# 2021 American Society of Nephrology (ASN) Kidney Week

November 4th–7th, 2021

## In-Depth Report

The 2021 American Society of Nephrology (ASN) Kidney Week took place under a virtual format for a second year on 4–7 November 2021 due to the ongoing impact of the COVID-19 pandemic. This year's presidential theme was 'Time to act', given that over the past year, incredible advances and opportunities for the field of kidney medicine have emerged. Opening the meeting, ASN President Susan Quaggin described kidney disease as an ongoing public health crisis, and highlighted the commitment of the kidney community to continuing education, learning more about the latest scientific advances, and improving care for the millions of people with kidney diseases.

"This year's Kidney Week will challenge every member of our community and beyond to take up the charge to transform kidney health and improve the lives of more than 850 million people worldwide living with kidney disease."

- ASN President Susan E. Quaggin

2021
**ASN Kidney Week**
**World's premier nephrology meeting**

200+
**educational hours**

50+
**attendees outside USA**

2000
**ePosters**

**Fully virtual for a second year**

9600+
**attendees from across 100 countries**

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## COVID-19 and the kidneys

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2021 ASN Kidney Week opened with a panel discussion on the impact that the COVID-19 virus can have on chronic kidney disease (CKD), along with vaccinating vulnerable populations as the best way to end the pandemic. Anthony Fauci, National Institute of Allergy and Infectious Diseases at the National Institutes of Health, explained how underlying conditions, such as CKD, are associated with an increased risk of severe COVID-19 infection. Studies conducted during the COVID-19 pandemic have provided insights into the pathophysiology of COVID-19-associated acute kidney disease, with more than 25% of patients hospitalised with COVID-19 developing acute kidney injury (AKI). While kidney disease is a potential outcome of long COVID, patients who already have kidney disease are also at increased risk of being infected with the virus.

> "Available data make it very clear of the extraordinary benefit of booster shots for getting maximal level of protection".
>
> **- Anthony Fauci, National Institute of Allergy and Infectious Diseases at the National Institutes of Health**

Focusing on the origin of COVID-19 and the development of the delta variant, Susan Weiss, University of Pennsylvania, Philadelphia, USA, noted that as the virus mutates, the need for widespread vaccinations becomes increasingly important. Vaccines remain imperative to prevent infection and reduce its spread.

> "The ongoing dominance of the delta variant may suggest that the spike protein is reaching a point where it may stop mutating."
>
> **- Susan Weiss, University of Pennsylvania, Philadelphia, USA**

Jeffrey Silberzweig, The Rogosin Institute, New York, USA, highlighted that patients undergoing dialysis do not appear to mount as strong an antibody response to COVID-19 vaccines compared with the general population, and this limited antibody response does also not appear to be as long-lasting. Therefore, the use of boosters are of particular importance for all patients with CKD, particularly those on dialysis given their increased risk of exposure during hospital visits for dialysis. Ashisha Jha, Brown University, Rhode Island, USA, highlighted the discrepancies of vaccine availability between countries and the need for all vulnerable populations to have access. There is an ongoing need to focus on individuals with chronic diseases, such as those with CKD, cardiovascular disease, and other high-risk conditions, based on the principle that even if some remain unvaccinated, there will be an immediate and dramatic decrease in mortality and healthcare burden. Amitava Banerjee, Institute of Health Informatics Research at University College London, UK, added that the key take-home messages were:

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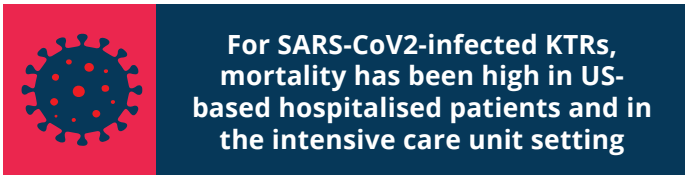
|---|---|---|
| **Infection suppression remains important** | **Vaccination availability needs to be improved** | **Underlying chronic diseases need to be optimally managed** |

"CKD is acting as a risk factor as a disease and as an outcome from infection with SARS-CoV-2."

**- Amitava Banerjee, Institute of Health Informatics Research at University College London, UK**

Experts in the field evaluated the different challenges confronted by the haemodialysis and transplant community during the COVID-19 pandemic, including diagnosis, treatment and evaluation of immune responses. The role of innate and adaptive immune responses in kidney transplant recipients (KTRs) is critical to patient outcomes. Enhancing the efficacy of the adaptive immune response may be an important issue both for infection resolution and for the appropriate generation of immunity on vaccination. Miklos Molnar, University of Utah, Salt Lake City, USA, highlighted that while the mortality rate for wait-list candidates (patients with end-stage kidney disease [ESKD]) is lower than in KTRs, there is an increased mortality in this population compared with healthy individuals. Transplantation has and should continue during the pandemic. COVID-positive donors have been used without disease transmission, but this is still a controversial area in kidney transplantation with no best practice currently in place.




Shruti Gupta, Brigham and Women's Hospital Department of Medicine, Boston, USA, highlighted that COVID-19 results in a significantly higher admission rate (11 times) and higher mortality rates (up to 75%) for US-based patients with ESKD compared with the general population, even after adjustment for patient age/comorbidities/other factors. Of note, there are some intriguing results regarding race that require confirmation. As studies of anti-viral treatments have excluded patients with ESKD, physicians are required to use their best judgement when considering this treatment approach.

