drugs (e.g. antihypertensives, phosphate binders, bicarbonates of calcium supplements) and reduced risk of associated side effects, better QoL by postponing dialysis, allowing better preparation/maturation of vascular access and allowing transplant preparation and pre-emptive transplantation. Biological benefits of protein-controlled diets include correction of metabolic acidosis and regulation of calcium and phosphates metabolism.

Protein-controlled diets should be considered as a precision medicine delivery with an emphasis on personalized approaches to CKD management. Patients' preference and acceptance, engagement, adherence, and compliance to the prescribed dietary therapy are important factors, which may influence the responses and outcomes to the prescribed LPD.

### **Ketogenic diet: a new tool to improve renal cyst growth in ADPKD**

*Thomas Weimbs, United States of America*



Autosomal dominant polycystic kidney disease (ADPKD) is a common genetic disease characterized by slowly progressive cyst growth in both kidneys, which leads to deterioration of renal function, necessitating dialysis or kidney transplantation. The only approved treatment with tolvaptan has only modest effects and is too expensive. Recent findings suggest that dietary interventions that induce a state of ketosis are very promising in both preventing ADPKD and inhibiting its progression. ADPKD cysts derived from tubule epithelial cells exhibit changes in proliferation, metabolism, and high mTOR activity, which may be related to recently observed changes in the energy metabolism of renal cysts characterized by increased glycolysis and mitochondrial abnormalities, decreased oxidative phosphorylation, and defective fatty acid oxidation similar to the Warburg effect in cancer.

## New nutritional targets in CKD

Previously, two separate studies reported a surprising observation that even a mild reduction in food intake (of just 20-40%) had a profound inhibitory effect on ADPKD progression in a mouse model. A recent study by Weimbs et al. analysed the effects of various dietary interventions on PKD progression in animal models. They reported that PKD rats that were kept on a time-restricted feeding regimen, i.e. intermittent fasting, showed improved kidney function and reduced cystogenesis, cyst expansion, and fibrosis compared with a control group that consumed a similar amount of calories but were fed ad libitum. In addition, oral administration of the ketone b-hydroxybutyrate (BHB) for 5 weeks strongly inhibited PKD progression. These findings corroborate previous clinical observations that patients with hyperglycaemia and type 2 diabetes and/or obese or overweight individuals have a faster progression of ADPKD.

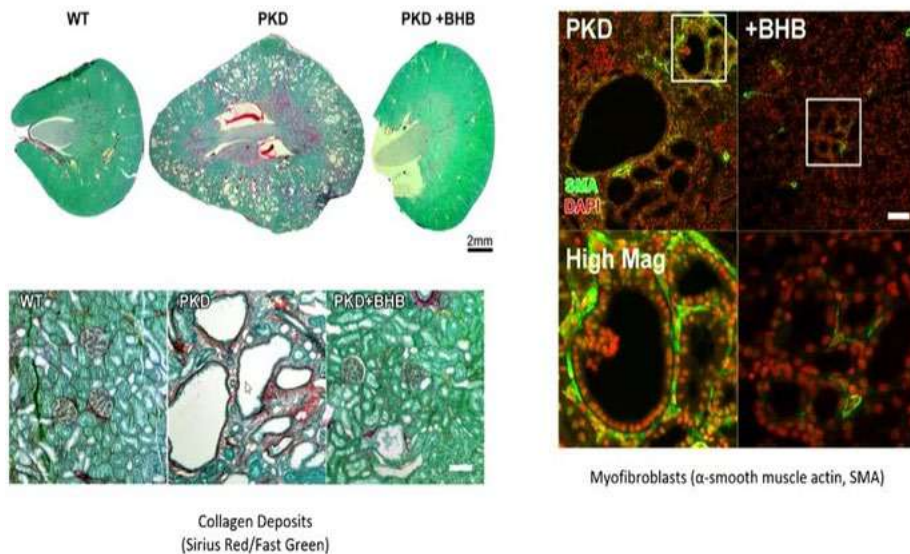


Figure 2. BHB ketone effectively inhibits fibrosis in the ADPKD model of mice (Torres et al., Cell Metab. 2019)

A recent retrospective case series study that surveyed 131 ADPKD patients who have experimented or are currently on a ketogenic diet showed that their overall health and well-being improved in 86% of them, whereas 67% of them reported that their major health issues related to ADPKD were reduced. Almost every single patient-reported improvement in blood pressure control and about 2/3 of patients even reported eGFR improvement. Ninety-two percent of the patients considered the ketogenic diet feasible and 83% of them would recommend it to everyone with ADPKD.

The ongoing KETO-ADPKD Feasibility Clinical trial is examining the safety, efficacy, feasibility and optimal dietary approach of the ketogenic diet in 63 ADPKD patients and the first results are expected in fall 2022.

## New nutritional targets in CKD

### Role of kidney proximal tubules to balance nutrient and uremic toxins levels

*Rosalinde Masereeuw, Netherlands*



The human gut is inhabited by a complex and metabolically active microbial ecosystem which is involved in a significant cross-talk between the human metabolism. Metabolites unique to microbial metabolism enrich the human metabolome, thereby providing energy, vitamins, and trophic signals. However, not every microbial metabolite is beneficial. On the contrary, most of them undergo intense phase II metabolism, and numerous metabolites are actively excreted from the body through the kidneys. Hence, the kidney excretory capacity is an essential part of the human microbial symbiosis. Several microbiota-derived metabolites, including Indoxyl sulfate (IS), p-Cresyl Sulfate (pCS) and Trimethylamine N-oxide (TMAO) were found to accumulate in the blood parallel to the loss of kidney function, and proven to be associated with clinical outcomes in patients with CKD. This paradigm has been coined the gut–kidney axis.

Remote metabolite sensing and signalling is a mechanism to minimize perturbations of body homeostasis due to environmental metabolic challenges. Membrane transporters such as the organic anion transporters (OATs) are thought to be involved in metabolite sensing and are widely expressed in epithelial barriers, including the kidney proximal tubule segment. Jansen et al. found that proximal tubule cells in kidneys sense elevated endogenous, gut microbiome-derived, metabolite levels through epidermal growth factor receptors (EGFR) and downstream signalling to induce their secretion by up-regulating OAT1. This was especially triggered after prolonged high-protein intake. Remote metabolite sensing and signalling were observed in kidneys from healthy volunteers and rats in vivo, promoting OAT1 expression and increased removal of IS. Using 2D and 3D human proximal tubule cell models, researchers also showed that IS induces OAT1 via aryl-hydrocarbon receptor (AhR) and EGFR signalling, controlled by miR-223. Furthermore, it was found that concomitantly produced reactive oxygen species control OAT1 activity and are balanced by the glutathione pathway, as confirmed by cellular metabolomic profiling.

# New nutritional targets in CKD

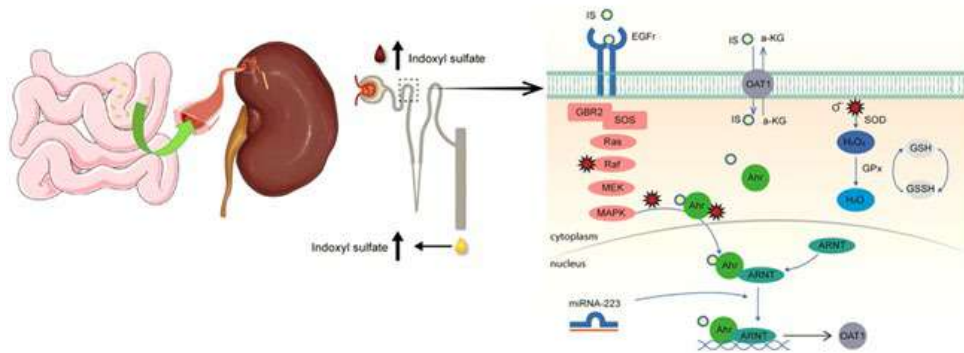


Figure 3. Remote sensing and signaling by indoxyl sulfate (Jansen et al., PNAS 2019)

Remote metabolite sensing and signaling is an effective OAT1 regulation mechanism to maintain plasma metabolite levels by controlling their secretion. Future studies should further characterize the gut metabolome in CKD.

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# Preeclampsia and kidney in 2021

## Endothelial dysfunction and activation in preeclampsia

*Elisa Llurba Olivé, Spain*



Preeclampsia (PE) is a pregnancy-specific complication characterized by high blood pressure and signs of multisystemic organ damage, predominantly affecting the liver and kidneys. Manifestations include severe headaches, changes in vision, upper abdominal pain, nausea, decreased urine output, swelling and shortness of breath, thrombocytopenia, haemolysis, abnormal liver enzymes, and proteinuria. PE is becoming an increasingly common diagnosis in the developed world and remains an important cause of maternal and foetal mortality in the developing world.

While the cause of this syndrome is still debated, clinical and pathological studies suggest that the placenta holds a central role in its pathogenesis. Deficient expression of decidual pro-angiogenic factors, the vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), reduce the activity of the heme oxygenase-1 (HO-1). Under normal conditions, HO-1 decreases oxidative stress and promotes an immune tolerant microenvironment thus allowing for placental development. It also plays a critical role in the prevention of vascular inflammation. Its impaired activity leads to trophoblast invasion and abnormal remodelling of spiral arteries, resulting in placental ischemia and eventually causing oxidative damage, endothelial dysfunction of the peripheral vasculature, and PE.

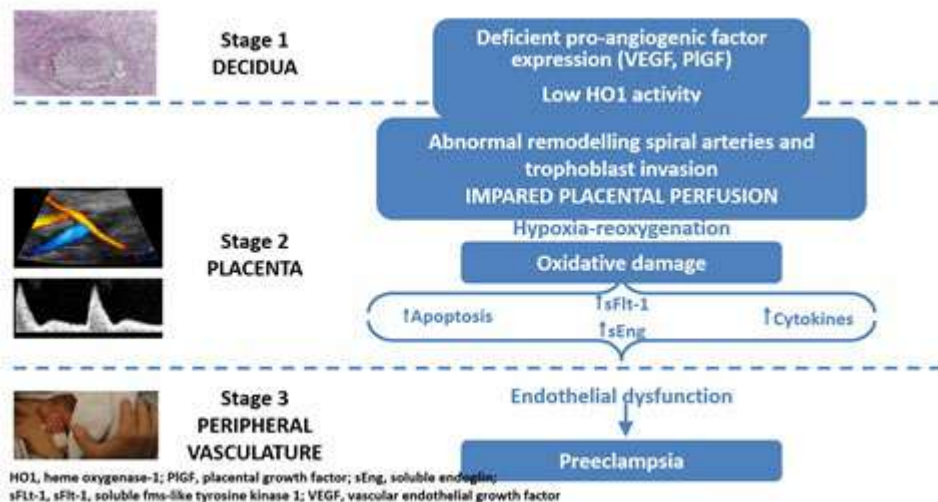


Figure 1. Stages of preeclampsia

## Preeclampsia and kidney in 2021

Risk assessment in women with established PE remains challenging. Clinical manifestations alone might not be sufficient to predict adverse outcomes as a significant proportion of women may develop complications including eclampsia and HELLP syndrome without elevated blood pressure or proteinuria. Conversely, some patients with PE are able to carry the pregnancy to near full term without progression. It has recently been suggested that in symptomatic patients presenting at <34 weeks a soluble fms-like tyrosine kinase-1 (sFlt-1)/PIGF ratio  $\geq 85$  predicts the occurrence of PE-related maternal and foetal adverse outcomes irrespective of the presence of an established diagnosis of PE.

Recently the shift has been made to perceive PE as a systemic disease with the potential to affect the future cardiovascular status of the woman. The magnitude of cardiovascular risk seems to be related to the earlier onset of PE. It appears that angiogenic factors released during PE, such as PIGF, could identify women at higher risk of future cardiovascular disease who might benefit from early preventive measures.

### Senescence and preeclampsia

*Vesna Garovic, United States of America*



Cellular senescence is a phenomenon characterized by cell cycle arrest and loss of cell proliferating ability. It can be triggered by several mechanisms, including DNA damage or genomic instability, oxidative and metabolic stress, oncogenes, inflammation, phototoxic and shear stress, which render cells resistant to growth-promoting stimuli. The biological role of senescence is essentially protective, as it prevents the growth and multiplication of malignant cells and contributes to adequate wound healing, tissue remodelling, and embryogenic development. Nevertheless, the number of senescent cells increases with age and they acquire a specific senescence-associated secretory phenotype (SASP) associated with age-related tissue dysfunction, loss of reparability, decreased resilience, and even chronic disease, including atherosclerosis, diabetes, neurodegenerative diseases, and cancer. Studies on animal models have proved that senescent cells can cause physical dysfunction and decreased survival even in young animals, while senolytics, i. e., agents that selectively clear senescent cells by inducing their apoptosis, can enhance remaining health- and lifespan in old mice. The SASP is easily identified with a senescence-associated beta-galactosidase (SABG) which is detected by histochemical staining.



# Preeclampsia and kidney in 2021

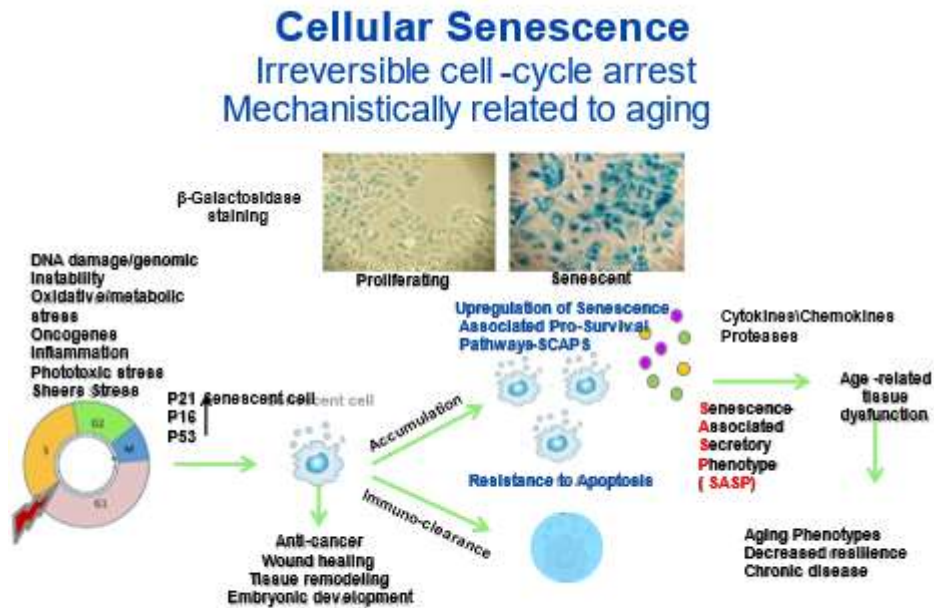


Figure 2. The mechanisms of senescence

Senescence is also a physiological phenomenon appearing in pregnancy, triggered by cell fusion, to establish and expand the syncytiotrophoblast and it progresses with placental aging. Nevertheless, there is increasing evidence that accelerated senescence may lead to placental and clinical pathology, including the appearance of PE. A recent study investigated the role of senescence of mesenchymal stem cells (MSC), i. e. multipotent cells with pro-angiogenic activities, as a possible mechanism by which systemic inflammation exerts inhibitory effects on angiogenesis in PE. MSC isolated from women with PE demonstrated a higher senescent phenotype identified by more abundant staining for SABG, upregulation of senescence markers and SASP components, and lower angiogenic potential than MSC from normotensive pregnancies. The mechanistic link between senescence and impaired angiogenesis in PE was further confirmed by the regained angiogenic potential of PE-MSC following the treatment with the senolytic agent. A study currently under review corroborates these results observing a higher senescence burden in women with PE compared to normotensive pregnant women, and improvement of angiogenic potential of MSC from PE pregnant women following senolytic administration

Future studies are expected to examine the possible role of autologous stem cell transplantation and senolytics to decrease senescent cell burden after affected pregnancies and before the next one, and decrease the risk for cardiovascular morbidity in females in post reproductive years.

