EMJ NEPHROLOGY

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+ ERA-EDTA VIRTUAL CONGRESS 2020

Reviewed

+ EDITOR'S PICK

New Aspects of Pathogenesis and Treatment of Membranous Glomerulopathy After the MENTOR Study

+ INTERVIEWS

Prof Hamid Rabb, Johns Hopkins University, USA, spoke to us about COVID-19 and its impacts on kidney transplant programmes

+ ABSTRACT REVIEWS

We are pleased to offer a broad range of abstract summaries of research presented at the ERA-EDTA Virtual Congress

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Spencer Gore, CEO

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EMJ is an online only, peer-reviewed, open access general journal, targeted towards readers in the medical sciences. We aim to make all our articles accessible to readers from any medical discipline.

EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

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EMJ Nephrology 8.1

Welcome

Dear Readers,

It is my pleasure to welcome you to our latest issue of *EMJ Nephrology*, including our independent review of the European Renal Association – European Dialysis and Transplant Association (ERA–EDTA) Virtual Congress 2020. This issue captures the full breadth of the critical role of the kidneys and their care, with articles addressing primary renal diseases such as membranous nephropathy, secondary renal complications of diabetes, and renal drug clearance in the complex setting of dialysis.

Attending this year's ERA–EDTA Virtual Congress highlighted the value of online platforms for connecting clinicians with the latest research insights, with the experience of experts in the field, and with a worldwide network of other nephrologists and renal physicians seeking to provide the best care for their patients, wherever they are. At EMJ, we are proud to continue to contribute to the provision of free, open-access research with this latest issue of *EMJ Nephrology*.

Read on for detailed analyses of the renal clearance of antibiotics in the settings of dialysis and cirrhosis, a look at immunotherapy for membranous nephropathy and the results of the MENTOR trial, and a narrative review of renoprotective strategies in diabetic kidney disease. In their article, Ponce et al. provide a global perspective with their insights into the challenges of management of acute kidney injury in low- and middle-income countries.

We are also pleased to offer a broad range of abstract summaries of research from the ERA–EDTA congress, along with our interview with expert transplant nephrologist Prof Hamid Rabb from the Johns Hopkins Kidney Transplant Program, Baltimore, Maryland, USA.

The collaborative spirit of researchers and clinicians worldwide in addressing the COVID-19 pandemic is a microcosmic example of the wider and continuing tradition of medical research and evidence-based medicine, built upon the shared experiences and insights of healthcare practitioners and scientists. We are proud that this fantastic issue, with global contributors and expert insights, adds to this legacy of research. Thank you to the authors, researchers, experts, and clinicians contributing to this issue, and to our EMJ publishing team for their work in bringing this research to you. I hope you enjoy reading this issue, and I look forward to seeing you all, hopefully in person, at ERA–EDTA 2021 in Berlin, Germany.

Spencer Gore

Chief Executive Officer, European Medical Group

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Foreword

Dear readers,

First of all, a note of thanks: thank you to all our authors, peer-reviewers, interviewees, and editorial board members for their commitment and dedication to this journal. Our speciality's importance has been highlighted by the current COVID-19 pandemic and many of our contributors are working on the front-line; we are enormously grateful to you.

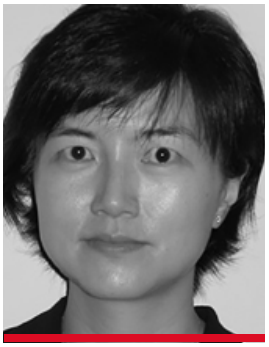
As usual, this issue of *EMJ Nephrology* includes original, peer-reviewed articles of archival value covering research and development topics, which span all areas from acute kidney injury to membranous nephropathy.

My Editor's Pick for this publication is the review by Salvadori et al. titled: 'New Aspects of Pathogenesis and Treatment of Membranous Glomerulopathy After the MENTOR Study.' The major cause of nephritic syndrome in adults, membranous nephropathy has an annual incidence of 1 per 100,000 population. The MENTOR study analysed the effects of rituximab over a 24-month follow-up, as the drug has previously been shown in several trials to induce remission of nephritic syndrome. Salvadori et al. provide a comprehensive analysis of the MENTOR study's results.

Diabetic kidney disease in childhood and adolescence is then discussed by Uwaezuoke and Ayuk, who present the conventional and novel renoprotective strategies that have emerged in recent years. Additionally, the topics of amoxicillin and cefepime during prolonged intermittent renal replacement therapy, ceftriaxone use in a patient with Child–Pugh B cirrhosis and ascites, and risk factors and management challenges in low- and middle-income countries in the treatment of acute kidney injury.

A full European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Virtual Congress 2020 review is also offered to our readers, whether you missed the congress and wish to read the highlights, or you would like to be reminded of the great success of the 57th Congress of ERA-EDTA.

Colleagues, I hope you find values and interests in these pages, and that you are keeping safe and well.



Dr Angela Wang
University of Hong Kong, Hong Kong

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Congress Review

Review of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Virtual Congress 2020

Location: ERA-EDTA Virtual Congress 2020 Review

Date: 6th June-9th June

Citation: EMJ Nephrol. 2020;8[1]:12-24. Congress Review.