Paolo Cravedi, Mount Sinai School of Medicine, New York, USA, explored cellular immune activity in COVID-19-infected KTRs. T-cell responses to SARS-CoV2 have not been fully characterised and are heterogeneous, depending on disease phase and severity. Anti-viral responses are impaired and/or delayed in KTRs as immunosuppressive therapy is targeted to B- and T-cell function. Available data are from circulating T-cells and do not fully capture the entire T-cell repertoire of the host. Likewise, it is no surprise that responses to the vaccines are also similarly affected.

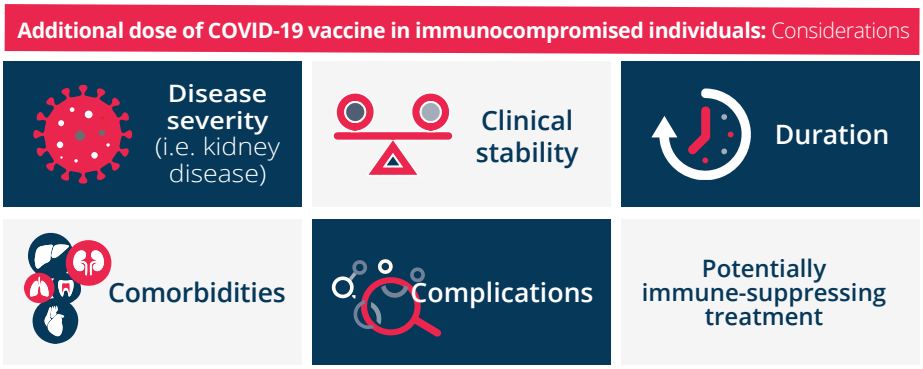
"There are no data to support stopping or altering immunosuppressive therapy in COVID-19-infected KTRs at this time."

**- Paolo Cravedi, Mount Sinai School of Medicine, New York, USA**

Shannon Novosad, Centers for Disease Control and Prevention, explored the use of COVID-19 vaccines in vulnerable kidney disease populations. In the USA, the Centers for Disease Control and Prevention recommends that moderately to severely immunocompromised individuals receive an extra dose of COVID-19 vaccine, including those who have previously received an organ transplant or stem cell transplant (within the previous two years) and are receiving immunosuppressive treatment.

The patient's clinical team is best positioned to determine the degree of immune suppression and appropriate timing of COVID-19 vaccination. An additional dose of vaccine (as with the primary vaccine) should ideally be given at least two weeks prior to the initiation or resumption of immunosuppressive therapy.

Data suggest that most patients on dialysis develop an immune response after a two-dose primary mRNA COVID-19 vaccine series. While an additional dose of COVID-19 vaccine is not recommended for immunocompetent dialysis patients, the patient's clinical team can assess the degree of any altered immunocompetence and whether the patient should receive an additional dose of vaccine.




Michael Anderson, US Department of Health and Human Services, explored novel COVID-19 therapies. In the USA, COVID-19 monoclonal antibodies are intended for individuals with mild-to-moderate COVID-19 who are at high-risk of developing severe disease. The use of monoclonal antibodies are most likely to be effective when given early on in the disease course. Early evidence appears to show promise of monoclonal antibody products in the outpatient setting – the combined use of bamlanivimab and etesevimab or casirivimab and imdevimab can reduce the relative risk of hospitalisation by up to 70% in high-risk patients.

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## Immunotherapy and the kidneys

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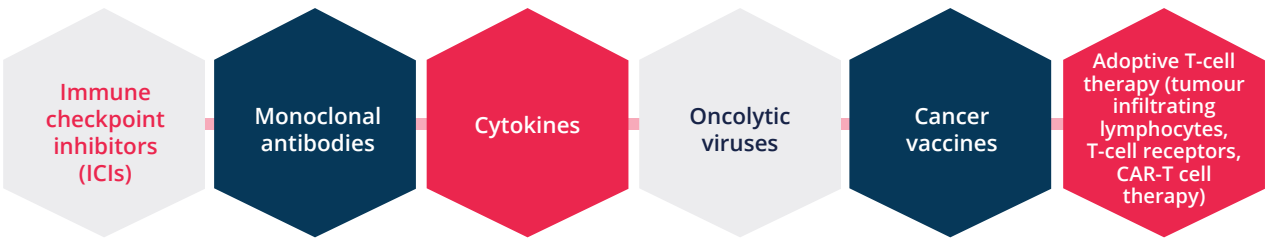
Harish Shanthanu Seethapathy, Massachusetts General Hospital, Boston, USA, explored AKI associated with chimeric antigen receptor T (CAR-T) cell therapy, a breakthrough in cancer treatment. With the widespread use of this therapy, increasing evidence has shown CAR-T cell therapy to be associated with AKI, requiring nephrologists to understand the potential nephrotoxicity arising from this therapeutic approach. Cytokine release syndrome (CRS), AKI, hyponatraemia, hypokalaemia, and hypophosphataemia are all common after CAR-T cell therapy. Of note, AKI is typically seen in the setting of CRS, but can also occur with mild or even no CRS. Neither ferritin nor C-reactive protein appear to be predictive biomarkers for AKI related to CAR-T cell therapy. While AKI in this setting has a high recovery rate, severe AKI is associated with higher mortality rates. Of note, CAR-T cell therapy has been used to treat a patient with systemic lupus erythematosus (SLE) for the first time, with this treatment approach inducing rapid clinical remission of severe and refractory disease with no notable adverse effects.