# Preeclampsia and kidney in 2021

## Preeclampsia and future renal disease

*Giorgina Barbara Piccoli, France*



Understanding of hypertension during pregnancy and, in particular, PE has changed significantly in the previous decade. The new diagnostic criteria for PE have been proposed in 2014 by the International Society for the Study of Hypertension in Pregnancy (ISSHP) defining PE as de-novo hypertension occurring after 20 weeks of gestation combined with either proteinuria (>300mg/day), or other maternal organ dysfunction or foetal growth restriction. This definition has allowed establishing the diagnosis of PE in absence of proteinuria if other disorders, such as renal insufficiency, liver involvement, neurological or haematological complications, are present. Nevertheless the heterogeneity of this disease concurs to our still limited understanding. Therefore, questions remain open on how to optimize PE classification, predict PE-related chronic kidney disease (CKD) and improve the outcome of these patients.

The strict link between PE and CKD has been highlighted in 2008 when PE was associated with an increased risk of subsequent end-stage renal disease (ESRD). A systematic review and meta-analysis eleven years later confirmed a significant association between PE and risk of ESRD but also acknowledged lack of sufficient data to define the natural history of CKD after PE.

Conversely, several studies have demonstrated that the risk of developing PE is significantly increased in women with all kind of kidney diseases, including single kidney after organ donation, reflux nephropathy, and even nephrolithiasis. Furthermore, patients with glomerulonephritis and immunologic diseases are at higher risk of developing or increasing proteinuria and hypertension, a picture often difficult to differentiate from preeclampsia. Thus, previous renal impairment, whether acknowledged or not, predisposes to PE development, confirming the bidirectional relationship between the kidney and placenta.

# Preeclampsia and kidney in 2021

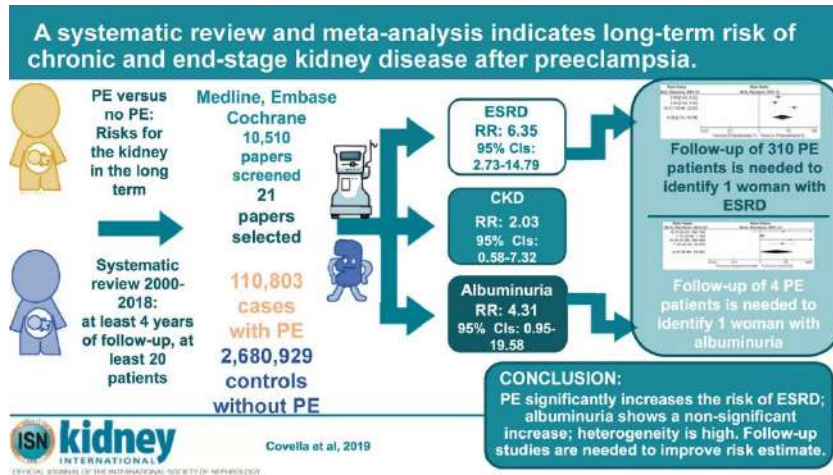


Figure 1. PE and the risk for ESRD

PE is no longer considered a transitory kidney disease healed by delivery. This condition is associated, reveals and predisposes women to renal and cardiovascular diseases in later life, thus representing a window to the future health of the mother and the child. While the search continues for biomarkers that would effectively discriminate between PE and CKD in pregnant women, simple steps can be embraced to improve pregnancy outcomes. The pregnancy workup should always include serum creatinine and urinalysis, all pregnancies in women with previously known CKD should be considered as high risk, and all women who experienced PE should be followed up, with particular attention to later pregnancies.

# Preeclampsia and kidney in 2021

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# COVID-19 in haemodialysis patients

## Prevention strategies for minimizing SARS-CoV-2 infection in dialysis facilities

*Mario Cozzolino, Italy*



The coronavirus disease 19 (COVID-19) initially emerged in China on December 8, 2019, and has since rapidly spread across the globe putting an enormous strain on healthcare systems worldwide. The disease is caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and in the majority of cases remains asymptomatic or only mildly symptomatic. Nevertheless, around 10% of the affected individuals develop severe respiratory symptoms requiring intensive care. According to the latest data the mortality rate among hospitalized patients is around 12%.

Impaired kidney function has emerged as an important factor for adverse outcomes in COVID-19 patients, along with older age, hypertension, type-2 diabetes, cardiovascular disease, and dementia. Patients on in-centre haemodialysis (HD) are particularly vulnerable since they must come together thrice weekly for the treatments and because they are at higher risk of complication and death due to older age and multiple comorbidities. For this reason, guidance has been provided by the proper authorities on how to best protect this population. All guidance emphasizes the importance of hand and respiratory hygiene, coughing etiquette, use of personal protective equipment (PPE), suggest active screening for the most common symptoms – fever, new cough, or dyspnoea; and establishing a triage protocol before patients arrive at the dialysis facility. Nevertheless, discrepancies exist concerning the suggested management of symptomatic or infected HD patients. While the majority of guidelines agree that multiple confirmed or suspected cases should be cohorted and cared for by designated staff, some also advise hospitalization and admission to an airborne infection isolation room, others recommend admission to infectious disease ward, and some suggest that positive but clinically stable HD patients can resume dialysis in designated outpatient units or dialysis shift, an isolation room, or merely a separate room with the door closed. It is generally agreed that being on chronic dialysis per se should not limit critically ill patients' access to intensive care, but directives in favour of or against intubation could be proposed on a case-by-case basis to frail and elderly patients or their relatives.

# COVID-19 in haemodialysis patients



Figure 1. General prophylactic measures and pathways for high-risk patients

The spread of the COVID-19 pandemic has highlighted the importance of limiting social activities to hinder the risk of exposure to the virus. This has emphasized considering home-based renal replacement therapies as possible advantageous alternatives to the in-centre HD. Besides peritoneal dialysis, home HD is also a reasonable choice due to the advantage of the isolation of patients but requires systemic measures to implement the program.

## Infection control in dialysis units

*Patricia De Sequera, Spain*



Spain was one of the most affected European countries in the current COVID-19 pandemic, and Madrid was the national epicentre. The epidemic evolved through four waves, with the first one exhibiting the highest peak, facing the city with one of the most draconian lockdowns in Europe and a collapse of the city's public hospital system. This situation has also affected the highly vulnerable group of haemodialyzed patients, among whom in the University Hospital Infanta Leonor, 13% were immigrants or refugees and 17% were older than 80 years putting them at especially high risk of a more severe form of the disease.

# COVID-19 in haemodialysis patients

A steep and sudden rise in the number of infected HD patients in the first wave of the pandemic in Madrid elicited a prompt response. Dialysis units were reorganized to assure a safe distance between the patients in the waiting areas and create designated posts for seropositive patients. Within days a protocol of action has been presented to the staff and everyone underwent training for placement and removal of PPE. An information sheet containing facts on COVID-19, preventive measures, and instructions on what to do in case of suspected infection were delivered to all dialysis patients. An active triage, which included temperature check and screening for respiratory symptoms, myalgia, and diarrhoea, was set up at the entrances to the dialysis units. Patients were advised to use masks at all times and change them frequently. Public transport and collective ambulances were identified as potential high-risk sites for disease spreading and patients were advised to use individual means of transport. All HD patients and their companions were issued documents for circulation to allow them to reach dialysis units during lockdowns. Snacks during dialysis were withdrawn eventually. Infected patients were dialyzed by designated staff members who did not attend to non-COVID patients. Treatment protocols ensued for infected patients who did not require hospitalization.

In the first wave of COVID-19, a high percentage of asymptomatic HD patients was identified by active screening, thus underlining the importance of the proactive approach in this particular population. Also important is the fact that 20% of the dialysis staff had required sick leave in this period in relation to COVID-19, and as many as 40% had positive antibodies against SARS-CoV-2. The lack of appropriate PPE was the single factor significantly associated with COVID-19 infection among Spanish nephrologists, coinciding with the fact that the majority of these professionals got infected in the first pandemic wave, more specifically in the first month.

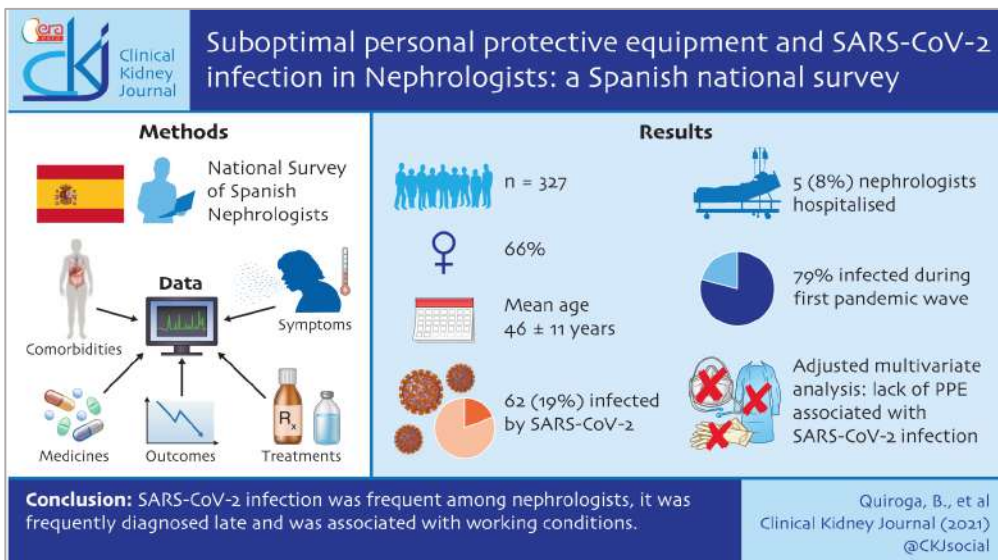


Figure 2. Risk factors for COVID-19 infection among nephrologists in Spain

# COVID-19 in haemodialysis patients

The development of vaccines brought up other questions. Initial reports communicated that the decline of anti-SARS-CoV-2 antibodies appeared to be more rapid in HD patients, especially the asymptomatic ones, compared to the general population. More recent studies, however, conclude that HD patients mount durable immune responses six months post SARS-CoV-2 infection, with fewer than 3% of patients showing no evidence of humoral or cellular immunity. Thanks to the initiative undertaken by the Spanish Society of Nephrology HD patients in Spain were placed high on the priority list for vaccination and the complete Spanish HD population has been successfully vaccinated. The currently ongoing follow-up shall provide insight into the level of protection from the infection and serious forms of the disease this vaccination has provided.

## Outcomes in dialysis patients infected with SARS-CoV-2

*Marian Goicoechea, Spain*



Initial reports on the epidemiology of COVID-19 identified older age, male sex, obesity, hypertension, diabetes, cardiovascular disease, and chronic lung disease as major mortality risk factors. More recently, however, it became clear that a graded association exists between the level of kidney dysfunction and the risk of COVID-19 mortality. Studies have even demonstrated that severe forms of CKD were associated with a higher risk of COVID-19 mortality than other known high-risk groups.

Spain was among the most affected countries by the COVID-19 pandemic in Europe with 3,636,000 cases and nearly 80,000 deaths confirmed by May 2021. As of May 2020, a Spanish COVID-19 registry started collecting data on end-stage renal disease (ESRD) patients who contracted COVID and within a year gathered data on 5,155 cases. The population registered was old (mean age 65 years), with a notable male preponderance. Mostly affected were haemodialyzed patients, followed by the transplanted ones. The mortality rate ranged from as low as 3% for the non-hospitalized patients, to as high as 63% for patients who required intensive care. Haemodialyzed patients exhibited a higher overall mortality rate than the transplanted ones. Older age was remarkably associated with mortality in hospitalized patients, especially in the transplanted group, but no clear correlation was found between mortality and patients' sex. Clinical features at admission



# COVID-19 in haemodialysis patients

associated with the 30-day-in-hospital mortality adjusted by age and dialysis vintage were dyspnoea, pneumonia, and need for mechanical ventilation. The main laboratory parameters associated with mortality in hospitalized HD patients were low lymphocyte count and high LDH, and total bilirubin and CRP levels at day 7 after clinical onset.

It is encouraging that the mortality rate among HD patients decreased by half in the second and third waves of the pandemic. Also, the ratio of hospitalized to non-hospitalized patients declined over time, thus suggesting a reduction in the burden to healthcare resources. These results corresponded well with the data collected in the ERACODA registry, the database that has been established by the ERA-EDTA to collect individual-level data of patients that receive kidney replacement therapy and have COVID-19.

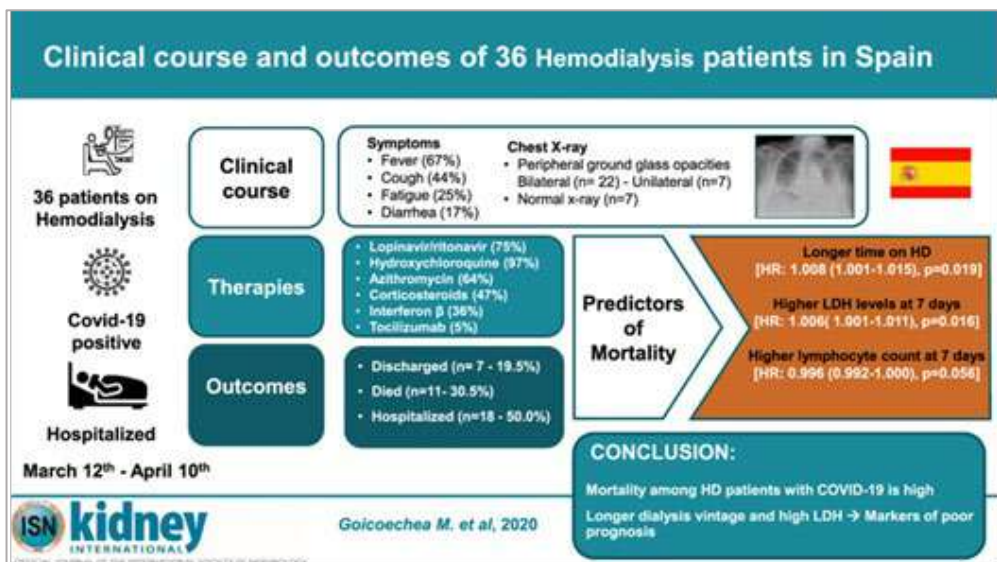


Figure 3. Predictors of mortality in COVID-19 patients on maintenance haemodialysis

The approach to treatment has also changed over time, as certain therapeutics gained or lost popularity in particular waves of the pandemic. Hydroxychloroquine, for example, was commonly applied in the first wave, but never in the later waves. On the other hand, corticosteroids use shows a steady increase over time. Unfortunately, none of the treatments used so far has shown superior results in reducing mortality. Even the administration of convalescent plasma has not significantly contributed to outcome improvement. Only the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization.