CAPITAL of Lombardy, one of the world's four fashion capitals, and unparalleled collector of works by Leonardo da Vinci, Michelangelo, and Caravaggio, Milan was set to offer an alluring backdrop to this year's 57th ERA-EDTA congress. The city was also home to the Italian physician Dr Carlo Urbani who discovered the severe acute respiratory syndrome (SARS) in 2003, the cause of which is a member of the coronavirus family; unwittingly, a coronavirus is the single cause of the shift to the congress' first ever virtual meeting this year.

Congregating not in Milan but in living rooms and houses all over the world, >10,000 delegates were gathered together on ERA-EDTA's virtual platform from 6th–9th June 2020. Attendees were welcomed by 200 speakers in 100 virtual sessions, alongside 1,800 e-posters and 350 virtual presentations. Prof Loreto Gesualdo, President of ERA-EDTA, greeted viewers in the Opening Plenary session, and admitted that "deciding not to give up our annual congress and to turn it into a special digital edition has been an act of courage, as well as a bet." He also paid respect to the country's healthcare workers, "who have been, and are still, in the front-line in the fight against the virus," and explained that the SARS-coronavirus-2 (CoV-2) virus has "forced us to adopt innovative and digital solutions" and "only accelerated a process that was already underway."

The pandemic has put a spotlight on nephrological expertise and highlighted its importance, as early observations have shown that the virus can cause kidney injury, albuminuria, and elevated creatinine levels. Therefore, the programme was subject to last-minute changes to accommodate for topical discussions and collaborations regarding COVID-19, including sessions on acute kidney injury and end-stage kidney disease in severe COVID-19, the particular risk of dialysis patients, and the prognosis for patients with kidney replacement therapy, as well as cytokine storm and the role of haemoperfusion.

Committed to education, science, and networking, the congress delivered an exemplary programme to aid all nephrologists in their daily practice, support and spread top quality scientific knowledge, and facilitate professional alliances. Despite holding an online meeting, ERA-EDTA's Chair of the Scientific Committee Prof Peter Blankestijn made sure this did not have an impact upon the congress' usual content, and attendees were still offered practical courses on renal molecular pathology and fistula imaging, as well as symposia, plenary sessions, and moderated poster sessions.

A great deal of attention in the scientific programme was paid to chronic kidney disease (CKD), and summaries of the Gold Plenary Sessions entitled: 'CKD: two decades of progress and challenges for the future' and 'AKI, CKD, and cancer - the costs of kidney repair', are included in our Congress Review Stories. Abstract summaries are also included in *EMJ Nephrology*, with topics such as mortality in haemodialysis patients in the Persian Gulf cooperation council countries, mepolizumab therapy in eosinophilic granulomatosis with polyangiitis, and the association between cystatin C and arterial stiffness in non-CKD patients. Congress review highlights containing summaries of the congress press releases can also be found within these pages, including updates and research on ANCA-associated vasculitis and the ADVOCATE study, specific kidney proximal tubular injury caused by SARS-CoV-2, and predictors of 5-year mortality in young dialysis patients.

Accumulatively, the 4-day congress left nephrologists with much to discuss, much knowledge gained, and an overwhelming sense of community in these unpreceded times. To turn the face-to-face congress into a successful virtual congress within a few short months was no mean feat, and, in the words of Prof Gesualdo, "I am sure this will be the starting point for change in the field of medical education."

The pandemic has put a spotlight on nephrological expertise and highlighted its importance, as early observations have shown that the virus can cause kidney injury, albuminuria, and elevated creatinine levels.

ERA-EDTA 2020 REVIEWED →

Add-on Belimumab Improves Long-Term Outcomes in Lupus

PROGNOSIS in systemic lupus erythematosus (SLE) is significantly impacted by renal involvement, with better outcomes seen when receiving belimumab as an add-on therapy. Addition of belimumab reduces the risk of renal deterioration or renal events associated with poorer prognosis over the long term.

The American BLISS-LN study of 448 patients with active lupus nephritis conducted a double-blind, placebo-controlled trial to assess the effect of add-on belimumab in patients treated with standard lupus treatment. The standard treatments were either mycophenolate mofetil (MMF) for both induction and maintenance (328 patients), or cyclophosphamide induction followed by azathioprine maintenance (118 patients). Belimumab is a human monoclonal antibody that blocks the activity of B lymphocyte stimulator (BLyS), which is overexpressed in SLE.

After 2 years, add-on belimumab significantly improved primary renal response (43% versus 32% with placebo; p=0.0311), where the composite endpoint was a urine protein creatinine ratio ≤0.7, and estimated glomerular filtration rate ≤20% below pre-flare value or ≥60 mL/min/1.73 m^2, with no rescue therapy required. There were also significantly more patients with a complete renal response with add-on belimumab (30% versus 19.7% with placebo; p=0.0167). The patients receiving add-on belimumab had a 50% reduction in risk of renal events associated with greater risk of poor renal prognosis, compared to placebo.

The study was presented at the ERA–EDTA Virtual Congress on 7th June 2020 congress as a late-breaking clinical trial by Dr Brad Rovin, Division of Nephrology, Ohio State University, Columbus, Ohio, USA. "MMF is already used in many patients. It has been shown to be equivalent to cyclophosphamide in the induction therapy of lupus nephritis [LN], and superior to azathioprine in the maintenance phase. Adding belimumab can further improve the treatment results."