### Immunotherapies which may cause AKI



Ala Abudayyeh, University of Texas MD Anderson Cancer Center, Houston, USA, explored the use of immunotherapy in dialysis and kidney transplant patients. Kaposi sarcoma is the most common form of cancer (300-fold higher risk than in the general population), followed by non-melanomatous skin cancers (2- to 40-fold higher risk than in the general population).

Cancer incidence in KTRs is at least **two- to four-fold higher** than the general population (age- and gender-matched), with a **5% incidence** of cancer within the first 5 years post-transplant (**>25% after 20 years**)

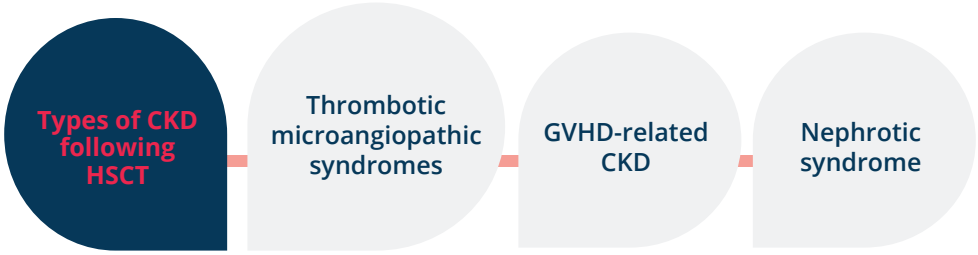
"Cancer is the third leading cause of death in KTRs, constituting up to 56% of all deaths in patients with a functioning allograft."

**- Ala Abudayyeh, University of Texas MD Anderson Cancer Center, Houston, USA**

ICI-associated graft rejection is attributed to the inhibition of programmed cell death protein 1. Thus, there remains a difficult 'trade-off' facing oncologists and transplant specialists managing transplant recipients with cancer, and there is an ongoing need for prospective data and novel biomarkers for identifying the patients likely to benefit from immunotherapy in the solid organ transplant setting. Of note, although there is significant molecular similarity between ICI-associated rejection and acute interstitial nephritis, biopsy-based measurement of *IFI27* gene expression represents a potential biomarker for differentiating these entities. As the use of ICI therapy becomes increasingly widespread across different types of cancer, their use in patients receiving dialysis is likely to increase. Based on available pharmacological information, ICIs require no dosing adjustment in patients with ESKD. Analysis of the reported cases in the literature demonstrates a similar incidence of immune-related adverse events in patients with ESKD receiving dialysis (49%) as compared with non-dialysis cancer patients (39–59%). As such, it is important that these patients are monitored very closely for immune-related adverse events; however, the risk of these adverse events should not preclude patients on dialysis from receiving these therapies.

Mitchell Rosner, University of Virginia School of Medicine, Charlottesville, USA, explored AKI associated with haematopoietic stem cell transplantation (HSCT).

Management of AKI following HSCT is largely supportive and includes the use of diuretics, avoidance of fluid overload (>10%), early initiation of renal replacement therapy, nutritional support, minimising unnecessary nephrotoxins, and maintenance of mean arterial pressure.




"Preventing and treating veno-occlusive disease and sinusoidal obstruction syndrome might reduce the occurrence of kidney damage."

- Mitchell Rosner, University of Virginia School of Medicine, Charlottesville, USA

Frank Cortazar, New York Nephrology Vasculitis and Glomerular Center, New York, USA, explored clinicopathological features and outcomes of ICI-associated AKI. Data from a retrospective study has provided insights into the risk factors, clinical features, histopathologic findings, and renal and overall outcomes in patients with ICI-associated AKI (N=138).

| Factors independently associated with an increased risk of ICI-associated AKI: | Lower baseline estimated glomerular filtration rate (eGFR) | Use of proton pump inhibitors | Combination ICI therapy |
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Median (interquartile range) time from ICI initiation to AKI was 14 (6–37) weeks, with subnephrotic proteinuria reported in most patients, and approximately half showing pyuria. Extrarenal immune-related adverse events occurred in 43% of patients (N=138); 69% were concurrently receiving a potential tubulointerstitial nephritis-causing medication. Tubulointerstitial nephritis was the dominant lesion in 93% of the 60 patients biopsied. Most patients (86%) were treated with steroids. Complete, partial, or no kidney recovery occurred in 40%, 45%, and 15% of patients, respectively. Concomitant extrarenal immune-related adverse events were associated with worse renal prognosis, whereas concomitant tubulointerstitial nephritis-causing medications and treatment with steroids were each associated with improved renal prognosis. Failure to achieve kidney recovery after immune checkpoint inhibitor-associated AKI was independently associated with higher mortality. Immune checkpoint inhibitor rechallenge occurred in 22% of patients, of whom 23% developed recurrent associated AKI.

"Rechallenge can be considered in most patients, but consider delaying rechallenge with ICIs for at least 2 months after ICI-associated AKI."

- Frank Cortazar, New York Nephrology Vasculitis and Glomerular Center, New York, USA

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## Maladaptive responses in AKI

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Recently, there has been an increased appreciation of the long-term sequelae of AKI and the potential development of CKD. Hypotensive, septic or toxic insults can initiate a series of events, resulting in impaired microcirculation, activation of inflammatory pathways, and tubular cell injury or death, ultimately resulting in AKI and the initiation of a repair response. However, maladaptive and incomplete repair leads to the development of fibrosis and, ultimately, CKD.