The monoclonal antibodies – bamlanivimab, etesevimab, casirivimab, and imdevimab, which have been recently authorized for COVID treatment in the United States of America, decrease viral load when administered early in the course of the disease and favourably impact clinical outcomes in patients with mild to moderate disease presentation. Still, their effect in patients with chronic kidney disease is yet to be investigated.

# COVID-19 in haemodialysis patients

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# ANCA vasculitis prognostic and treatment

## ANCA vasculitis and treatment - Where are we now?

David Jayne, United Kingdom



Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis is an autoimmune disorder that predominantly affects small blood vessels. It is a rare, but potentially serious and life-threatening condition, with variable clinical presentation dependent on organ involvement and disease stage and activity. In the last decades, significant progress has been made in understanding the pathogenesis and improving the treatment and prognosis of these patients. Nevertheless, the most acute and severe disease manifestations, including kidney disease and alveolar haemorrhage, continue to be associated with increased mortality from disease activity or treatment complications and risk for the development of end-stage kidney disease.

Management of ANCA vasculitis consists of remission induction, maintenance, and relapse therapy. High-dose glucocorticoids administered for 3 to 6 months remain the cornerstone of induction therapy, but this treatment is associated with numerous dose-dependent adverse effects. In more severe disease presentations, cyclophosphamide, rituximab, or their combination, with or without glucocorticoids, represent an effective and relatively safe alternative. Plasma exchange (PLEX) has long been proposed and used for the most severe disease manifestations, but its role remains controversial. Recently published results from the PEXIVAS study did not report substantial benefits from adding plasma exchange to standard therapy in patients with severe ANCA-associated vasculitis. Patients in this study were also randomly assigned to follow either a standard-dose regimen or a reduced-dose regimen of oral glucocorticoids, and the infectious complications were significantly less common in the reduced-dose group.

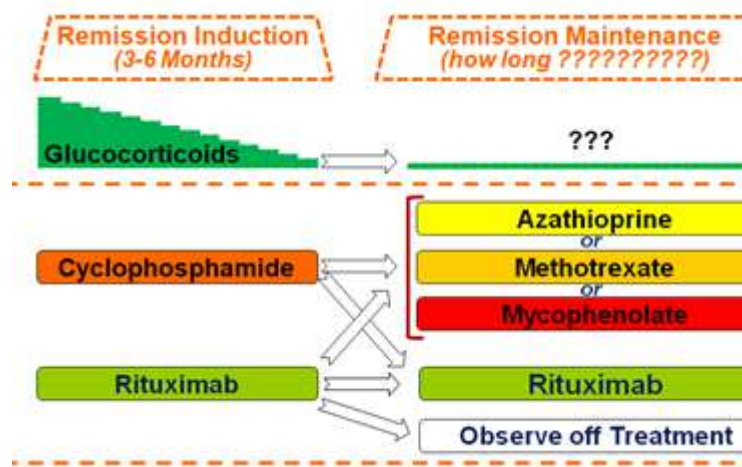


Figure 1. The current standard of care for ANCA-associated vasculitis

# ANCA vasculitis prognostic and treatment

Remission maintenance in ANCA vasculitis still represents a challenge. Azathioprine and methotrexate have been demonstrated as safe and effective alternatives to oral cyclophosphamide to maintain remission. Mycophenolate-mofetil is another option with a similar safety profile, but has not been shown to be superior to azathioprine. Rituximab has also been studied in this context with promising results as it ensured higher relapse-free survival during periods of treatment than azathioprine. The RITAZAREM trial demonstrated a high level of efficacy of rituximab and glucocorticoids as a therapy to induce remission after relapse in ANCA vasculitis.

The concerns that remain with the current treatment options for ANCA-associated vasculitis include high relapse rates, limited effect on preserving renal function, detrimental or no effect on the quality of life, and high levels of toxicity, especially with glucocorticoid use. Targeting complement component 5a with avacopan, an orally administered selective C5a receptor inhibitor, was effective in replacing high-dose glucocorticoids, but more studies are needed to confirm these results.

## Urinary CD163 in antineutrophil cytoplasm antibody-associated glomerulonephritis

*Gema Fernandez-Juarez, Spain*



CD 163 is a transmembrane protein mainly expressed by macrophages type 2 (M2) that infiltrate tissues during the “healing phase” of inflammation. CD 163 positive M2 are largely present in endocapillary, extra capillary and peritubular areas in patients with early stages of ANCA-associated glomerulonephritis (GN), as well as in those with fibrinoid necrosis and cellular crescents. However, this phenomenon is not restricted to ANCA vasculitis and can also be found in pauci-immune necrotizing GN, anti-glomerular basement membrane GN and immune complex-mediated GN. Thus, the question arises whether there is a correlation between the intensity of infiltration with CD 163 positive M2 and urinary CD 163 levels and whether CD 163 positive M2 may be useful in clinical practice, given their lack of specificity.

# ANCA vasculitis prognostic and treatment

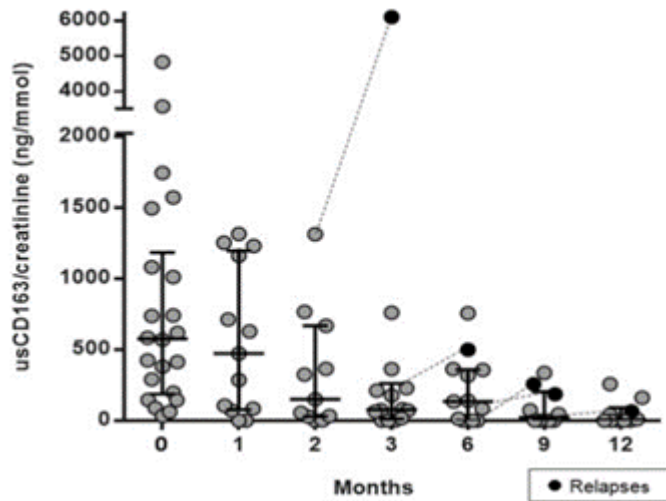


Figure 2. Changes in usCD163 concentrations following treatment and during follow-up of patients with ANCA-associated glomerulonephritis

A recent study reported an excellent correlation between urinary soluble CD 163 and histologic features of ANCA GN, such as fibrinoid necrosis, capillary breaks, and/or crescent formation. Furthermore, active renal ANCA vasculitis is associated with markedly higher urinary CD 163 levels than the inactive or extrarenal form of the disease. Especially high levels of urinary CD 163 were found with the crescentic form, followed by the mixed-class and sclerotic form of the disease. Therefore, urinary CD 163 is found to be closely associated with disease activity thus representing an accurate biomarker for the detection of active renal vasculitis and relapse. Even more so, urinary CD 163 levels' decline corresponded well with response to treatment. Otherwise, an increase of 20 ng / mmol as absolute change, or an increase of 20% as relative change, with respect to the previous value in each patient makes it possible to discriminate the presence of renal relapse with a sensitivity of 100% and, a specificity of around 89%. All this findings suggest that in the future this marker may have an important role in monitoring the response to treatment and disease activity and may even eventually lead to the abolishment of biopsies for these purposes.

# ANCA vasculitis prognostic and treatment

## Renal risk score for ANCA vasculitis

*Juan Manuel Mejia Vilet, Mexico*



Renal involvement in ANCA vasculitis varies in the diversity of the histopathological findings and clinical presentation. The timely establishment of disease development prognosis remains the ultimate goal and the most challenging task for clinicians involved in the treatment of these patients as it provides the foundation for therapeutic considerations, resource administration, and timely arrangement of renal replacement therapy. Among the predictors studied so far, the level of renal function at disease presentation has received the most attention. However, when adjusted to the histopathological class of the disease, the crescentic and mixed histological forms seem to exhibit a similar prognosis, regardless of the baseline eGFR. Therefore, two scoring systems have been introduced to contribute to treatment decisions and more accurate prognosis.

The Chronicity Score is a systematic and semiquantitative approach to assessing and reporting chronic lesions. It grades the level of irreversible changes in the renal tissue, including glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arteriosclerosis. The Renal Risk Score, on the other hand, combined clinical and histological parameters to classify the risk of end-stage renal disease development into low, medium, and high based on the proportion of normal glomeruli, eGFR at presentation, and proportion of interstitial fibrosis and tubular atrophy. Neither of these scoring systems took crescents as a parameter to predict renal outcome and both proved to be applicable in small cohorts. The Renal Risk Score proved to be properly calibrated for use in patients with mixed and sclerotic classes, but it was observed that other parameters, not included in this score, are also associated with renal prognosis. Nevertheless, both scores provided reproducible results in different patient groups and appear predictive of long-term kidney survival in ANCA-associated vasculitis. They exhibited significantly greater discrimination than histopathological classification alone, with Renal Risk Score demonstrating a slight superiority over the Chronicity Score.

# ANCA vasculitis prognostic and treatment

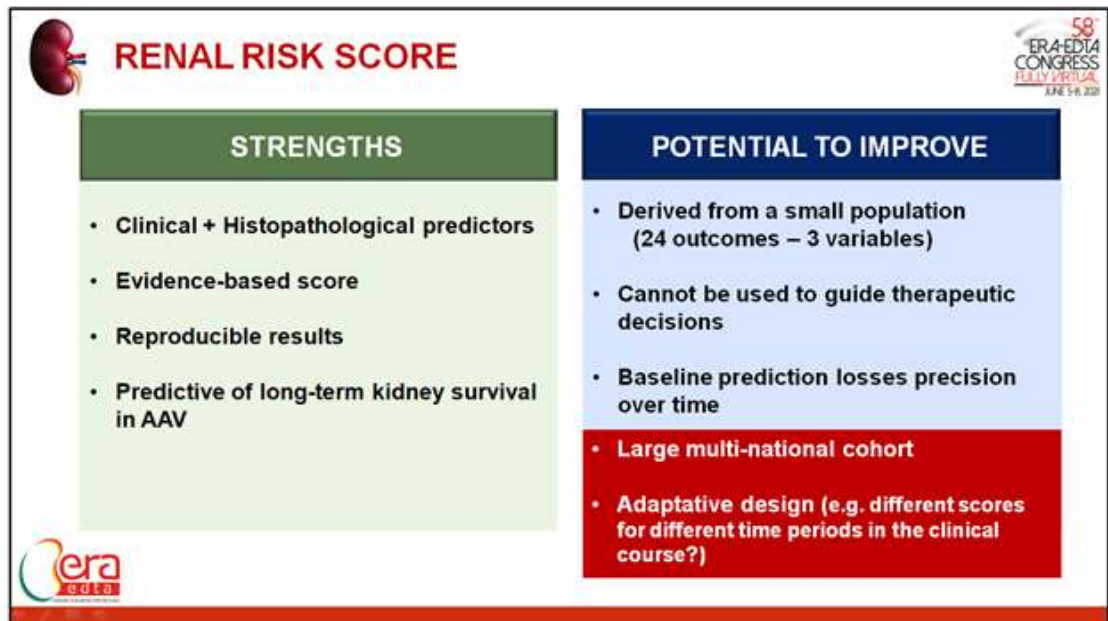


Figure 3. Current strengths and further potentials of the Renal Risk Score

Even with these promising results, there is still room for improvement as neither of these scores can be used to guide therapeutic decisions, and their baseline predictive power declines with time.

Prognostication in AAV is not exclusively performed at baseline (where the RRS is calculated), but also in other important timepoints in the course of the disease, such as post-treatment or during relapses. A limitation of the RRS is that estimates prognosis at baseline, excluding from the score important variables for prognosis on follow up as response to therapy and disease relapses.

Therefore, large international cohort studies and adaptations to these instruments are needed in the future to improve their accuracy and applicability.

# ANCA vasculitis prognostic and treatment

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## Complicated lupus nephritis

### Management of refractory lupus nephritis

*Hans-Joachim Anders, Germany*



Intense immunosuppression is the treatment of choice for LN to control systemic autoimmunity and intrarenal inflammation. However, failing to respond to induction therapy with immunosuppressive drugs is associated with an unfortunate long-term kidney prognosis and lower overall survival. A major challenge in determining the optimal treatment approach for refractory lupus nephritis (RLN) is the lack of a consensus definition for complete response following induction treatment. Current treatment guidelines suggest evaluating the response to immunosuppressive drugs with biomarkers (i.e. serum creatinine level, haematuria, proteinuria), but the time point of assessment is not clearly defined.

Importantly, not all RLN cases are due to lupus. Some patients with RLN may also have unrecognized drug nonadherence, especially because oral medications prevail, and some individuals may have unrelated genetic factors promoting the persistence of proteinuria or CKD progression. Moreover, persistent proteinuria may not be an immunological phenomenon of LN and could be driven by hyperfiltration provoked by obesity or diabetes.

The latest KDIGO guidelines have proposed an algorithm for a structured approach to RLN aiming to assist practitioners.

Some centres perform kidney biopsies after completion of treatment for an episode of LN as a part of the treatment evaluation. These biopsies are often termed "repeat biopsies". Several studies have reported that these biopsies show the activity of the disease at the tissue level, even in patients with normal routine blood and urine markers. Such data is essential and should be taken into consideration when deciding on the treatment. To provide evidence for this, a collaborative project within the frame of the Lupus Nephritis Trials Network has been designed. In this ongoing research project, the investigators will compare the results of treatment between the groups of patients who did and did not undergo repeat biopsy, concerning complete disease inactivity at month 24 and renal function at month 60 from treatment initiation. This will provide a rationale for performing repeat biopsies as a part of the treatment evaluation. In addition, genetic testing is also significant. For instance, lupus podocytopathy can be confirmed as a cause of RLN by functional genetics on patient-derived podocytes.

A better understanding of what RLN is and how definitions can be integrated into treatment pathways has the potential to enhance LN outcomes. Hence, the poor prognosis of RLN demands individualization of LN treatment, regular review of patient response, and the flexibility to switch or augment therapy.

## Complicated lupus nephritis

### Urinary exosomal miRNA expression profile in lupus nephritis

*Benedetta Bussolati, Italy*



Extracellular vesicles (EVs) are a heterogeneous group of particles released by almost any cell that include exosomes, micro-vesicles, and apoptotic bodies. During their formation, they incorporate different bioactive molecules from their cells of origin, such as soluble proteins, membrane receptors, nucleic acids (mainly small RNA species, such as micro RNAs (miRNA)), and lipids, which in turn can be transferred to target cells. MiRNAs are a family of small non-coding RNAs, which play an important role in a variety of biological processes, through their regulation of post-transcriptional gene expression.