There is a higher mortality risk for patients with renal involvement of their SLE. Improvement in renal disease significantly improves 10-year survival; ongoing study is needed, but belimumab may help to improve this longer-term survival by improving renal outcomes.

"The patients receiving add-on belimumab had a 50% reduction in risk of renal events associated with greater risk of poor renal prognosis, compared to placebo."

Majority of Hospitalised COVID-19 Cases Have Renal Injury

PATTERNS of renal injury in patients hospitalised with COVID-19 reflect Fanconi syndrome in the majority of cases. A French study assessed patterns of renal injury and determined that the effect of the SARS-CoV-2 virus on kidney function may be a potential prognostic marker for the course of the illness. This was announced in a press release at the ERA-EDTA Virtual Congress on 8th June 2020.

Up to 80% of patients hospitalised with COVID-19 display acute kidney injury, with evidence that the virus directly affects proximal renal tubular cells. These cells express angiotensin-converting enzyme-2 (ACE-2) cell surface receptors, the avenue by which SARS-CoV-2 invades affected patients. Injury to the proximal tubules can lead to Fanconi syndrome, where impairment of their usual function to reabsorb glucose, bicarbonate, potassium, phosphate, and amino acids and proteins into the bloodstream leads to loss of these substances in the urine.

The study in Nancy, France examined data from 42 hospitalised patients with COVID-19, for a mean follow-up period of 19.7 (±12) days. 75% of the patients met criteria for Fanconi syndrome (≥2 tubular abnormalities), with a greater proportion of patients in intensive care affected (96% versus 62%). Fanconi syndrome preceded severe acute kidney injury in 88% of the patients studied. Seven of the 42 patients studied died from their illness, but for those patients who clinically improved, this improvement was matched by a reversal of the renal Fanconi syndrome.

"The proximal renal tubules seem to be a specific target of SARS-CoV-2 because of their ACE-2 receptors, and we see verification of our hypothesis that this is the cause of the tubular disorders and AKI that so many of our COVID-19 patients have developed," outlined Dr Raphaël Kormann, University of Lorraine, Vandoeuvre-lès-Nancy, France and first author of the study. "This should be subjected to further systematic investigation – with regard to the significance of Fanconi syndrome as a biomarker of tubular cell infection and as a potential predictive prognostic marker."

"The proximal renal tubules seem to be a specific target of SARS-CoV-2 because of their ACE2 receptors, and we see verification of our hypothesis that this is the cause of the tubular disorders and AKI"

The RITAZAREM Trial: ANCA-Associated Vasculitis Remission Success

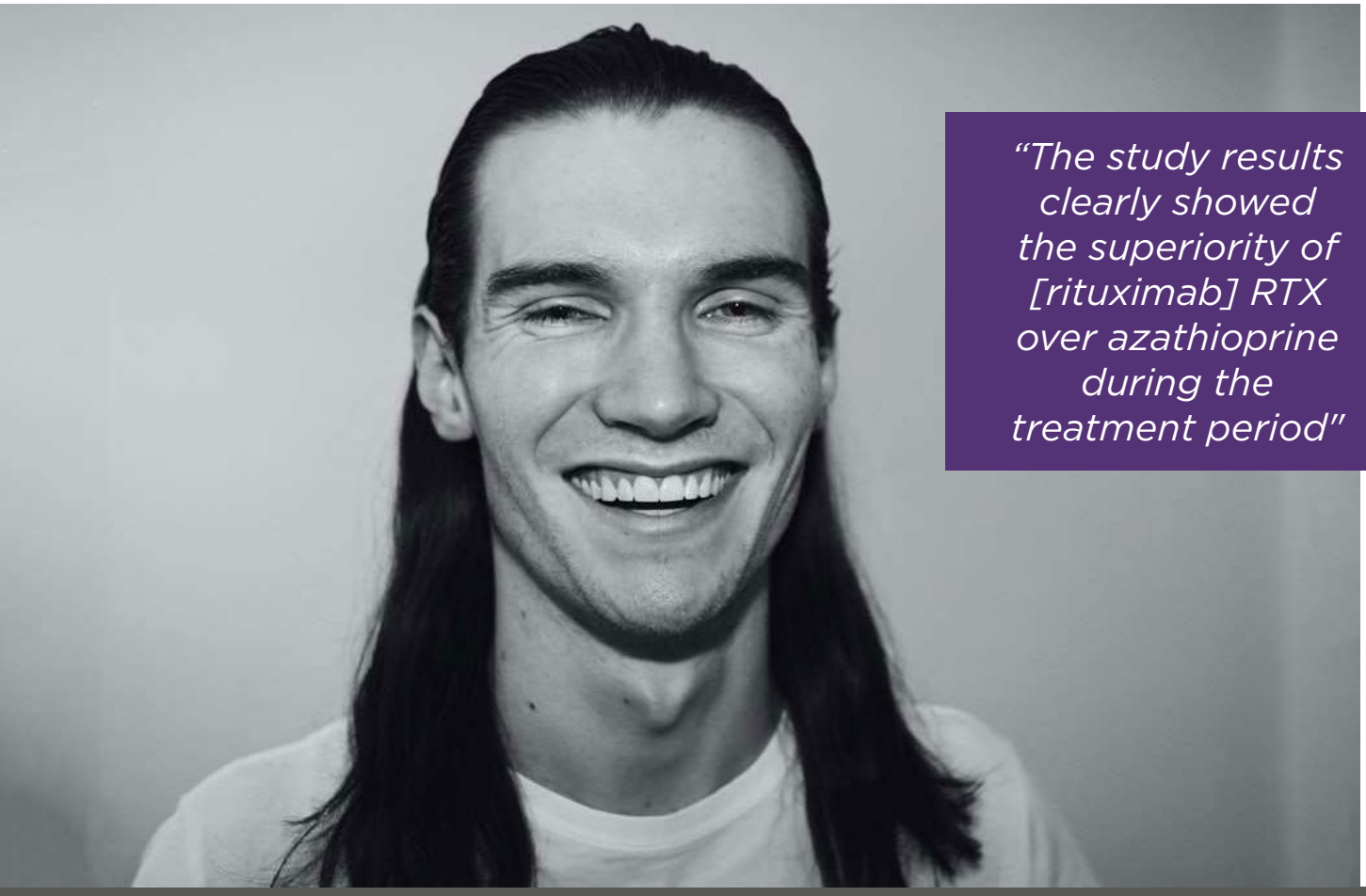
RECURRENT episodes of ANCA-associated vasculitis (AAV), an autoimmune disease involving vascular inflammation, have been successfully reduced with the treatment of the monoclonal antibody rituximab. Results from the RITAZAREM study, which trialled rituximab and glucocorticoids for preventing relapse of AAV, were announced in a press release at the ERA-EDTA virtual congress on 7th June 2020.