**Maladaptive repair of AKI leads to CKD**


Shuei-Liong Lin, National Taiwan University Hospital, Taipei, Taiwan, discussed the methylation of pericytes in maladaptive repair. Following ischaemia/reperfusion injury-induced AKI, myofibroblasts were activated from quiescent pericytes, with a subsequent increase in cell numbers. While myofibroblasts underwent apoptosis during renal recovery, one-fifth survived in the recovered kidneys allowing cell numbers to increase again. Microarray data show distinctive gene expression patterns of quiescent pericytes, activated pericytes (myofibroblasts), and inactivated pericytes isolated from kidneys before and after AKI. Hypermethylation of the *Acta2* repressor Ybx2 during AKI resulted in epigenetic modification of inactivated pericytes to promote transition to CKD. The administration of 5-azacytidine reversed the hypermethylation of pericytes and prevented AKI-CKD transition.

> "Intervention to erase hypermethylation of pericytes after AKI provides a strategy to stop the transition to CKD."
>
> **- Shuei-Liong Lin, National Taiwan University Hospital, Taipei, Taiwan**

Tomokazu Souma, Duke University School of Medicine, Durham, USA, explored the role of oxidative stress in the transition of AKI to CKD. Overwhelming lipid peroxidation induces ferroptotic stress and ferroptosis, a non-apoptotic form of regulated cell death that has been implicated in maladaptive renal repair. Available data broaden the roles of ferroptotic stress from simply being a trigger of regulated cell death to include the promotion and accumulation of proinflammatory cells that underlie maladaptive repair.

> "Ferroptotic stress in proximal tubular cells reprograms them to a pathological inflammatory state, and promotes accumulation of inflammatory proximal tubular cells in maladaptive repair."
>
> **- Tomokazu Souma, Duke University School of Medicine, Durham, USA**

Paola Romagnani, University of Florence, Florence, Italy, discussed AKI-induced carcinogenesis, with data collected from several single-centre and multicentric studies showing that AKI increases the risk of papillary renal cell carcinoma development and tumour relapse in humans. Among AKI-related pathways, *NOTCH1* gene overexpression in human papillary renal cell carcinoma was associated with worse outcome and specific for type 2 disease. In addition, mice overexpressing *NOTCH1* in tubular epithelial cells developed papillary adenomas and type 2 papillary renal cell carcinomas, with AKI accelerating this process.

> "AKI drives tumourigenesis from local tissue progenitor cells."
>
> - Paola Romagnani, University of Florence, Florence, Italy

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## Lupus nephritis and the kidneys

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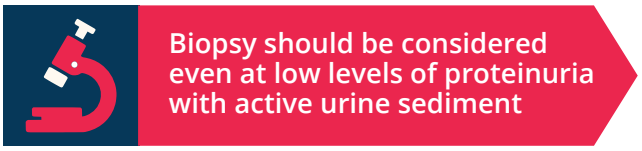
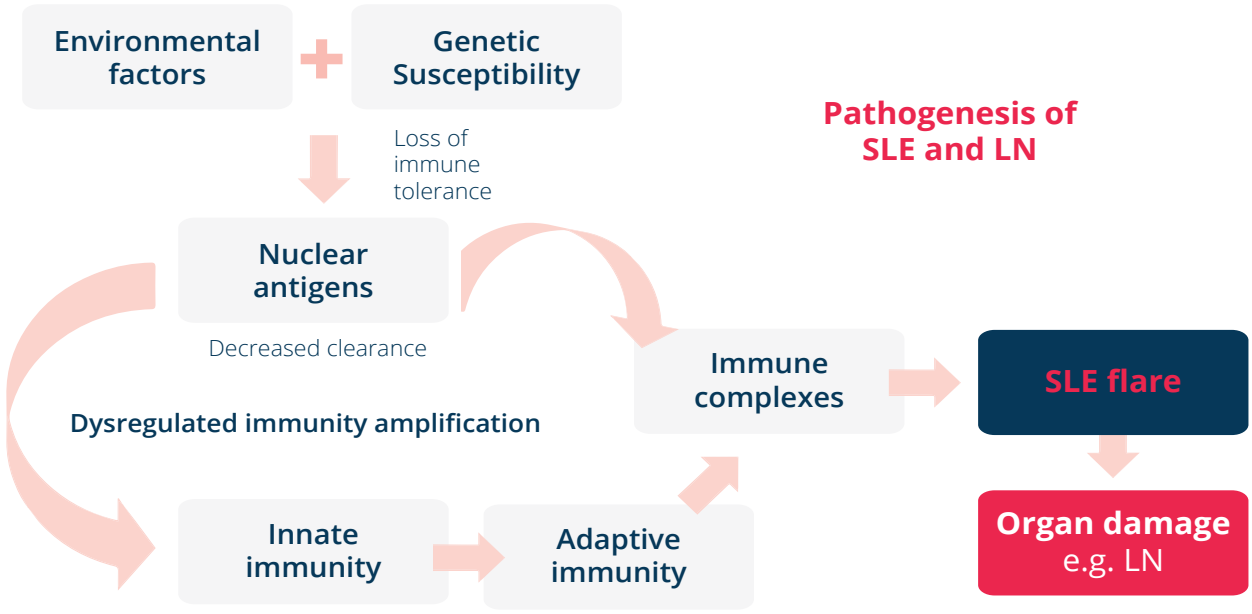
SLE is a multisystem autoimmune disease in which up to 50% of patients show clinically evident kidney disease. Lupus nephritis (LN) is the most common cause of kidney injury in SLE and a major risk factor for morbidity and mortality given that up to 10% of patients progress toward ESKD. Samir Parikh, Ohio State University Medical Center, Columbus, USA, explored the pathogenesis, diagnosis, and surveillance of LN. Pathogenesis of LN is complex, heterogeneous, and is still not fully understood, although it appears to contribute to heterogeneity in both presentation and treatment response. Several risk alleles associated with SLE have also been implicated in LN, but genetic studies specifically evaluating LN are lacking. Kidney biopsy remains gold standard for LN diagnosis. Revised classification schema may be more informative for both diagnosis and prognosis. By definition, proteinuria must be present to clinically diagnose LN, although even at low levels of proteinuria, severe LN is possible.