The discovery of miRNAs in various biological fluids suggests that they may be functioning as paracrine or endocrine signals between cells. In the kidney, miRNAs are indispensable to the regulatory mechanisms for renal development, maintenance of renal function, and homeostasis processes. Urinary miRNAs may be filtered from the circulation but are more frequently released from nephron cells actively secreted into exosomes enriched in kidney-specific miRNAs. Changes in urinary miRNAs have been reported in several renal diseases. The fact that exosomal-derived urinary miRNAs can accurately reflect structural damage and renal dysfunction makes them good biomarkers for the diagnosis and prognosis of renal diseases. In LN, microRNA alterations may be directly related to the presence of autoantibodies against Dicer and Ago, proteins involved in miRNA maturation and stability. Alternatively, miRNAs can be expression of tissue alterations, as EV cargo reflects the physio pathological state of the originating cell facing the urinary lumen.

# Complicated lupus nephritis

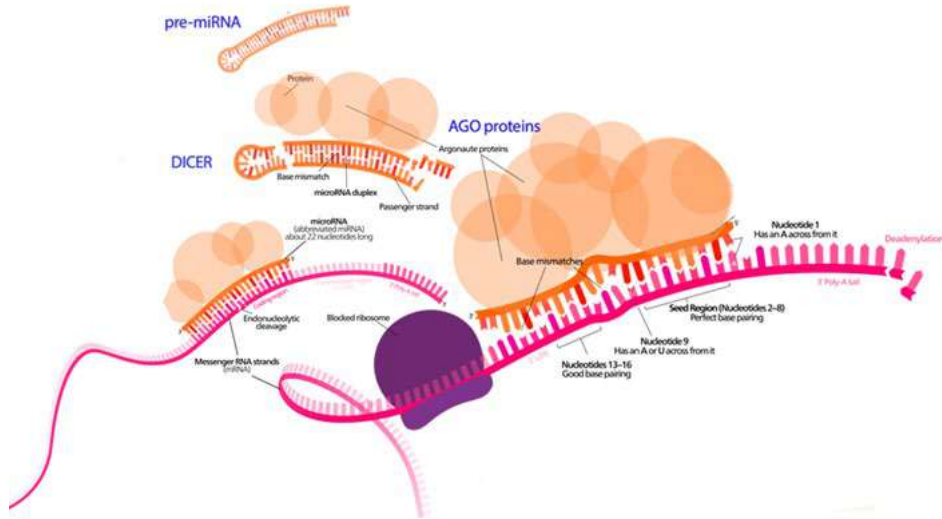


Figure 1 MiRNAs are altered in patients with LN

In LN, several exosomal-derived miRNAs have been identified as markers of early fibrosis, podocyte injury, type IV class of nephritis, and the presence of cellular crescents, and can discriminate active LN. For instance, Li et al. demonstrated that Type IV LN (LNIV) with crescents has a unique miRNA expression profile of urinary exosome and complex regulatory network. They found that miR-3135b, miR-654-5p, and miR-146a-5p in urinary exosomes could be used as novel non-invasive diagnostic markers for LNIV with crescents. Moreover, the microRNA miR-146a is a negative regulator of the interferon pathway. Under expression of miR-146a contributes to alterations in the type I interferon pathway in lupus patients by targeting the key signalling proteins. Additionally, miR-29c, miR-21, and miR-150 have been identified as novel markers that contribute to fibrosis in patients with LN. Specifically, miR-29c is identified as an early marker of fibrosis in LN.

All these findings may also provide potential novel strategies for therapeutic intervention. Preclinical data suggest that the inhibition of miR-654 expression aggravates pristane-induced LN. However, there is rare news on the advance of miRNA drugs. One miRNA generally targets tens and even hundreds of genes, which means that miRNA therapeutics would trigger a series of unknown and unpreventable consequences.

# Complicated lupus nephritis

## Urinary exosomal miRNA expression profile in lupus nephritis

*Agnes Fogo, United States of America*



LN can be defined as a glomerular immune complex disease that occurs in patients with systemic lupus erythematosus (SLE). The varying glomerular immune complex patterns are diagnosed according to the ISN/RPS classification. These include predominantly mesangial deposits (classes I, II), subendothelial deposits with endocapillary hypercellularity or prominent glomerular basement membrane (GBM) duplication and wire-loop lesions, often with necrotizing and crescentic lesions (classes III and IV, focal and diffuse LN), or membranous forms (class V).

Clinical Feature	I n=5	II n=54	III n=107	IV-G n=111	IV-S n=87	V n=159	VI n=18
Asymptomatic hematuria	40	19	22	4	6	5	0
Asymptomatic proteinuria	40	42	25	7	6	13	0
Nephrotic syndrome	20	15	17	40	38	65	11
Nephritic syndrome	0	20	34	27	26	7	0
Acute kidney injury	0	4	2	18	16	2	0
Chronic kidney disease	0	0	0	4	8	8	89
	100%	100%	100%	100%	100%	100%	100%

Figure 2. Presenting clinical features of different LN classes (Seshan S, Jennette JC. Arch Pathol Lab Med 2009; 133:233-48)

To improve the LN classification using an evidence-based approach and refine the definitions for glomerular lesions a working group for LN classification met in Leiden (Netherlands) in May 2016 to reach a consensus on this topic. Their recommendations for LN classification are summarized in Figure 3.

# Complicated lupus nephritis

Category	Recommendation	Comments on ISN/RPS guidelines
Class II	Definition for mesangial hypercellularity adjusted: Four or more nuclei fully surrounded by matrix in the mesangial area not including the hilar region (A)	Cutoff for mesangial hypercellularity unclear
Class III and IV	The term endocapillary proliferation is replaced by endocapillary hypercellularity (B)	Definition for endocapillary proliferation unclear; the term proliferation was considered imprecise
	The term crescent is used for a lesion consisting of extracapillary hypercellularity, composed of a variable mixture of cells. Fibrin and fibrous matrix may be present; 10% or more of the circumference of Bowman's capsule should be involved.	Extracapillary proliferation involving > 25% of the circumference of Bowman's capsule was original cutoff. There were no definitions for fibrous or fibrocellular crescents
	Cellular crescent: more than 75% cells and fibrin and less than 25% fibrous matrix (C)	
	Fibrous crescent: more than 75% fibrous matrix and less than 25% cells and fibrin (D)	
	Fibrocellular crescent: 25%–75% cells and fibrin and the remainder fibrous matrix (E)	
	Adhesion: an area of isolated continuity of extracellular matrix material between the tuft and capsule even when the underlying segment does not have overt sclerosis (F)	There was no definition for an adhesion
	Fibrinoid necrosis: fibrin associated with glomerular basement membrane disruption and/or lysis of the mesangial matrix; this lesion does not require the presence of karyorrhexis	There was no definition for fibrinoid necrosis
	Elimination of segmental and global subdivisions of class IV	Definitions for segmental and global were unclear; interobserver variability was large; clinical significance uncertain
Modification of the NIH lupus nephritis activity and chronicity scoring system (Table 2) to be used instead of the currently used A, C, and A/C parameters	Designation of activity/chronicity through A, C, and A/C considered too broad and nonspecific; preference for a semiquantitative approach to describe active and chronic lesions	
Tubulointerstitial lesions	Indicate whether interstitial inflammation occurs in presence or absence of interstitial fibrosis	Lack of cut-off values for reporting the severity of tubulointerstitial lesions

Figure 3. Working group for LN classification: Phase 1 recommendations for LN classification (Bajema IM, Wilhelmus S, Alpers CE, et al. *Kidney Int.* 2018;93(4):789-796)

Decisively, the group proposed two important alterations in the classification system, namely to abandon the segmental and global designations in class IV, and to replace the A, C, and A/C designations of classes III and IV by use of modified NIH LN activity and chronicity scoring indices.

Currently, the ISN/RPS lupus classification does not evaluate vascular lesions. The group believes in the importance of a standardized approach and terminology to distinguish ordinary arterial or arteriolar sclerosis from lupus-related lesions, such as vasculopathy associated with immune complex deposition, vasculitis, and TMA. They propose that lupus vasculopathy should be defined as luminal narrowing of arterioles or terminal interlobular arteries by intramural immune deposits, typically admixed with fibrinoid changes, without inflammation of the vessel wall. Regarding tubulointerstitial lesions, the group at this time advocates indicating in biopsy reports whether interstitial inflammation occurs in the presence or absence of interstitial fibrosis. In phase 2 it has to be determined whether interstitial fibrosis and tubular atrophy should be considered separately or combined into one parameter and whether making a distinction between interstitial inflammation in areas with or without interstitial fibrosis has clinical significance.

# Complicated lupus nephritis

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## Personalized targeting of the microbiome

*Laetitia Koppe, France*



Current research findings have enough evidence to suggest that intestinal microbiota is a new organ system made up of several billion microbial cells with a total weight of over 1kg. This system is important for the regulation of multiple functions, such as the immune system, inflammation, weight regulation, etc. Nevertheless, gut microbes also produce uremic toxins such as p-cresyl sulfate (pCS) and indoxyl sulfate (IS), which are normally excreted by the kidneys. Patients on dialysis with an intact colon exhibit higher plasma levels of these uremic toxins compared to patients with normal renal function. Interestingly, hemodialysis patients who underwent colectomy have levels of these uremic toxins similar to healthy volunteers.

Many studies point to the fact that the modulation of the intestinal microbiota is an appealing target for reducing the production of uremic toxins that can improve CKD outcomes. One study found that *Fusobacterium nucleatum* and *Eggerthella lenta* are enriched in CKD patients and strongly correlate with the production of uremic toxins. Authors also demonstrated that CKD rats without intestinal microbiota exposed to these bacteria had greater CKD progression and higher levels of uremic toxins and that the probiotic strain of *Bifidobacterium animalis* reduced levels of uremic toxins and the severity of the disease.

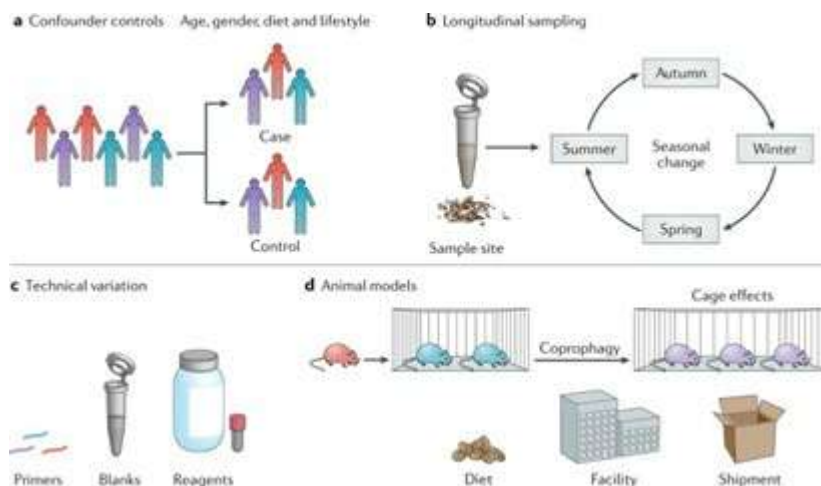


Figure 1. Characterizing the gut microbiota in CKD

Another reasonable strategy to decrease the production of uremic toxins by the microbiota is dietary modification. For instance, the selective decrease in dietary tyrosine, tryptophan, and phenylalanine intake, which are the precursors of phenols and indoles, decreases pCS and IS levels in CKD mice. These beneficial changes are similar to those found in low protein diets. On the other hand, increased intake of sulphur-containing amino acids (e.g. methionine and cysteine) can regulate indole, ammonia, and urea production by *Escherichia coli*. This occurs through inhibition of enzyme tryptophanase by S-sulhydration and can decrease IS production and CKD progression. Targeted drug therapies also make sense. One study demonstrated that the use of a specific inhibitor of the bacterial enzyme tyrosine phenol lyase decreases the production of phenols and IS and slows the progression of CKD in mice. Another interesting solution is the use of transgenic bacteria. In one study, the IS production in mice was reduced when researchers replaced the bacteria of the *Bacteroides* family with genetically modified *Bacteroides* which do not contain enzyme tryptophanase. Finally, completely or partially replacing the microbiota during CKD is also an interesting therapeutic target. Faecal transplantation in mice proved to be effective in improving dysbiosis and decreasing pCS production.

Finding individualized strategies to reduce the production of uremic toxins is important for improving the health of CKD patients. Exploring the intestinal microbiota is fascinating and opens up new innovative therapeutic targets for CKD.

## Microbiota in CKD: how promising are gut-targeted approaches?

*Carmela Cosola, Italy*



High urea concentration in CKD leads to alterations in the intestinal flora that can increase the production of gut-derived uremic toxins and negatively affect the intestinal epithelial barrier. In ESRD patients, the presence of dysbiotic gut microbiome is characterized by the reduction of short-chain fatty acids production by beneficial bacteria and the abundance of “bad” bacteria as well as urease, uricase, and tryptophanase enzymes. Such a state leads to increased production of gut-derived uremic toxins such as indoxyl sulphate (IS), p-cresyl sulphate (PCS), indole-3 acetic acid (IAA), trimethylamine N-oxide (TMAO), and phenylacetylglutamine. Dietary restrictions and CKD-associated medications (antibiotics, phosphate-binders, iron-containing compounds) further worsen gut microbiota dysbiosis, intestinal permeability, and constipation in these patients. Moreover, the disruption of colonic epithelial tight junctions subsequently leads to translocation of bacteria and endotoxins across the intestinal wall to the systemic circulation, which additionally contributes to uremic toxicity, local and systemic inflammation, progression of CKD, and associated cardiovascular disease.



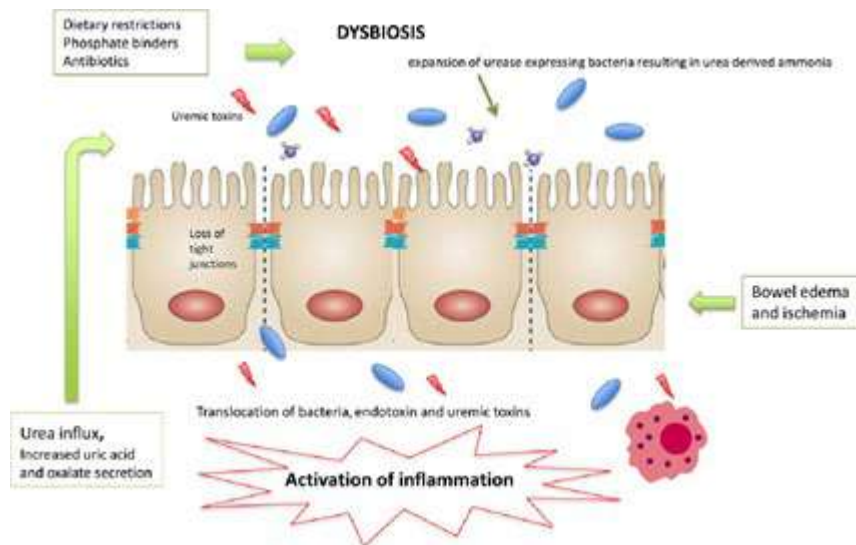


Figure 2. Intestinal permeability in CKD

Recent studies showed that the addition of butyrate promotes colonic mucin and tight junctions' proteins expression, strengthens the gut wall, and reduces the intestinal epithelial barrier permeability in CKD rats. Furthermore, very low protein vegan diets (VLPD) increase the number of the main butyrate-producing bacteria families, Lachnospiraceae and Ruminococcaceae, and this is probably correlated with a reduced intestinal permeability in CKD patients, as recently observed by Di Iorio et al. (doi: 10.3390/jcm8091424).