An international, multicentre, randomised controlled trial, the RITAZAREM study assessed relapse of AAV in patients after remission induction with fixed interval repeated rituximab or daily oral azathioprine. Patients were followed-up for at least 24 months, the median age was 59, and the median duration of disease was 5.3 years. After 4 months, 170 patients had achieved remission and these patients were randomised equally to receive either 1,000 mg of rituximab every 4 months (for a total of 5 times) or daily doses of azathioprine at 2 mg/kg.

20 months after randomisation, 11 of the 85 patients in the rituximab group had relapsed, though only two were classified as severe "major relapses." Conversely, 32 of the 85 in the azathioprine group presented with AAV relapse, of which 12 were classed as severe major relapses. Regarding severe adverse events, hypogammaglobulinaemia and infection occurred in 29% and 49% of patients in the rituximab group, respectively, compared to 25% and 48% of patients in the azathioprine group, respectively.

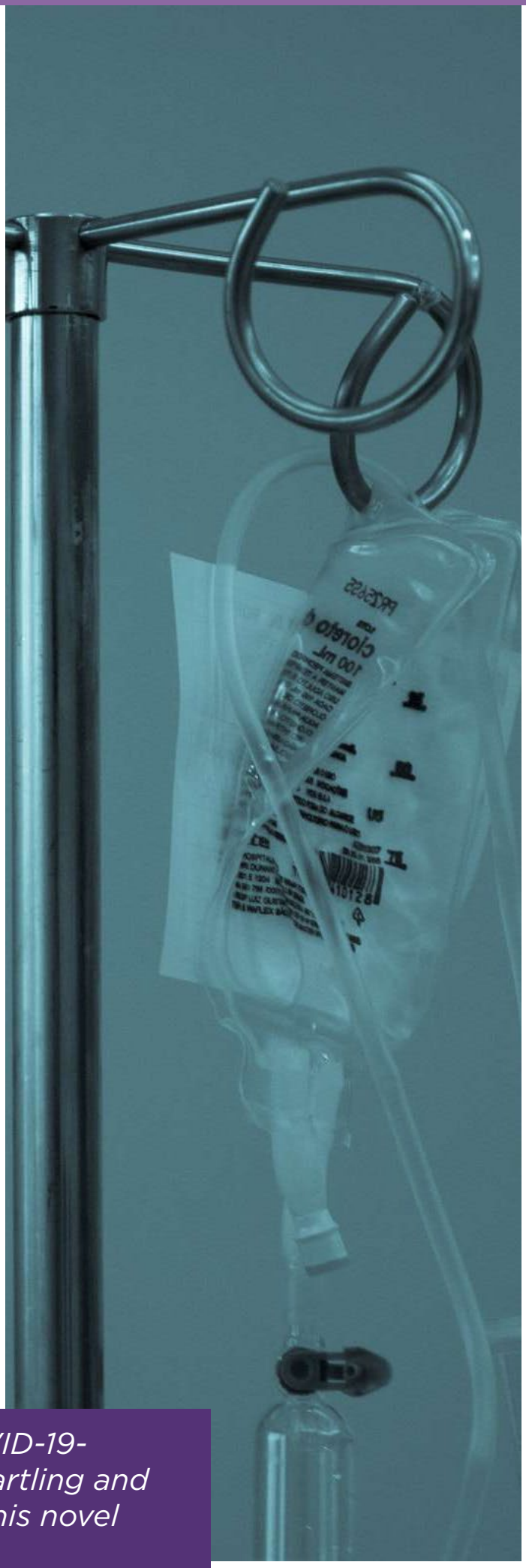
Dr Rona Smith from Cambridge, UK and the first author of the study, summed up the results with: "The study results clearly showed the superiority of [rituximab] RTX over azathioprine during the treatment period, without our finding any evidence that the substance has a worse risk profile – on the contrary."