Flare prevention is critical to preserve long-term kidney health. Maintaining disease control over the long-term (≥5 years) results in a better prognosis (versus a lack of control during this period). Activity index at repeat kidney biopsy after prolonged treatment may help to risk stratify patients for flare and need for continued treatment. Promising urine biomarkers, such as CD163 (reflects histologic inflammation), have emerged and while their validation is still needed, they may soon be available for use in clinical practice.

> "Rapid control and reduction of proteinuria may lead to improved renal and patient survival."
>
> - Samir Parikh, Ohio State University Medical Center, Columbus, USA




*LN, lupus nephritis; SLE, systemic lupus erythematosus*

Brad Rovin, Ohio State University Wexner Medical Center, Columbus, USA, explored new treatment options for LN. The management of LN varies according to disease severity and risk of progressive kidney damage, with the current approach to LN management having significant room for improvement given that renal outcomes remain suboptimal. Voclosporin (calcineurin inhibitor) and belimumab (anti-BAFF) have recently been approved by the FDA for the treatment of active LN. Clinical data has shown that adding voclosporin or belimumab to background immunosuppression significantly increases the number of complete LN responses at 1 or 2 years – achieving a complete response should lead to better preservation of kidney function over the long-term. While it could be argued that all patients with LN should simply be treated with background belimumab or voclosporin there are a number of considerations:

- **No biomarkers currently available to identify which patients would benefit most from belimumab or voclosporin**
- **Long-term safety data for belimumab and voclosporin are lacking**
- **Increased 'pill burden'/polypharmacy for patients who already have adherence issues**
- **Costly treatment may be a barrier for some patients**
- **A significant proportion of patients will respond to background immunosuppression therapy**

"In trials with voclosporin and belimumab, more than half of all patients failed to achieve complete renal response or primary efficacy renal response, suggesting additional treatments are needed."

**- Brad Rovin, Ohio State University Wexner Medical Center, Columbus, USA**

So where should these new therapies be incorporated into the LN care pathway? Available study data suggest that voclosporin may be particularly suitable for patients with impaired eGFR and the need to avoid LN flares at all costs, while belimumab may be more useful where a rapid reduction in proteinuria is required and there are concerns about podocyte health.

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## Microbiome and the kidneys

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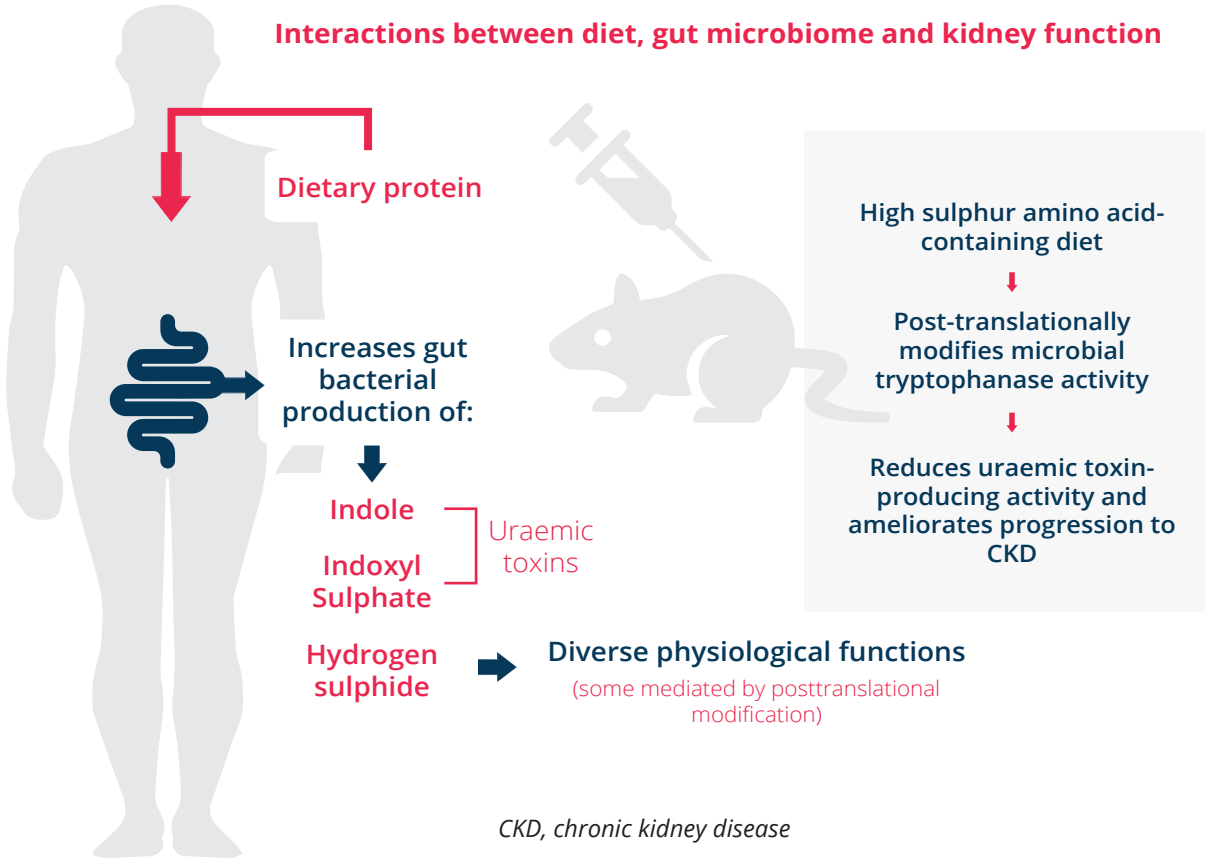
The microbiome can directly modulate metabolic pathways relevant to kidney function or modulate the immune system both at local and systemic levels. The influence of the microbiome has potential consequences for organ transplantation outcomes and kidney disease progression. Wendy Garrett, Harvard University, Cambridge, USA, explored the interactions between diet, gut microbiome, and kidney function.