Altered gut microbiota and uremic toxins production can also lead to aggravated constipation in CKD patients, which is associated with the growth of Bacteroidetes phylum and reduction in Bifidobacterium and Lactobacillus phyla. Constipation status and severity are associated with a higher risk of incident CKD and ESRD and with progressive eGFR decline, independent of known risk factors. Circulating uremic toxins accumulate more as the patient becomes constipated. Constipation may also be involved in the pathogenesis of atherosclerosis through lipopolysaccharide/uremic toxins-induced chronic inflammation, contributing to adverse cardiovascular outcomes in the CKD population.

In CKD patients the gut also becomes important in maintaining potassium balance. However, constipation can enhance intestinal potassium absorption and provoke hyperkalaemia. Non-pharmacological measures including fibre, water, good fats intake, and physical activity along with prebiotics and probiotics are recommendable options in reducing constipation in CKD patients. Animals' studies also proved that laxatives such as lubiprostone, linaclotide, and lactulose can positively modulate gut microbiota, increase expression of intestinal tight junction's proteins, and reduces uremic toxins and inflammation. Finally, a recent study found that VLPDs are effective in the beneficial modulation of gut microbiota, reducing IS and PCS serum levels, and restoring intestinal permeability in CKD patients.

## Exploring functional interactions between microbiota and host

*Alessandra Perna, Italy*



There are currently many proposed uremic toxins, all of which exhibit characteristic biological and/or biochemical activities. They can be classified according to their molecular weight and their protein-binding ability (i.e. small water-soluble, middle, or protein-bound molecules) or according to their origin (i.e. dietary, mammalian metabolism, or microbial metabolism).

One of the first experimental studies on the interaction between the gut microbiome and kidney function of the mammalian host was the observation that germ-free mice that underwent bilateral nephrectomy lived longer than control mice. Over the years, several uremic toxins derived from microbial metabolism were identified including IS, PCS, and TMAO. It has also been shown that CKD substantially alters intestinal microbial flora causing a reduction of SCFA-generating bacteria such as *Bifidobacterium spp* and *Streptococcus spp*, and an increase in aerobic bacteria including Enterobacteriaceae and *E.coli*. Additionally, more frequent haemodialysis cannot effectively clear protein-bound azotemic uremic toxins derived from the gut microbial metabolism. Likewise, a low protein vegetarian diet can counter-attack the production of uremic toxins and increase their excretion in CKD patients.

Recent findings also suggest that alterations in sulphur metabolism characterized by low hydrogen sulphide (H<sub>2</sub>S) levels produced by sulfate-reducing and fermentative bacteria and high levels of lanthionine (a novel sulphur-containing uremic toxin) are prominent features in CKD, and are strictly linked to changes in the microbiota composition and function. A recent study demonstrated that H<sub>2</sub>S is significantly lower in the plasma of haemodialyzed uremic patients than in control subjects. Another study confirmed that plasma H<sub>2</sub>S runs progressively lower in stages CKD stages, eventually reaching a third of the level found in control subjects. Nevertheless, the CSE gene, one of the most important H<sub>2</sub>S producing enzymes, is down-regulated in uraemia.

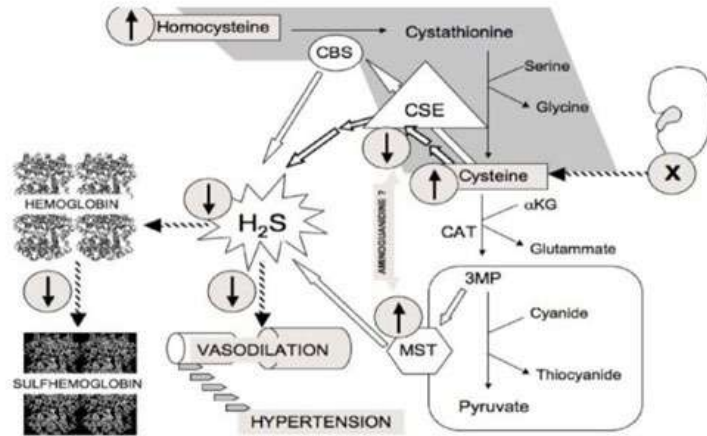


Figure 3. Schematic representation of the metabolic pathways related to H<sub>2</sub>S production and relevant alterations in uraemia

On the other hand, one in vitro study showed that lanthionine inhibits H<sub>2</sub>S production. This finding represents the basis for a hypothesized mechanism purporting that lanthionine can induce at least in part the alterations of sulphur compounds seen in CKD patients, supporting the concept that lanthionine is a new uremic toxin. In Zebrafish, for instance, lanthionine can induce heart tissue fibrosis and trigger alterations of regulatory RNA molecules involved in cardiovascular and kidney diseases. However, the exact contribution of the microbiota to lanthionine increase in CKD patients still needs to be elucidated.

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## New aspects in AKI prevention and treatment

### Cost-effective prevention strategies for AKI

*Melanie Meersch, Germany*



Acute kidney injury (AKI) is among the most common complications for all hospital admissions. Its incidence keeps rising among hospitalized patients, especially those requiring intensive care. Despite major advances in treatment strategies, this syndrome is still associated with significant mortality and dialysis dependence. In light of these facts, it is essential to develop nephroprotective strategies in hospital settings. The latest recommendations from the Acute Disease Quality Initiative Consensus Conference support the use of a combination of damage and functional biomarkers, along with clinical information, to identify patients at high risk for AKI, improve the diagnostic accuracy and therapeutic response.

One possible strategy to prevent AKI is remote ischemic preconditioning (RIPC). RIPC was first applied in cardiac tissue in which brief episodes of myocardial ischemia and reperfusion decreased the size of infarcted tissue. In renal medicine, RIPC attempts to invoke adaptive responses that protect against AKI by triggering brief episodes of ischemia and reperfusion applied in distant tissues or organs before the injury of the kidney. A recent multicentric study on 240 high-risk patients who underwent cardiac surgery concluded that RIPC significantly reduced the rate of AKI and the use of renal replacement therapy. The patients in this study were randomized to receive either remote ischemic preconditioning (3 cycles of 5-minute ischemia and 5-minute reperfusion in one upper arm after induction of anaesthesia) or sham remote ischemic preconditioning (control), both via blood pressure cuff inflation. A more recent study showed that different doses of RIPC significantly increased the production of urinary tissue inhibitor of metalloproteinases 2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7), both inducers of G1 cell cycle arrest, thus suggesting that one possible mechanism behind the effect of this intervention is the cell cycle arrest. It is significant to note that the sedative-hypnotic agent propofol seems to interfere with the protective effect of RIPC.

# New aspects in AKI prevention and treatment

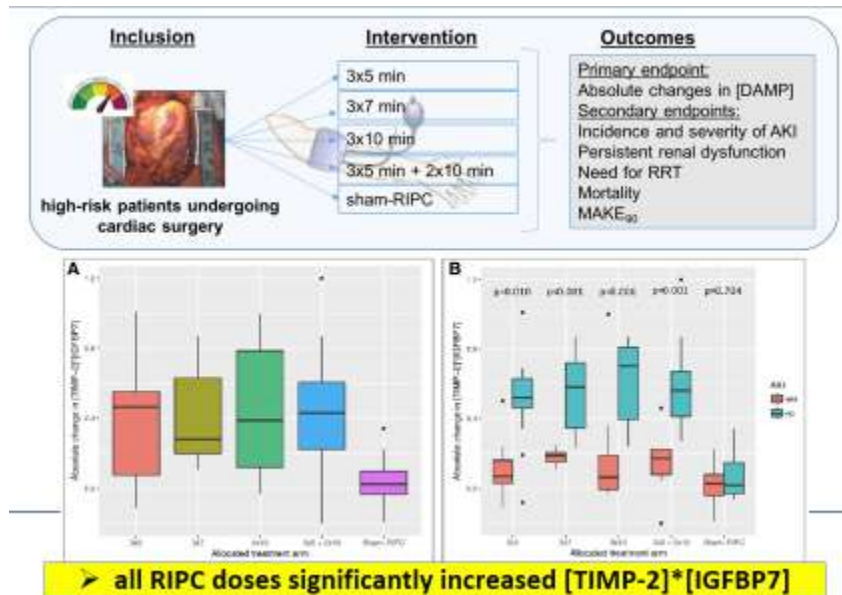


Figure 1. The effects of different doses of RIPC on the risk of AKI development in patients undergoing cardiac surgery (Meersch M et al. Critical Care Medicine 2020)

Another possible option to prevent AKI in high-risk patients is to implement the KDIGO bundles, i.e. a combination of preventive measures including discontinuation of nephrotoxic agents, considering alternatives to radiocontrast agents, maintaining adequate volume status and renal perfusion, applying functional hemodynamic monitoring, tracking serum creatinine and urine output, and avoid hyperglycemia. Despite their feasibility and proven efficacy in preventing AKI, compliance with the KDIGO recommendations in routine clinical practice is low and, according to the recently published results, only 5% of cardiac surgery patients receive the complete bundle. Therefore, more effort is needed to introduce this strategy in routine clinical practice.

# New aspects in AKI prevention and treatment

## “Subclinical” AKI – does it matter?

*Jill Vanmassenhove, Belgium*



Despite considerable progress over the last decade in the standardization of the AKI definition, the currently available classification criteria still rely on traditional and imperfect parameters such as serum creatinine and urinary output, which may not reliably and timely identify subtle signs of AKI. Namely, the increase in glomerular filtration rate (GFR) during amino acid infusion reveals a “renal reserve,” which can be utilized when the physiological demand for single nephron GFR increases. This suggests that in subclinical renal disease before basal GFR begins to reduce, the renal functional reserve can be recruited in a manner that preserves renal function. Thereupon, once a decline in basal GFR becomes detectable, renal disease is already well progressed. This concept seems to apply in both chronic kidney disease (CKD) and AKI, which led to the introduction of three new entities: subclinical AKI, subclinical acute kidney disease, and subclinical CKD. Subclinical AKI is a condition where there is an increase in biomarkers but without clinical manifestations of AKI.

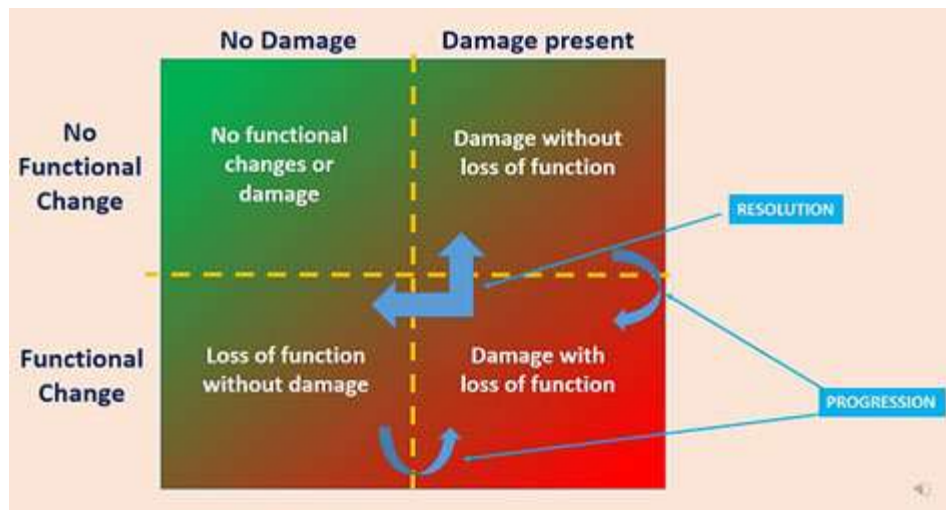


Figure 2. Entities of AKI syndrome by damage and/or dysfunction

# New aspects in AKI prevention and treatment

For all these reasons, an extensive search for new biomarkers indicative of early structural renal damage and able to reliably predict the outcome of renal injury has been undertaken. The ideal biomarker should be easily obtained and measurable, preferably from non-invasive sources, organ-specific, able to identify AKI in a stage when functional damage is not yet detectable, and well correlated with the severity of the damage. The test should be easy to perform, with a rapid turnover and high reliability. Several substances have been evaluated for this purpose, including neutrophil gelatinase-associated lipocalin (NGAL) and plasma proenkephalin A 119-159 (penKid), but neither has proven to be causally associated with subclinical AKI. Nevertheless, many more candidates still exist and further studies are needed to evaluate them. For the time being, more effort should be focused on preventing AKI in the clinical setting.

## New treatment options for AKI – does anything work?

*John A. Kellum, United States of America*



AKI management still represents a challenge in clinical practice. The treatment approach depends on clinical context and can vary by resource availability. Existing preventive strategies for AKI include electronic alerts and KDIGO bundle actions, but there are also several emerging novel therapeutics that deserve high attention.

The use of a clinical decision support system is based on the presumption that early detection of AKI could trigger an early nephrologist consultation which might contribute to improve outcome. Although testing such systems has rendered conflicting results, it does appear that they contribute to a discrete but sustained decrease in in-hospital mortality, dialysis use, and length of stay in AKI patients. Therefore, this intervention might contribute to substantial improvements in outcomes and financial savings globally. The KDOQI bundle is a set of general, stage-based management principles in AKI. Their implementation in practice significantly reduced the frequency and severity of AKI, postoperative creatinine increase, length of intensive care, and hospital stay after both cardiac and noncardiac surgery in high-risk patients. Nevertheless, their success depends on the early identification of patients at risk to develop AKI and for this purpose, several biomarkers have been investigated. According to the latest results, both TIMP-2 and IGFBP7, as well as their product, seem to be superior to other existing markers, providing additional information over clinical variables and adding mechanistic insight into AKI.





## **New aspects in AKI prevention and treatment**

Recent publications offer an insight into the novel agents that are expected to transform the therapeutic landscape of AKI. These are most notably related to mitochondrial dysfunction which has recently been recognized to have an enormous role in kidney injury and regeneration. The three most promising interventions to treat AKI at present include targeting genes that encode mitochondrial transcriptional factors, coenzyme NAD<sup>+</sup> which holds key roles in the regulation of redox status and energy metabolism, and peroxisome proliferator-activated receptor delta nuclear receptor which controls genes that regulate mitochondrial levels and function thus decreasing inflammation and fibrosis. Another possible approach is to promote renal cell regeneration by expanding the renal progenitor cell population.

The impracticality of conducting large individual clinical trials, especially for existing drugs, have recently shifted attention to adaptive clinical trial design which allows evaluation of multiple treatment options simultaneously and efficiently and looks for interactions between them. The potential candidates for AKI to be investigated by this study design include metformin, glutamine, biotin, theophylline, acetaminophen, corticosteroids, cyclosporin, tocilizumab, fenoldopam, and dexmedetomidine.