AAV can be a life-threatening disease and it is therefore imperative to prevent relapses. Dr Smith hopes that the results of the study will lead to future research and guidelines being updated to indicate which patient groups would benefit most from the therapy.



"The study results clearly showed the superiority of [rituximab] RTX over azathioprine during the treatment period"

Study Finds COVID-19-Associated Acute Kidney Injury Prevalence of 80%



THE FIRST of its kind, a study characterising the occurrence of COVID-19-associated acute kidney injury (AKI) has recorded the incidence, severity, clinical presentation, and short-term outcomes in a large number of critically ill patients in France.

This was announced in a press release at the ERA-EDTA virtual congress on 8th June 2020.

71 patients with severe lung injury and COVID-19 participated in the study, which took place over 6 weeks in March and April 2020. On admission, patients presented with an average basal serum creatinine level of 69±21 µmol/L and eight patients were subsequently diagnosed with AKI, as per the Kidney Disease Improving Global Outcomes (KDIGO) criteria.

Over the course of the follow-up, which was a median of 17 days, AKI developed in 57 of the 71 patients (80%): 35% were at Stage 1, 35% at Stage 2, and 30% at Stage 3. Ten of the 57 required renal replacement therapy (dialysis) and two died within the first 72 hours. Seven days after AKI development, of the remaining 55 patients there were six patients still on dialysis and nine had serum creatinine >200 µmol/, though renal recovery had occurred in 28%. 14 days post-AKI diagnosis the renal recovery increased to 52%.

The study is in agreement with reports from China and the USA, where AKI has been diagnosed in up to 15% and 20%, respectively, of intensive care patients with COVID-19. Dr Sébastien Rubin, of Bordeaux University Hospital, Bordeaux, France and an author of the study, commented: "This high rate of COVID-19-associated AKI cases is startling and shows how renotropic this novel virus can be."

"This high rate of COVID-19-associated AKI cases is startling and shows how renotropic this novel virus can be."

Risk Factors for High Haemodialysis Mortality Identified

"The variety of retained risk factors probably highlights the importance of multimodal intervention strategies in addition to adequate HD treatment,"

HAEMODIALYSIS (HD) is an essential lifeline for those with severe kidney disease, but the mortality rates associated with its use are highly concerning. For the first time, an analysis into the risk factors associated with mortality in patients on chronic HD treatment since childhood has been completed. The results from this analysis were presented at ERA–EDTA 2020 and announced in a press release from the congress dated the 9th June.

Although the percentage of children and young people with severe kidney damage and requiring renal replacement therapy is low (2%), the condition is life-changing for these individuals. Without transplantation, they are dependent on dialysis, a treatment that is carried out typically three times a week for 4 hours each time, resulting in the possibility of a 'normal' childhood being reduced significantly. In addition to this diminished quality of life, the mortality risk of children on dialysis treatment is 55-fold higher when compared with healthy children. This highlights the need to characterise the risk factors associated with this staggering mortality risk, especially those that are modifiable.

In the analysis, the significance of 105 variables relating to demographics, HD treatment, and laboratory measurements as predictors of 5-year mortality were evaluated in a cohort of 363 patients who were <30 years old and had started dialysis therapy as a child (<19 years old). A flexible machine learning approach (random forest) was utilised.

The results identified two important risk factors: low albumin and elevated lactate dehydrogenase. Other factors that showed an importance in mortality risk included a reduced red blood cell count, haemoglobin level, albumin/globulin ratio, ultrafiltration rate, z-score weight for age, or inadequate dialysis dose (single pool Kt/V below target). By identifying these risk factors, a more encompassing approach to dialysis therapy can be taken to address these risk factors and reduce the mortality risk associated with it.

"The variety of retained risk factors probably highlights the importance of multimodal intervention strategies in addition to adequate HD treatment," explained corresponding author Dr Verena Gotta, University Children's Hospital Basel, Basel, Switzerland.

Positive Results for Primary Hyperoxaluria Type 1 RNA Interference Therapy

RNA INTERFERENCE (RNAi) therapeutics tap into the natural biological gene silencing mechanism and are being utilised for treatment of a plethora of diseases, many of which are rare diseases, including lumasiran (Alnylam Pharmaceuticals Inc., Cambridge, Massachusetts, USA) for primary hyperoxaluria Type 1 (PH1). In a press release dated 7th June from ERA–EDTA 2020, the positive results from a Phase III study of lumasiran were announced.