*CKD, chronic kidney disease*

"Diet can tune microbiota function to support healthy host physiology through posttranslational modification without altering microbial community composition."

**- Wendy Garrett, Harvard University, Cambridge, USA**

Diabetic kidney disease (DKD) is a major cause of renal failure that urgently necessitates a breakthrough in disease management. Takaaki Abe, Tohoku University, Sendai City, Japan, explained that phenyl sulphate, a gut microbiota-derived metabolite, is a cause and predictive marker of albuminuria in DKD. Phenyl sulphate accumulates in plasma as a metabolite and has deleterious effects on the vasculature and kidneys. In DKD, phenyl sulphate damages podocytes, accelerates glomerular basement membrane thickening, and induces proteinuria. In microalbuminuric patients, serum and urine phenyl sulphate levels appear to predict 2-year albumin-creatinine ratio deterioration.

Thus, interventions to reduce phenyl sulphate levels may be a novel therapeutic approach for the management of DKD. Inhibition of tyrosine phenol-lyase, a bacterial enzyme responsible for the synthesis of phenol from dietary tyrosine before it is metabolised into phenyl sulphate in the liver, has been shown to reduce albuminuria and plasma phenyl sulphate levels in diabetic murine models. Possible future interventions will include the laxative elobixibat and the SGLT-1-specific inhibitor SGLT5213. Elobixibat provides renoprotection and reduces levels of phenyl sulphate, while SGLT5213 has been shown to ameliorate renal failure with altering gut microbial community in mice with adenine-induced renal failure.

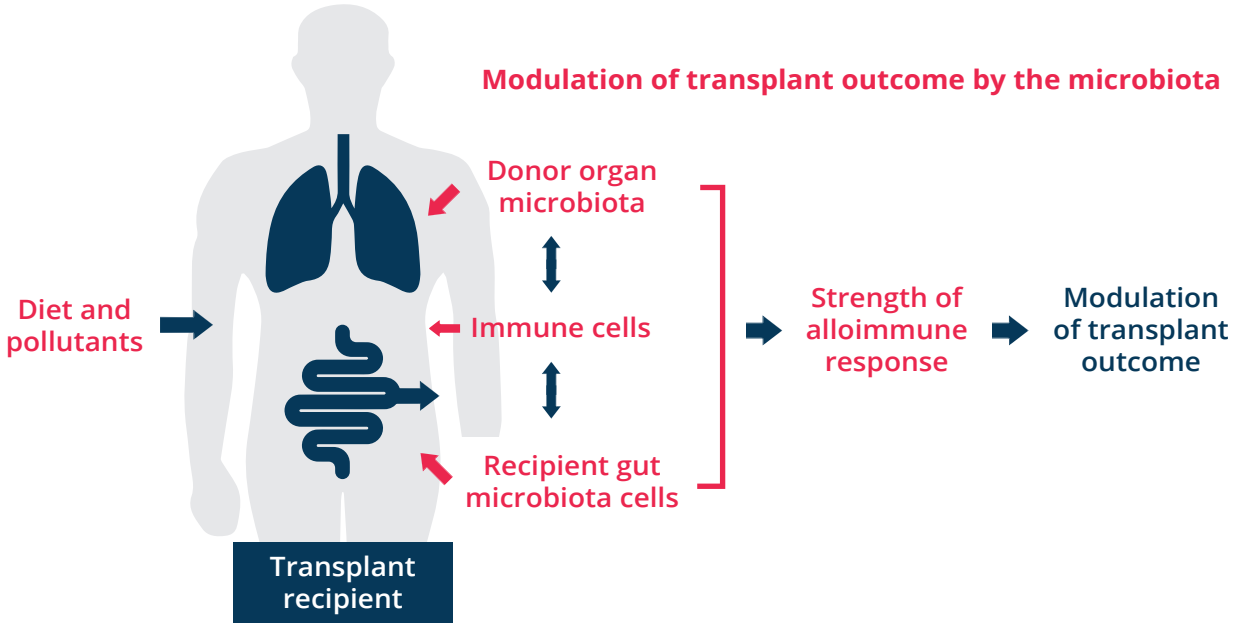
"Phenyl sulphate contributes to albuminuria and could be used as a disease marker and future therapeutic target in DKD."