# New aspects in AKI prevention and treatment

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# Recent advances in kidney transplantation: focus on immunity

## NON-HLA incompatibilities: what's new?

*Rainer Oberbauer, Austria*



Human leukocyte antigen (HLA) molecules are expressed on almost all nucleated cells, representing the major molecules that initiate graft rejection. HLA matching reduces the risk of rejection, contributes to better graft function and longer graft survival, and permits reduced immunosuppression. HLA matching has had the greatest clinical impact in kidney and bone marrow transplantation. Nevertheless, finding a well-matched donor may not be possible in all cases and often prolongs the waiting time.

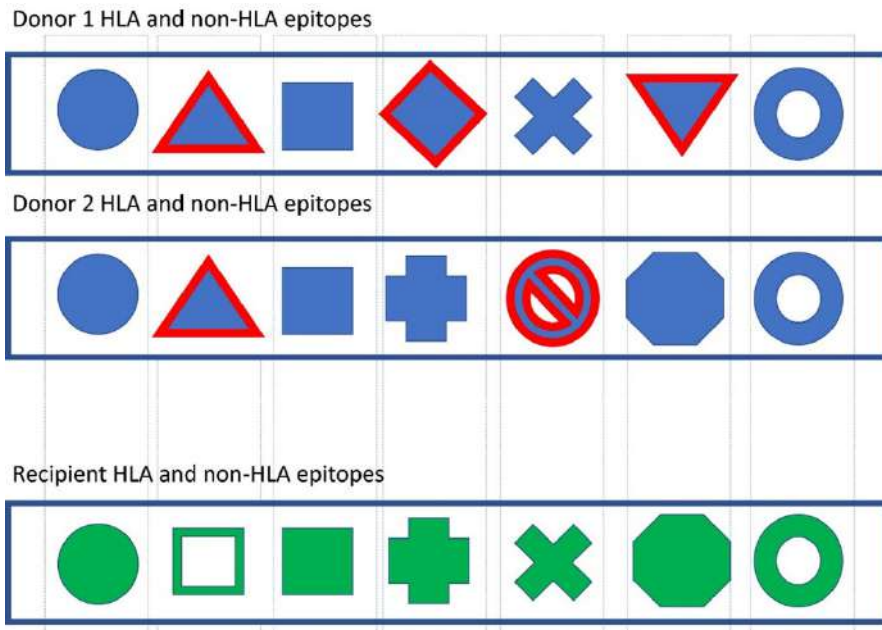


Figure 1. The quantitative approach to HLA matching

## Recent advances in kidney transplantation: focus on immunity

In approximately one-half of histologic antibody-mediated rejection (ABMR) cases circulating HLA donor-specific antibodies (DSA) are not detectable by the current methodology at the time of biopsy. Three main reasons have been identified for failing to detect HLA-DSAs: failure to type all eleven HLA loci in donor and recipient, absorption of HLA-DSA by the allograft, and HLA-DSA directed against a very public epitope expressed on many single antigen beads (SABs) diluting down the mean fluorescence intensity (MFIs) of any single bead. Nevertheless, ABMR histology is not solely determined by the histomolecular presentation but is also predicted by the underlying etiologic factor irrespective of HLA-DSA status. Thus, it appears that non-HLA immunity has a much stronger role in clinical transplantation than previously thought and is primarily associated with chronic graft loss. Recently published works suggest a broader concept of immunological non-self that goes beyond HLA incompatibility and expands the current concept of polymorphic non-self epitopes on cell surface molecules from HLA to non-HLA targets.

A quantitative concept of B cell epitope, developed to assess immunological risk, showed superiority in terms of prediction of development of ABMR compared to HLA antigen mismatch. Epitets represent the central parts of an epitope, consisting of a few amino acids located on the antibody-accessible site of the HLA-molecule, thus presenting the smallest functional unit of the antibody-antigen binding site and deciding the antibody specificity. To provide large cohorts to investigate the genetic architecture of comorbidities that may impact graft and recipient life expectancy, the International Genetics & Translational Research in Transplantation Network has been assembled. This consortium delivered pioneering insights into the genetic architecture of transplant-related outcomes across a range of different solid-organ transplant studies. Namely, genetic mismatch of non-HLA haplotypes coding for transmembrane or secreted proteins are associated with an increased risk of functional graft loss independently of HLA incompatibility. As in HLA alloimmunity, donor-specific alloantibodies can be identified against genotype-derived non-HLA epitopes.

The genetic heterogeneity of HLA and non-HLA alleles prevents further optimization of transplantation outcomes through histocompatibility matching. Tolerance induction by mixed chimerism without toxic conditioning and with a low risk of graft versus host disease is a visionary but realistic goal. The ongoing Vienna Trex study is expected to shed more light on this topic.

# Recent advances in kidney transplantation: focus on immunity

## Targeting immuno-inflammation in kidney transplantation: a new weapon against organ fibrosis

*Gianluigi Zaza, Italy*



Kidney allograft fibrosis or interstitial fibrosis (jointly to tubular atrophy, IF/TA) is a complex, dynamic and progressive process characterized by deep remodelling, production, and deposition of extracellular matrix (ECM) resulting in disruption of the tissue architecture that leads to organ failure. IF/TA is detectable in about 40% of kidney allografts at 3-6 months and increases to about 65% at two years. For more than two decades calcineurin inhibitors (CNI) nephrotoxicity has been considered the main cause of allograft fibrosis. However, in the last few years, thanks to the introduction of new biomolecular technologies, inflammation in scarred and fibrotic parenchymal areas has been recognized as a pivotal element able to accelerate the onset and development of the allograft chronic damage.

The intra-graft inflammation may drive the development of fibrotic damage, a process characterized by four distinct phases. In the first, "trigger phase", tubular and glomerular cells produce pro-inflammatory cytokines, which facilitate the recruitment of new interstitial mononuclear cells. Then, M1 macrophages release cytokines and chemokines with pro-fibrotic potentials, whereas M2 macrophages release TGF- $\beta$  which induces the expression of pro-fibrotic genes. During the second "activation phase", myofibroblasts, fibroblasts, fibrocytes, bone marrow-derived cells, epithelial cells, endothelial cells, and pericytes are activated by pro-fibrotic cytokines and growth factors secreted by lymphocytes upon injury of the endothelium. The third, "formation phase", is characterized by the excessive production and deposition of interstitial matrix and formation of collagen fibers enhancing the pro-fibrotic network. Lastly, during the "progression phase", the collagen matrix is susceptible to proteolysis, thus making the fibrosis potentially reversible. As fibrosis progresses, the fibrotic kidney matrix becomes a cause of irreversibility and stabilization. During stabilization, matrix proteins are induced by enzymes, which make them rigid and resistant to proteolysis.

A large number of innovative pharmacological agents have been proposed to slow down the progression of allograft fibrosis, including pirfenidone, THR-123, pentoxifylline, tranilast, neutralizing antibodies against different isoforms of TGF- $\beta$  and anti-TNF- $\alpha$  monoclonal antibodies.

# Recent advances in kidney transplantation: focus on immunity

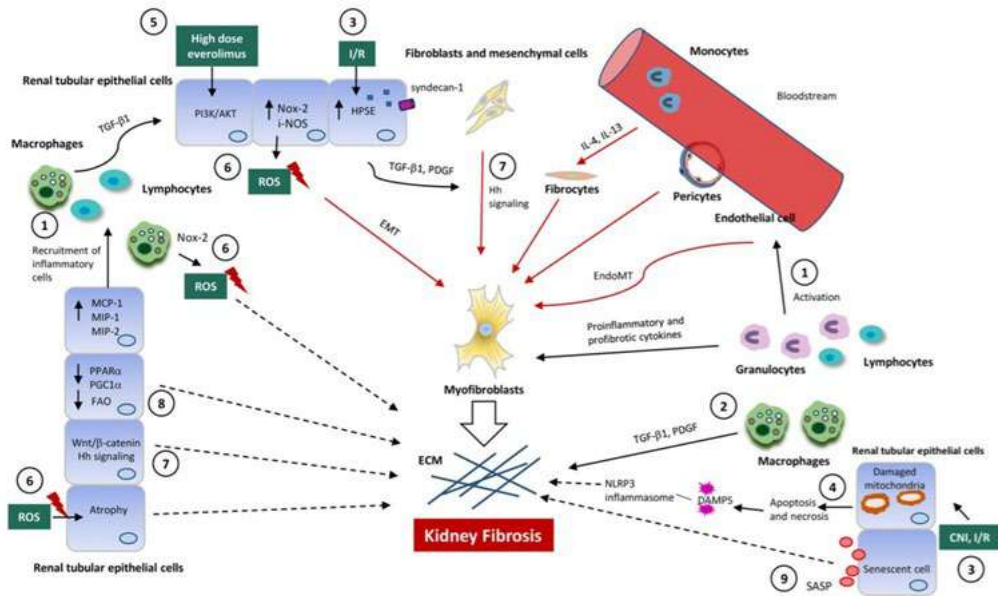


Figure 2. Schematic representation of the major biological elements involved in kidney allograft fibrosis

There is also a close link between oxidative stress, dysfunctional mitochondria, inflammation, and kidney allograft fibrosis. Furthermore, oxidative stress plays a key role in chronic CNI toxicity. Among the most important biological elements involved in CNI toxicity is NADPH oxidase 2, a protein that generates superoxide reactive oxygen species whose synthesis is mediated by TGF-B. There are a large number of antioxidants available as dietary supplements on the market able to reduce mitochondrial dysregulation/ oxidative stress and the consequent activation of the pro-fibrotic machinery. Unfortunately, these antioxidants are not able to reach adequate mitochondrial concentrations. However, there are several molecules currently under development synthesized by the conjugation of antioxidants with the triphenylphosphonium lipophilic cation (TPP) that can cross biological membranes and, thanks to their positive charge, enter the mitochondria.

A series of studies are currently underway aimed at analysing and identifying new elements potentially involved in the extensive pro-fibrotic pathway of the transplanted kidney (such as heparanase). Key elements of the immune-inflammatory machinery associated with fibrosis may represent good therapeutic candidates, but additional studies are still needed.

# Recent advances in kidney transplantation: focus on immunity

## Immunologic monitoring and biomarkers in kidney transplant recipients

*Chan-Duck Kim, Korea, Rep. of South*



Transplant biopsy has always been the gold standard for assessing the immune response to a kidney allograft. However, the procedure is not without risk, it is unable to predict rejection, and is only diagnostic once rejection has already commenced. Fortunately, there is a wide range of novel methods and biomarkers for post-transplant immunologic monitoring which are divided into antigen-specific (i.e. anti-HLA antibodies, non-HLA DSA, MLR, and ELISPOT) and non-antigen-specific assays (i.e. ATP measurement, soluble CD30, flow cytometry, gene expression monitoring and OMICs study of biomarkers).

Detection of a circulating anti-HLA antibody is now a widely used immunologic monitoring assay in the clinical setting. The presence of anti-HLA DSAs is considered a diagnostic criterion for antibody-mediated rejection (AMR). According to the Transplantation Society (TTS) Consensus guideline, the desensitized, high-risk patients should be monitored by DSA and protocol biopsy in the first 3 months after kidney transplantation (KT). Intermediate-risk patients, with a history of DSA but currently negative, should be monitored for DSA within the first month and if DSAs are present, a biopsy should be performed. Low-risk patients (non-sensitized, first KT) should be screened for DSA at least once in 3-12 months after KT. If DSA is present, a biopsy should be performed.

OMICs study is also a highly effective tool in the hunt for biomarkers as many biological molecules are expressed during the process of acute rejection which can be detected by this procedure. The candidate molecules for the ideal biomarker should be detectable early in the allograft rejection process and be able to differentiate rejection from other causes of allograft dysfunction.



# Recent advances in kidney transplantation: focus on immunity

Complement-Related Biomarkers/Chemokines/ dd-cfDNA/miRNAs/Immune Cells Biomarkers/Metabolomics				Transcriptomic Studies/miRNAs/Biomarkers of EMT/ Immune cell biomarkers/Extracellular vesicles			
✓ Biomarkers	Type of Rejection	Results	Studies	✓ Biomarkers	Type of Rejection	Results	Studies
Complement fragments	ABMR	Levels correlate with ABMR	Sitas E et al. Mol Immunol 2020	13-gene renal tissue signature (GoCAR study)	CAD	It predicts CAD at the 12th month even with normal histology at the 3rd month	O'Connell PJ et al. Lancet Long Engl 2016
CXCL9 / CXCL10	TCMR & ABMR	High NPP; low levels at 6 months predict low risk of rejection; It predicts rejection	Mühlbacher J et al. Front Med 2020 Rabant M et al. JASN 2015	85-gene renal tissue signature	IFTA	Associated with IFTA	Li L et al. Sci Rep 2017
dd-cfDNA	ABMR & TCMR	It could help rule out especially ABMR and play a role for surveillance after a rejection episode	Bloom R et al. JASN 2017 Oellrich M et al. AJT 2019	Urinary mi-R21 and mi-R200b	CAD & IFTA	Increased expression predicts IFTA and CAD	Zunari V et al. Clin Biochem 2017
Peripheral blood miRNAs	TCMR	miR-15b, miR-16, miR-103a, miR-106A, miR107 predict vascular TCMR	Matz M et al. Transplantation 2016	Urinary vimentin and CD45 relative to uroplakin 1a urinary mRNA	IFTA	This ratio based on urinary mRNAs may detect EMT and early graft fibrogenesis	Mezzi J et al. Nephrol Ther 2018
Assessment of Immunologic Risk and Tolerance in Kidney Transplantation (ARTKT-1 study)	TCMR	Phenotype and molecular signature of CD8+ T subsets showed a significant relationship to the development of TCMR	Ko EJ et al. PLoS ONE 2020	Assessment of Immunologic Risk and Tolerance in Kidney Transplantation (ARTKT-1 study)	Chronic ABMR	Monitoring of CD151+ T cells can be useful to detect the progression of Chronic ABMR	Kim WW et al. PLoS ONE 2018
Assessment of Immunologic Risk and Tolerance in Kidney Transplantation (ARTKT-1 study)	TCMR	Metabolic profiling is a promising method to discriminate between acute TCMR and stable groups	Kim SY et al. J Chromatogr B 2019	Assessment of Immunologic Risk and Tolerance in Kidney Transplantation (ARTKT-1 study)	Chronic ABMR	Six proteins (APOA1, TTR, PIGR, HPX, A2GP1, and C7) were distinguishable between Chronic ABMR and long-term stable KTRs	Jung HY et al. J Chromatogr B 2020

Figure 3. Potential biomarkers for acute rejection, chronic allograft dysfunction, and IFTA

To achieve transplantation tolerance, the "Holy Grail" of transplantation, it is first necessary to have a reliable and reproducible method for detecting a biomarker that can identify recipients in whom tolerance is likely to occur. The ideal tool for clinical monitoring should be non-invasive, inexpensive, reproducible, and accessible to clinicians and patients. Currently, there is no optimal immunological monitoring method, but promising advancements have been achieved over the past few years. With the development of these technologies, understanding the strengths and weaknesses of each test will allow clinicians to integrate new monitoring methods with a clinical assessment to achieve the best long-term outcomes in transplant recipients.