PH1 is a rare disorder that often leaves many patients requiring dialysis from an early age. This autosomal recessive inherited disorder is caused by numerous defects in the enzyme alanine-glyoxylate aminotransferase which causes overproduction of oxalate in the liver. Oxalate is excreted in the urine, meaning that overproduction can manifest symptoms such as recurrent kidney stones, renal calcification, and kidney injury, which can lead to kidney failure. Although there are a handful of treatment approaches targeting oxalate overproduction and the associated outcomes, currently no treatment that addresses the cause of the disease is available.

In the Phase III, randomised, double-blind, placebo-controlled study, 39 patients with a confirmed PH1 diagnosis (age ≥6 years, 24-hour urinary oxalate ≥0.70 mmol/24 hour/1.73 m^2, estimated glomerular filtration rate ≥30 mL/min/1.73 m^2) either received placebo or the investigational drug lumasiran (randomised 2:1) once a month for 3 months followed by one dose every 3 months. The least square mean change from baseline after 6 months for 24 hour urinary oxalate excretion was 65.4% with lumasiran and -11.8% with placebo (p=1.7x10-14). Additionally, 84% and 52% of patients on lumasiran achieved near-normalisation or normalisation of urinary oxalate, respectively, compared with 0% of those treated with placebo. No severe or serious adverse events associated with lumasiran were reported, and the most frequent adverse event was injection-site reactions, which were mild and transient.

"Lumasiran resulted in rapid, sustained, and statistically significant reductions in urinary and plasma oxalate levels and had an encouraging safety profile," concluded lead author Dr Sander Garrelfs, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands. It was added that prevention of long-term injury to the kidneys needs to be demonstrated, which would provide evidence that this could be the long-desired treatment that would negate the need for dialysis in those with PH1.

"Lumasiran resulted in rapid, sustained, and statistically significant reductions in urinary and plasma oxalate levels and had an encouraging safety profile"

Empagliflozin Induced Estimated Glomerular Filtration Dip

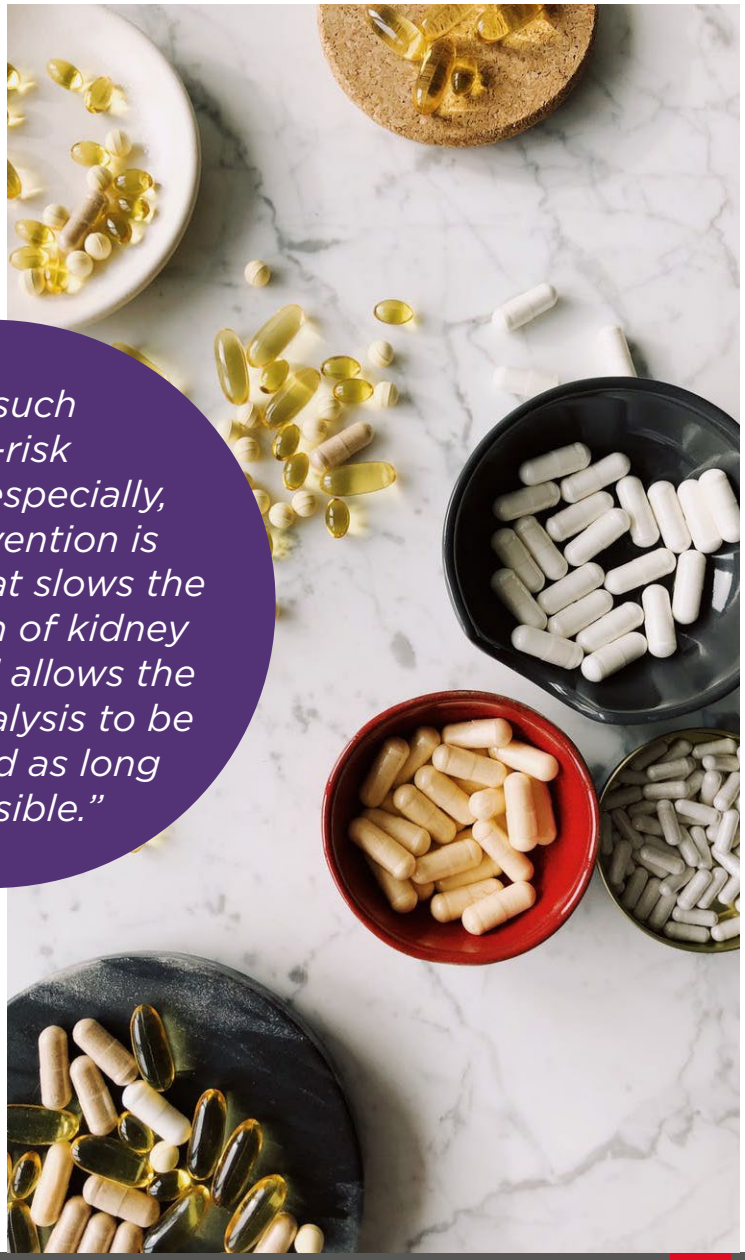
EMPAGLIFLOZIN has been shown to induce an initial 'dip' in estimated glomerular filtration rate (eGFR) in patients on diuretic therapy and/or belonging to a higher Kidney Disease Improving Global Outcomes (KDIGO) risk category. These findings were presented during a press release at the ERA-EDTA Virtual Congress on 7th June 2020.