**- Takaaki Abe, Tohoku University, Sendai City, Japan**

Maria-Luisa Alegre, University of Chicago, Chicago, USA, explored modulation of transplant outcome by the microbiota and its metabolites. As an environmental factor in intricate symbiotic relationship with its hosts' immune system, the microbiome has the potential to shape transplant responses. There is a large interpersonal variability in intestinal microbiome composition – such variations appear to alter the kinetics of transplant rejection. For example, transplant models using genetically similar mice, which differ in their gut microbiome composition (supplied by different vendors) exhibit differing rates of graft survival – this difference is eliminated following cohousing and faecal transfer. In animal models of chronic graft rejection, Bifidobacterium species have been shown to confer a survival benefit and offer insights into possible future therapies. Bifidobacterium upregulates anti-inflammatory cytokines and homeostatic chemokines in antigen-presenting cells, and causes increased induction of regulatory T-cells and decreased T-cell activation.

"Colonised organs have a shorter half-life than sterile organs, suggesting that graft-resident microbiota promote transplant rejection."

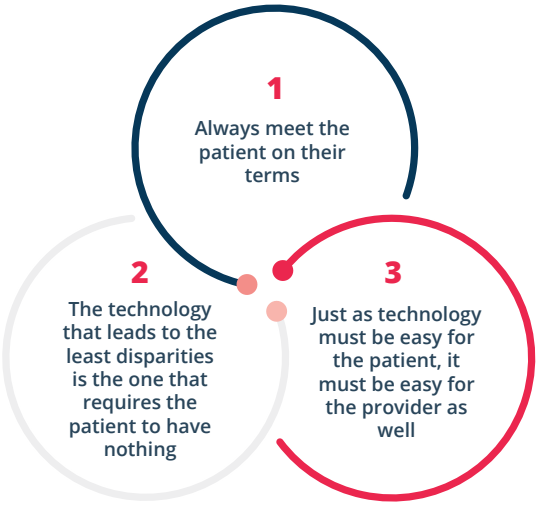
**- Maria-Luisa Alegre, University of Chicago, Chicago, USA**



## Telenephrology

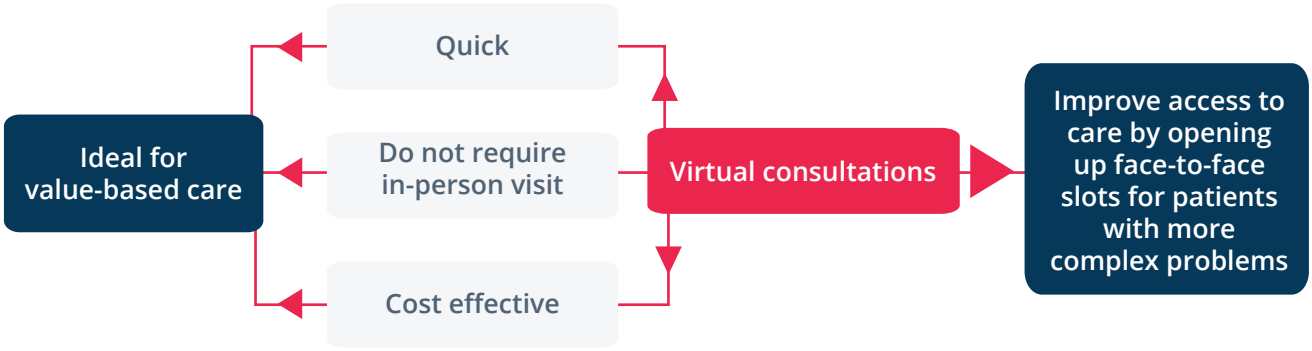
The COVID-19 pandemic has forced the accelerated use of telehealth in nephrology practice, which has facilitated continual monitoring in a time of social distancing. However, telehealth is not without its challenges. Eric Wallace, University of Alabama at Birmingham, Birmingham, USA, discussed best practice and ground rules for the delivery of patient-centered kidney care via telehealth.

Ground rules for optimal telehealth




In the US, ambulatory visits occurring virtually have increased substantially following the start of the COVID-19 pandemic (up to around 75% of visits being undertaken virtually at the peak of the COVID-19 pandemic from 0%, which has now stabilised to around 20%). Satisfaction with video visits has been more consistent than with audio only visits, highlighting the need to consider the type of modality selected for patient engagement.