# Recent advances in kidney transplantation: focus on immunity

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# Diabetic nephropathy 2021

## Nephroprotective antidiabetic drugs: a prescription algorithm

Clara Garcia Carro, Spain



Diabetic kidney disease (DKD) is one of the major complications of diabetes and the leading cause of chronic kidney disease (CKD) worldwide. Around 10% of these patients progress to end-stage renal disease (ESRD), but even more develop cardiovascular disease and infections and die before needing renal replacement therapy. The main strategies to prevent the development and attenuate progression of DKD in the last decades were intensive glycaemic control and renin-angiotensin-aldosterone system (RAS) blockade. However, this approach has not achieved optimal results. In recent years two new groups of therapeutic agents, the sodium-glucose co-transporter-2 (SGLT2) inhibitors and the glucagon-like peptide-1 (GLP-1) receptor agonists, have been introduced and presented promising results in reducing cardiovascular risk and progression to ESRD in DKD patients. Several biological mechanisms could explain the nephroprotective effects of these agents, including restoration of normal tubule-glomerular feedback, direct anti-inflammatory and antifibrotic effects, and mitigation of renal hypoxia.

Summary Reports

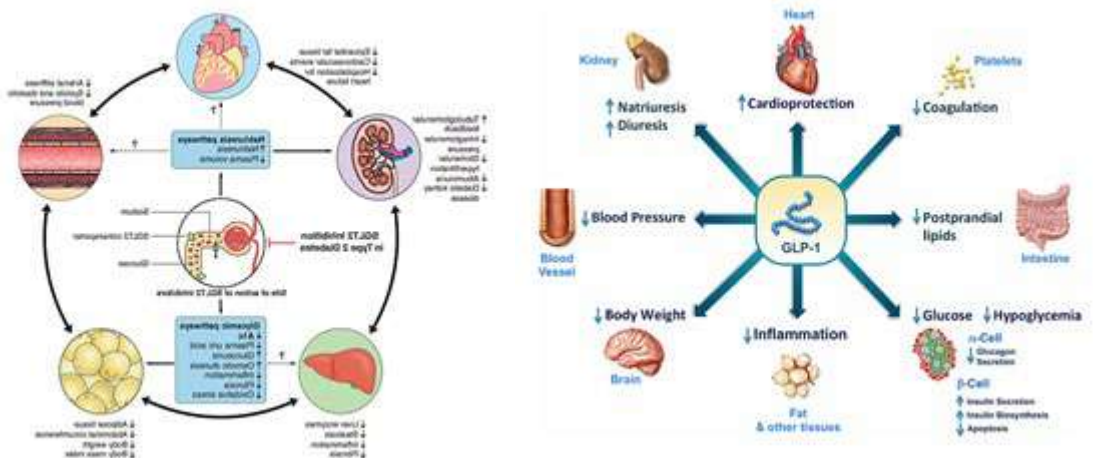


Figure 1. Mechanisms of action of SGLT2 inhibitors and GLP-1 receptor agonists

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According to the latest guidelines on the treatment strategies for type 2 diabetes mellitus (T2DM) issued by the American Diabetes Association, the first-line interventions are lifestyle changes and the introduction of metformin. The choice of the second antidiabetic depends on the assessed cardiovascular risk. In patients with the established atherosclerotic disease, either GLP-1 agonists or SGLT2 inhibitors are the first option, provided that eGFR is  $\geq 30$  mL/min. Otherwise, SGLT2 inhibitors are the preferred option in patients with heart failure or CKD with eGFR  $\geq 30$  mL/min. Based on recent researches, these therapies are suitable in more than 30% of diabetic patients, and the number may rise if the eGFR threshold for SGLT2 use is lowered to 25 mL/min based on the results from the DAPA-CKD study. The recently published KDIGO guidelines have already embraced this lower threshold for dapagliflozin initiation. Also, the KDIGO guidelines embrace SGLT2 inhibitors as first-line therapy with metformin and GLP1 agonists as the second preferred choice for patients with cardiac and cardiovascular comorbidities.

Nevertheless, despite the proven benefits and safety profile of both SGLT2 inhibitors and GLP1 agonists, they remain underused in practice. Older age, long duration of diabetes, malignancies, recent hospitalizations, and clinicians' inertia are common barriers to their initiation. Thus, besides clear therapeutical algorithms, greater attention to dissemination and implementation of best practices is needed in both clinical and community settings.

### Beyond antidiabetic drugs for DKD: what is new and upcoming

*Beatriz Fernandez Fernandez, Spain*



Type 2 diabetes mellitus has become an epidemic with rapidly increasing prevalence worldwide. The recently introduced SGLT2 inhibitors have changed the landscape of antidiabetic treatment presenting promising results in reducing renal and cardiovascular risk in these patients. Nevertheless, there are several ongoing phases 3 and 2 trials evaluating other therapeutic approaches in this population which target different levels of pro-inflammatory response in DKD: gene expression, abnormal cell events, activation of signalling pathways, functional and structural changes.

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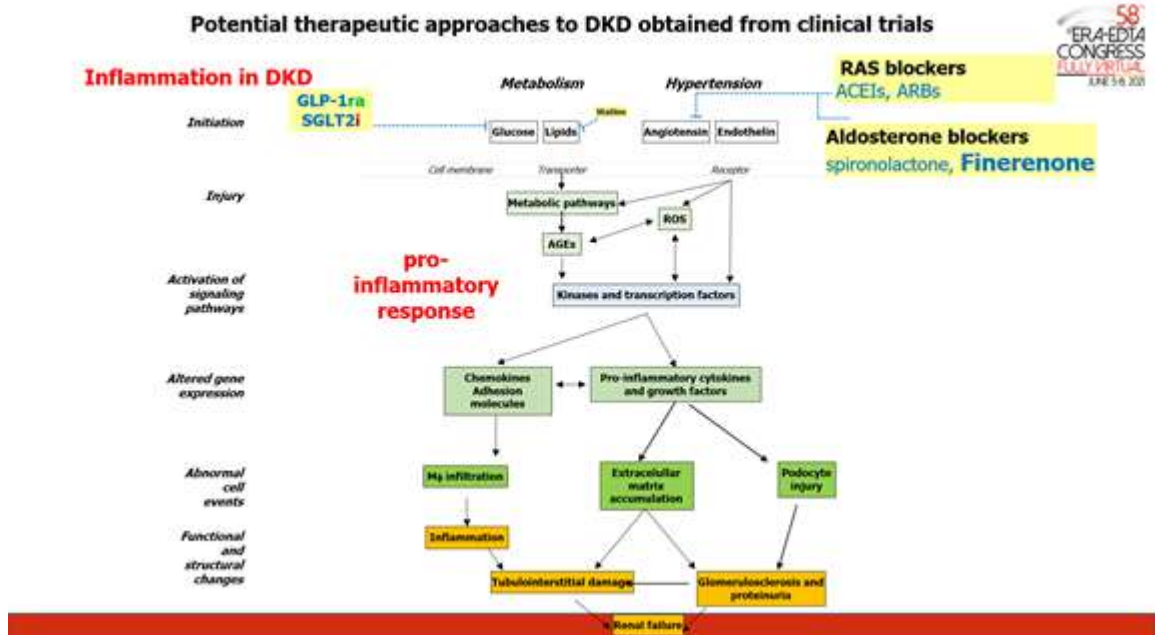


Figure 2. Potential therapeutic approaches to DKD in clinical trials

Finerenone, a nonsteroidal, selective mineralocorticoid receptor antagonist, reduced albuminuria in short-term trials involving patients with CKD and type 2 diabetes. Furthermore, results from the recently concluded FIDELIO-DKD study added lower risks of CKD progression and cardiovascular events to the benefits demonstrated by this therapeutic. Bardoxolone is an investigational, once-daily, orally administered anti-inflammatory and tissue-protective antioxidant inflammation modulator which has initially been investigated a decade ago in stage 4 CKD patients with type 2 diabetes. Even though initial results were promising in terms of increasing eGFR, the research was terminated for safety concerns. Nevertheless, three years ago a Phase 3 Bardoxolone Methyl in DKD (AYAME) study was initiated and results are expected next year. Endothelin receptor (ETR) antagonists are a class of strong vasodilators capable of stopping the process of cell division. They act on ETRA and/or ETRB to prevent endothelin 1 effects including hypertension, albuminuria, insulin resistance, inflammation, fibrosis, and endothelial dysfunction. Avosentan was the first ETR antagonist investigated in overt DKD, but the study was terminated due to excess cardiovascular events. Atrasentan, predominantly targeting ETRA, was investigated in RADAR and SONAR studies which included type 2 diabetic patients with DKD treated with the maximum tolerated dose of RAS inhibitor. Atrasentan reduced the risk of renal events in the examined cohort, but this effect was associated with a high risk of heart failure hospitalization. A highly selective ETRA antagonist zibotentan initially investigated as an anti-cancer drug candidate, is currently being considered alone and combined with dapagliflozin for renoprotective effect in patients with CKD and eGFR between 20 and 60 mL/min.

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The results of this trial are expected next year. Pentoxifylline is a nonspecific phosphodiesterase inhibitor with rheologic and anti-inflammatory properties clinically used for decades in the treatment of peripheral vascular disease. A currently recruiting trial shall examine the possible renoprotective role of pentoxifylline in DKD on estimated 2510 participants and a follow-up period of ten years. Thromboxane is another possible target for anti-inflammatory action in glomerular blood vessels. Selonsertib, a selective apoptosis signal-regulating kinase 1 was also evaluated for safety and efficacy in moderate to advanced DKD, and although it didn't meet its primary endpoint, exploratory post hoc analyses suggest that it may slow DKD progression. Last but not least, mesenchymal stem cell (MSC)-based therapy has important biological and therapeutic implications for curtailing DKD progression. Thus, there are several ongoing randomized controlled trials considering the source, optimal cell number, and route of delivery in diabetic patients expected to advance the MSC-based therapy.

### How should future trials for DKD look like

*Christoph Wanner, Germany*



Kidney failure is an important outcome for all stakeholders in the healthcare system - patients, physicians, researchers, insurance companies, pharmaceutical firms, and regulators. In recent years the number of studies involving CKD patients has increased. However, it is sometimes difficult to achieve recruitment in numbers necessary to obtain plausible treatment effects. Last year, the International Society of Nephrology convened an international multi-stakeholder meeting to develop a consensus on this topic. A consensus was reached that clinical trial outcomes to represent kidney failure should be comprised of a composite including receipt of a kidney transplant, initiation of dialysis, and death from kidney failure, and may also include outcomes based solely on laboratory measurements of GFR — a sustained low GFR  $<15\text{mL/min}$  and a sustained percent decline in GFR  $\geq 40\%$ . For example, in the EMPAREG-OUTCOME study evaluating the effect of empagliflozin versus placebo on the risk of decline in estimated GFR the composite of 40% decline in eGFR, ESRD, or renal death provided reliable results similar to the traditional 57% decline in eGFR. Nevertheless, it might take years, even decades, to reach suggested endpoints when assessing drugs that are highly efficient in preserving renal function, such as the SGLT2 inhibitors which have been adopted as the new standard of care in DKD patients. This has led to a dilemma on how to design future trials to assess evolving therapeutic options for DKD.

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One possibility, as adopted in the recent trials evaluating cardiovascular effects of SGLT2 inhibitors, is to enrol patients with lower baseline eGFR, namely  $\leq 60$  mL/min, to reach the suggested eGFR threshold sooner. Another alternative is to use the GFR slope as a surrogate endpoint for CKD progression, as is done in the studies on rare diseases. This approach is based on the fact that with sufficient sample size, a treatment effect of 0.75 mL/min/1.73 m<sup>2</sup>/year or greater on the total slope over three years or chronic slope predicts a clinical benefit on CKD progression with at least 96% probability. Nevertheless, this alternative has not yet been endorsed in larger trials. Finally, a recently published proposal by the renal guideline groups within the European Renal Association – European Dialysis and Transplantation Association, suggested yet another option which is to adopt a unified set of variables termed Major Adverse Renal Events (MARE). MARE could include three to five items, considered relevant to patients and regulators, while patients reported outcomes should be reported in parallel as a standard set of primary or secondary endpoints in studies on kidney disease of diabetic, hypertensive-vascular, or another origin.

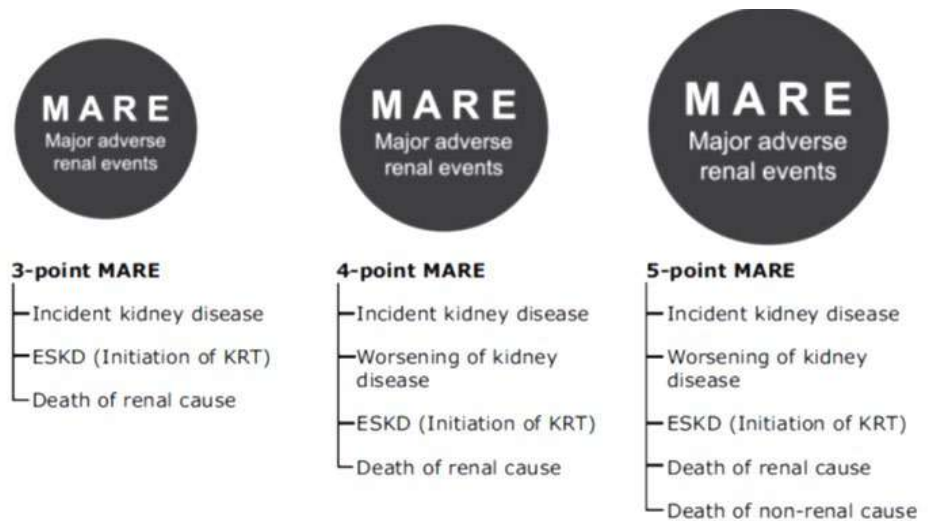


Figure 3. Renal outcome points – Major Adverse Renal Events

A recently published set of proposals addressing this issue suggests creating a network of sites that are continuously recruiting individuals with a certain condition, such as DKD, collecting crucial information and serving as a pool of participants for recruitment to randomized trials, defining endpoints based on lesser declines in eGFR or changes in albuminuria to shorten follow-up, enrolling patients based on biomarker profiles, and new trial design to simultaneously assess several therapeutic agents. More work is needed to overcome current obstacles in adopting these options in the future and certain experiences from the COVID era may be useful in this process.

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## High cut-off filters and multiple myeloma

*Paul Cockwell, United Kingdom*



Onco-nephrology is an emerging subspecialty that focuses on the complex relationships between the kidney and cancer. With the steadily increasing number of cancer patients, the aging population, improved cancer diagnostic tools, and survival, this field has been constantly evolving in the last years.