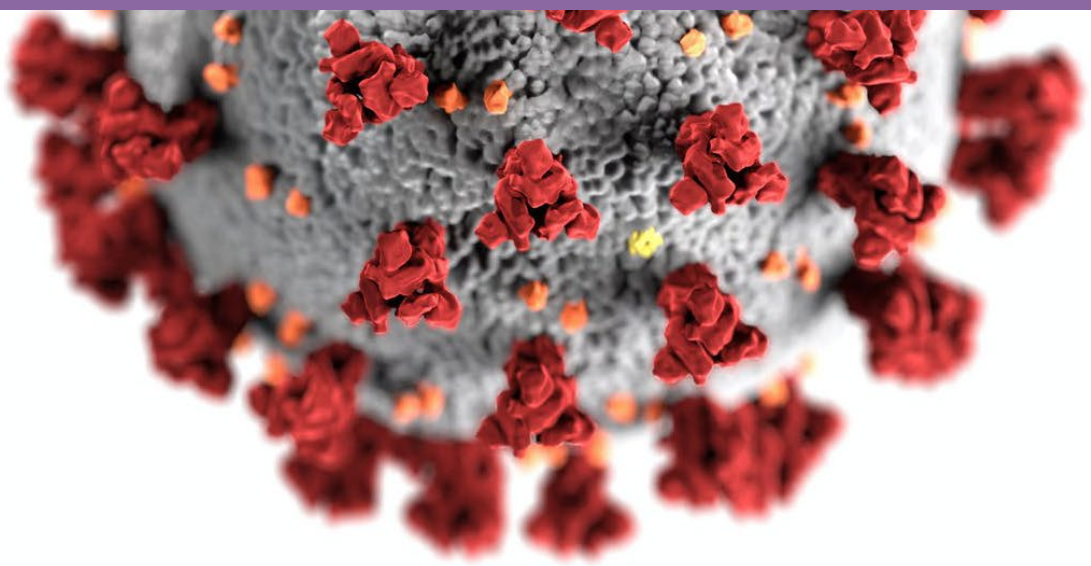
The sodium/glucose cotransporter-2 (SGLT2) inhibitor empagliflozin reduces the progression of chronic kidney disease in Type 2 diabetes mellitus patients with cardiovascular disease, by lowering intraglomerular pressure. However, the observed initial reduction in GFR after introducing an SGLT2 inhibitor has raised questions of uncertainty. Administration of empagliflozin causes an increase in tubular flow rate leading to reduced reabsorption of glucose and sodium from the glomerular filtrate. This then triggers the tubuloglomerular feedback mechanism in the kidneys which ultimately results in a decrease in GFR.

However, termination of empagliflozin stops this feedback mechanism and the GFR increases again. For this reason, Dr Bettina J. Kraus and her team at the University Hospital Würzburg, Germany, investigated whether the initial GFR dip post empagliflozin initiation was affected by baseline characteristics and/or might impact the empagliflozin induced risk reduction in kidney outcomes. Data from the EMPA-REG OUTCOME trial, a study in which Type 2 diabetes mellitus patients with cardiovascular disease had been treated (1:1:1) with empagliflozin 10 mg, 25 mg, or placebo, was analysed to identify patients who had experienced an initial eGFR dip of >10% from baseline at Week 4 after treatment initiation. Results showed that 28% of patients on empagliflozin experienced an eGFR dip and diuretic use and/or a higher KDIGO risk category at baseline correlated with an initial eGFR dip of >10% in empagliflozin, compared to placebo treatment. Furthermore, an eGFR dip >10% had no major impact on empagliflozin induced risk reduction and rates of kidney adverse events, which was consistent across the subgroups.

Prof Christoph Wanner, ERA-EDTA President-Elect, noted that these findings were more likely in those taking diuretics and/or had a more advanced stage of chronic kidney disease. However, he concluded: "For such high-risk patients, especially, any intervention is welcome that slows the progression of kidney disease and allows the need for dialysis to be postponed as long as possible."

"For such high-risk patients, especially, any intervention is welcome that slows the progression of kidney disease and allows the need for dialysis to be postponed as long as possible."





Genetic Background of Kidney Injury and SARS-CoV-2

GENETIC analysis has revealed a link to SARS-CoV-2 associated kidney injury as exemplified in findings presented during a press release at the ERA-EDTA virtual congress on 8th June 2020.

According to current studies, as many as 80% of critically ill COVID-19 patients are hospitalised with SARS-CoV-2-associated kidney injury. In half of these cases, proteinuria and haematuria are present and renal tissue examination of deceased patients revealed injury to glomeruli, podocytes, and tubular cells. In this study, two COVID-19 patients (>50 years old) presented with injury to renal structures. Both were known to have high blood pressure, and one had cardiac insufficiency while the other had hepatitis B. Kidney biopsies revealed capillary collapse in the glomeruli, podocyte swelling, glomerular deposits of immunoglobulins (IgM and complement component C3), tubule injury, partial tubule atrophy and necrosis, while inflammatory cells (monocytes, macrophages) were also present.