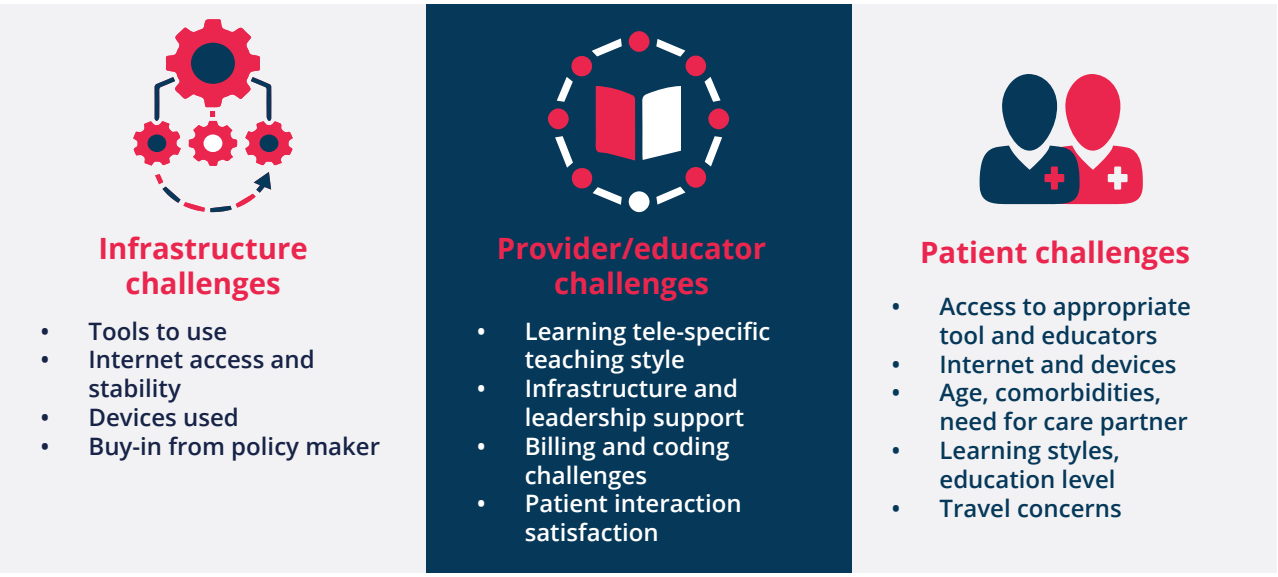
### Benefits of virtual consultations




Careful planning is important for remote patient monitoring and, while everything that can be monitored can be done so remotely, this does not imply that anything and everything should be monitored remotely.

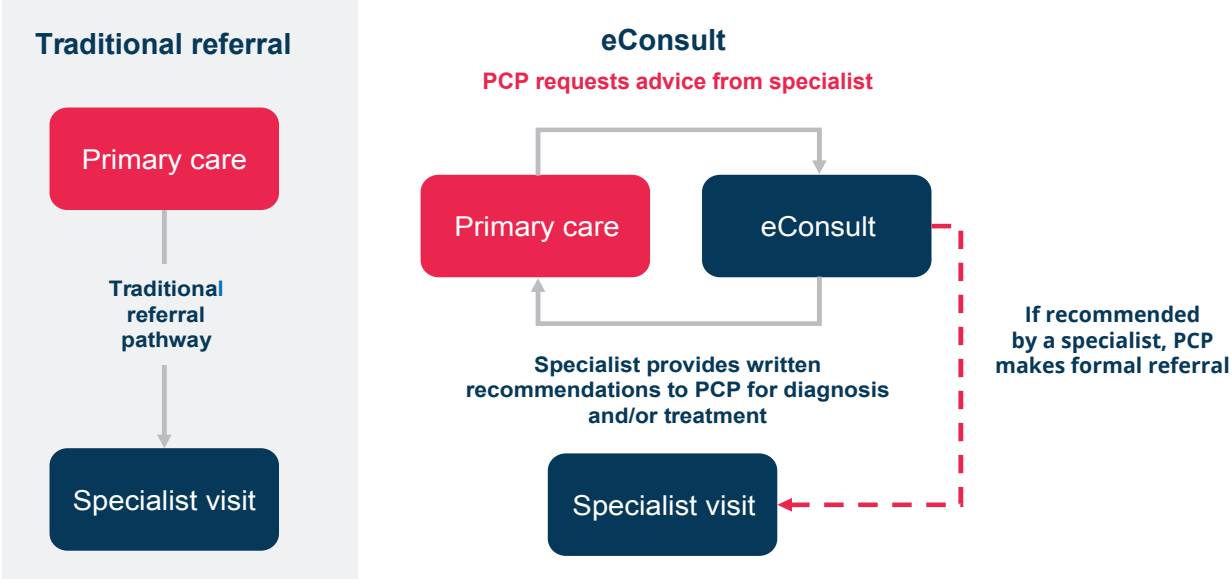
Manisha Singh, University of Arkansas for Medical Sciences, Little Rock, USA, explored the value of telehealth for patient education based on lessons learned. Data from a 3-year pilot study which evaluated the effectiveness of comprehensive predialysis education through telemedicine for patients with CKD compared with a standard care group (face-to-face education) showed that both approaches were comparable with approximately 90% of US-based patients able to make an informed treatment choice.

However, telehealth has a number of challenges:




Blake Cameron, Duke University Medical Center, Durham, USA, explored the use of nephrology eConsults to support primary care – these are written, provider-to-provider communications based on chart review which provide an efficient alternative to the traditional referral process. This approach reduces the challenges of traditional referrals, such as long wait times for appointments, unreliable scheduling, and the potential for over-referral.

**eConsults can provide an efficient alternative to the traditional referral process**




*PCP, primary care provider*

"eConsults must be considered as part of a larger technical and social system of healthcare delivery."

- Blake Cameron, Duke University Medical Center, Durham, USA

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## Closing remarks

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As a virtual event for the second year running, 2021 ASN Kidney Week continued to provide the unique and unparalleled opportunity to connect one of the largest audiences in nephrology, along with enabling wider access to ground-breaking science and practice-changing research, cutting-edge topics, patient care, clinical disparities, and more.

ASN Kidney Week is expected to return to a live face-to-face format next year and planning is currently underway for the meeting to take place on **1–6 November 2022 in Orlando, USA.**