Multiple myeloma (MM) is typically characterized by the neoplastic proliferation of clonal plasma cells producing a monoclonal immunoglobulin. Although it is still considered a single disease, in reality, MM is a collection of several different plasma cell malignancies resulting in the accumulation of paraproteins in blood. Survival of MM patients has improved significantly in the last decade with the development of new treatment regimens. Nevertheless, the disease is commonly complicated with acute kidney injury (AKI) due to myeloma cast nephropathy, sometimes requiring haemodialysis (HD) treatment. Biopsy findings in these patients typically show cast formation, direct tubular injury, and interstitial inflammation caused by nephrotoxic monoclonal free light chains (FLC). Although most of them do not recover renal function, an improvement in survival rate has been observed in recent years, driven by the introduction of novel chemotherapeutic regimens. The latest recommendations by the International Myeloma Working Group acknowledge the significance of renal involvement in MM by emphasizing the importance of determining serum creatinine, electrolytes and FLC, estimating glomerular filtration rate (GFR), and performing urine electrophoresis at diagnosis and disease assessment.

The current standard of care for MM-related AKI includes disease-specific and supportive measures. These include the rapid introduction of dexamethasone and bortezomib, adequate hydration to maintain a urine output of 3L/day, avoidance of renin-angiotensin-system (RAS) blockade, and diuretics, and hypercalcemia treatment with pamidronate. The single predictor of good renal prognosis in MM patients is sufficient early reduction in serum FLC. One possible intervention to achieve this is performing high cut-off (HCO) HD using a dialyzer membrane that provides significant clearance of molecules up to a molecular weight of albumin.



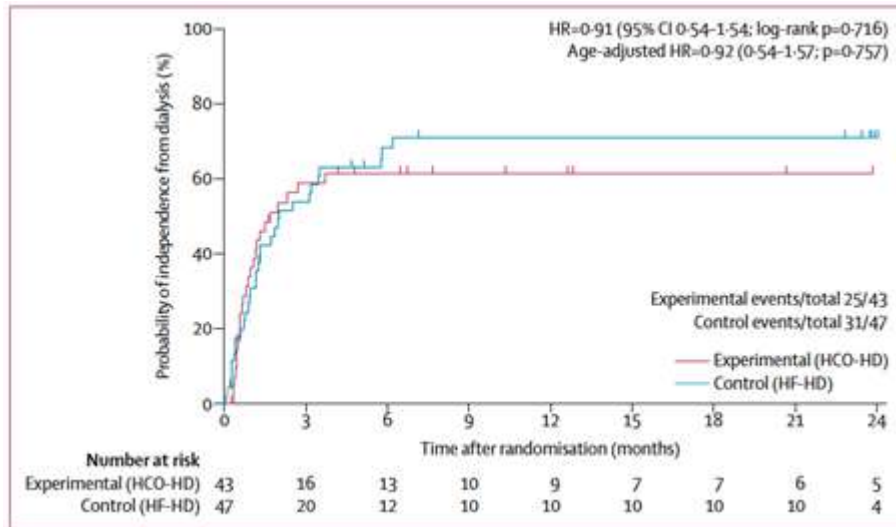


Figure 1. Effect of HCO-HD vs high-flux HD on survival of MM patients

Several open-label retrospective studies evaluated the efficacy of this approach from 2007 to 2015 highlighting the benefits achieved regarding renal function recovery. Nevertheless, more recent prospective randomized controlled trials did not fully corroborate these findings. Even though they confirmed an improved renal recovery among patients with myeloma cast nephropathy treated with a bortezomib-based chemotherapy regimen, no significant difference was observed in survival. One possible explanation for these disappointing results is the high early infection rate in patients treated with HCO-HD, and another is that a significant drop in FLC levels has already been achieved by chemotherapy, thus precluding an exceptional effect of the dialytic intervention. More studies are expected to further elucidate this topic.

## Cancer immunotherapies (checkpoint inhibitors, CAR-T cells, IL-2) and the kidney

*Laura Cosmai, Italy*



Many anticancer agents may directly or indirectly affect renal function. The recent development of multiple molecularly targeted agents and their introduction in clinical practice has substantially widened the spectrum of possible adverse events. These include recombinant IL-2 (rIL-2), immune checkpoint inhibitors (ICIs), and the evolving CAR-T cells.

IL-2 stimulates the growth and differentiation of B cells, NK cells, lymphokine-activated killer cells, monocytes, macrophages, and oligodendrocytes. As a potent lymphocyte activator rIL-2 has mainly been used in the treatment of melanoma and metastatic renal cell carcinoma. However, in recent years it has been nearly abandoned as it does not selectively activate cytotoxic lymphocytes but extends its effect on T regulatory cells as well, thus ultimately extinguishing the anticancer immune response. Furthermore, it requires high doses to achieve efficiency, thus causing cardiotoxicity and renal adverse events. ICIs are humanized or human IgG monoclonal antibodies that inhibit the immune system through various mechanisms. Their discovery was a breakthrough in cancer immunotherapy since they specifically target the key regulators of the immune system. Currently in use are programmed cell death receptor 1 (PD-1) inhibitors, programmed cell death ligand 1 (PD-L1) inhibitors, and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors. PD-1 blockade prevents PD-1 mediated signalling and restores the antitumor activity of T cells. CTLA-4 blockade prevents CTLA-4-induced inhibition of T cells. CAR-T cells are human T-cells genetically modified to express chimeric antigen receptors (CARs). So far, they have been approved for the treatment of certain types of lymphoma and acute lymphoblastic leukaemia, but are also being investigated in various solid cancers.

Nephrological management of cancer immunotherapies is focused on the prevention and treatment of renal toxicities of these agents and avoiding unnecessary treatment interruptions and dose reductions that could hinder the therapeutic effects. The most common manifestation of renal toxicity of these agents is acute interstitial nephritis, but a wide spectrum of glomerular diseases may also develop. The risk factors for the progression to AKI include low baseline eGFR, use of proton pump inhibitors, and combination therapy with anti-PD-1 and anti-CTLA-4. The underlying mechanisms of kidney damage encompass re-activation of drug-specific T-cells, loss of tolerance versus self-antigen, and release of pro-inflammatory cytokines. The usual therapeutic intervention in the case of AKI is corticosteroid treatment which elicits complete or partial recovery of renal function in 85% of the patients. Alternatives include infliximab, rituximab, eculizumab, mycophenolate-mofetil, and cyclophosphamides, which have been evaluated in small studies. Fortunately, the event rate of recurrent AKI is low.

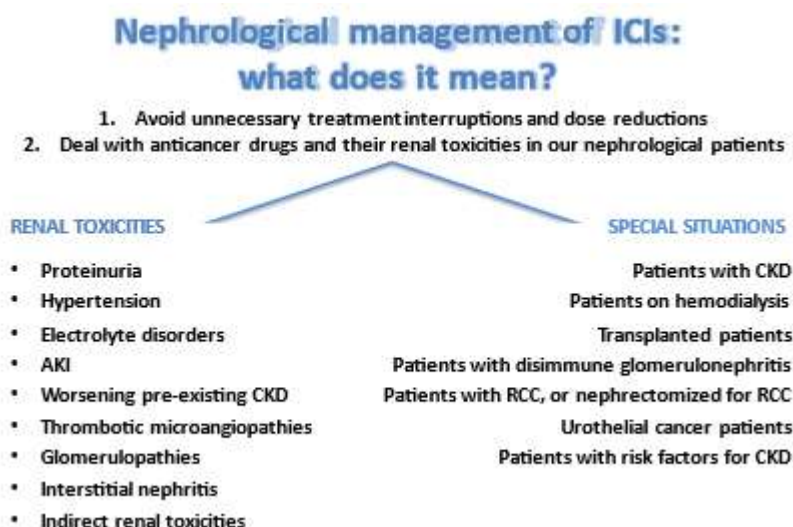


Figure 2. The scope of nephrology-related considerations in patients treated with ICIs

Recent studies have challenged the role of ICIs in AKI development based on the fact that PD-L1-related AKI incidence is <1%, suggesting that other drugs may be involved in the pathogenesis of renal impairment. Thus, kidney biopsy might be warranted in some cases.

Patients on renal replacement therapies represent challenging populations requiring special considerations concerning ICIs use. In HD patients these therapeutics seem to be safe to use, require no dose adjustment and are not dialyzable. Transplant patients, on the other hand, may experience acute rejection in over 40% of the cases, thus requiring strategies to minimize allograft dysfunction while maintaining antitumor response. In conclusion, even though ICIs and CAR-T cells exhibit promising results in oncology, additional larger studies are needed to more precisely define the incidence and outcomes of immune-related adverse events in patients with impaired renal function receiving these agents.

## Hematological disorders in transplant recipients

*Jolanta Malyszko, Poland*



Renal transplantation is associated with a risk of developing various blood disorders. These can be typically divided into two main categories: common disorders, including posttransplant anaemia (PTA), posttransplant cytopenias (PTC) and posttransplant lymphoproliferative disorder (PTLD); and uncommon but serious disorders, including therapy-related myelodysplasia (t-MDS) and therapy-related acute myeloid leukaemia (t-AML), hemophagocytic syndrome (HPS), and thrombotic microangiopathy (TMA).

Post transplantation anaemia is common and generally benign among kidney transplant recipients. The typical risk factors for its development include older donor/recipient age, surgical and/or chronic blood losses, hyperparathyroidism, iron deficiency, infection, inflammation, graft dysfunction, and chronic exposure to immunosuppressive agents. PTA increases the risk of allograft loss and is associated with increased mortality. The optimal treatment approach to PTA remains elusive. Randomized controlled trials found no difference between oral and parenteral iron supplementation in restoring haemoglobin levels. Studies on the correction of anaemia with erythropoiesis-stimulating agents in the immediate post-transplant period are underpowered and therefore not suited to give definitive answers.

Several immunosuppressive drugs (e. g. azathioprine, mycophenolate mofetil, calcineurin inhibitors, alemtuzumab), anti-viral agents (e. g. valganciclovir), antibiotics (e. g. trimethoprim-sulfamethoxazole), and the nutritional deficiency (e. g. folic acid, B12) have all been linked to post-transplant leukopenia or neutropenia. Neutropenia is present in nearly one-third of kidney transplant recipients and linked to a greater incidence of infection (mainly bacterial). Optimal treatment of this condition has not been established so far. Granulocyte colony-stimulating factors were effective and safe, albeit not benign, in short-term studies. Nevertheless, milder cases warrant a cautious approach. Posttransplant thrombocytopenia can be treated with transfusions, corticosteroids to enhance platelet production and thrombopoietin receptor agonists as second-line therapy.

PTLD is a well-recognized complication of solid organ transplantation. Polymorphic lesions are either monoclonal or polyclonal lymphoid proliferations, showing evidence of malignant transformation, but not meeting criteria for lymphomas as specified by WHO classification. Monomorphic PTLDs are equivalent to lymphomas in immunocompetent hosts. The most frequent monomorphic PTLD is diffuse large B-cell lymphoma. PTLD is usually caused by Epstein-Barr virus (EBV) infection due to therapeutic immunosuppression after renal transplantation. The diagnosis should rely on histopathological examination and staging should be performed with contrast CT or PET. Treatment options include tapering immunosuppression, discontinuing antimetabolic drugs, introducing rituximab monotherapy, immunochemotherapy, chemotherapy, EBV-specific cytotoxic lymphocytes, and local surgical or radiological interventions.

Therapy-related neoplasms, t-MDS and t-AML, are clonal disorders occurring following exposure to genotoxic agents and radiation. The pathogenesis of these disorders is vague and likely multifactorial, probably related to immunosuppression, antigenic stimulation by graft, opportunistic infections with oncogenic potential and direct mutagenicity of medications. Tapering of immunosuppressive medication is mandatory, although not sufficient, to achieve a complete response, and chemotherapy is also needed. Several promising new agents, including liposomal formulations of cytarabine and daunorubicin, venetoclax, glasdegib, midostaurin, endasidenib, and gemtuzumabozogamicin have emerged in the recent trials.

The hemophagocytic syndrome is a life-threatening, hyper-inflammatory clinicopathologic entity characterized by the uncontrolled proliferation of hemophagocytic monocytes/macrophages/histiocytes that are actively ingesting other blood cells. Diagnostic criteria for HPS may include fever, cytopenia of two lines, hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia (>500 µg/L), hemophagocytosis, elevated soluble IL-2 receptor (CD25), decreased NK-cell activity, and hepato-splenomegaly. Renal symptoms include AKI and sometimes nephrotic syndrome as a manifestation of focal segmental glomerulosclerosis or minimal change disease. The range of associated infections is wide and includes viral and protozoal agents. The condition is associated with a high mortality rate and graft loss. Treatment relies on reduction or cessation of immunosuppression and treatment of underlying infection or malignancy. High-dose immunoglobulin may be beneficial.

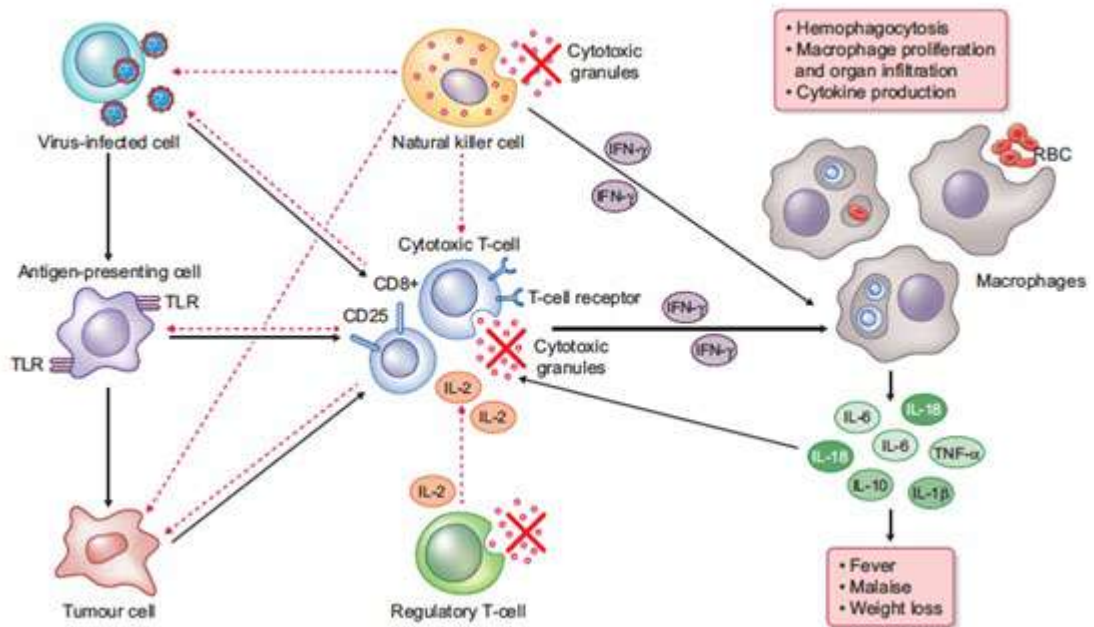


Figure 3. Pathogenesis of hemophagocytic syndrome following transplantation

Thrombotic microangiopathy is a rare and fatal condition characterized by thrombocytopenia, Coombs negative haemolysis with microvascular occlusion, AKI, neurological symptoms, fever, and involvement of other organs. In renal transplant recipients, TMA may occur de novo or recur in patients with a previous history of the haemolytic uremic syndrome. Reduction or withdrawal of calcineurin inhibitors is the first step in the management of TMA and may be accompanied by plasma exchange, eculizumab, or rituximab treatment.

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