SARS-CoV-2 was not detected in blood, urine, or kidney tissue samples despite highly sensitive real-time PCR testing and positive virus detection from the throat swab. Molecular genetic analysis showed variants of the *APOL1* gene (homozygous G1 polymorphism and G1/G2 heterozygosity), which is associated with increased risk of kidney disease. Corresponding author Prof Ziad Massy, Hôpital Universitaire Ambroise Paré, Boulogne Billancourt, France, stated that it is probable that the injury was not caused by direct viral infection but rather by a SARS-CoV-2-induced inflammatory reaction. He added: "Particularly in the context of genetic *APOL1* risk variants, SARS-CoV-2 might have triggered the 'collapsing focal segmental glomerulosclerosis' in accordance with the 'second hit' hypothesis."

"Particularly in the context of genetic APOL1 risk variants, SARS-CoV-2 might have triggered the 'collapsing focal segmental glomerulosclerosis' in accordance with the 'second hit' hypothesis."

According to Prof Alberto Ortiz, Autonomous University of Madrid, Madrid, Spain, because SARS-CoV-2 has spread across the world, SARS-CoV-2-induced kidney injury will be most prevalent in regions where the *APOL1* gene variants G1/G2 are more common. He further highlighted that because of greater rates of expression of *APOL1* risk variants in people of African-American descent, lung problems, renal complications, and associated conditions can be particularly expected in the USA, among other countries.

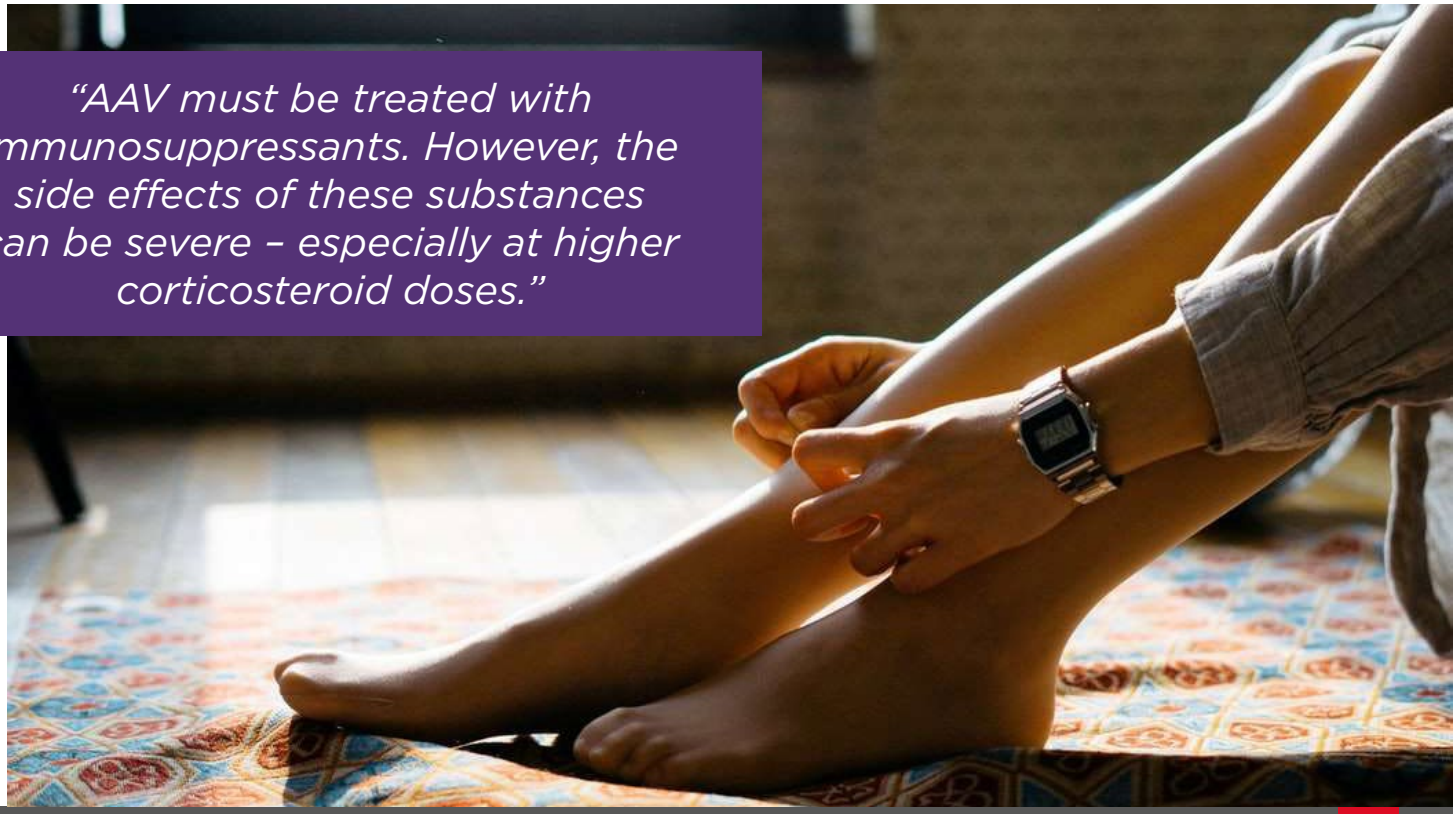
The ADVOCATE Study Showed the Benefits of Avacopan in Rare Autoimmune Disease

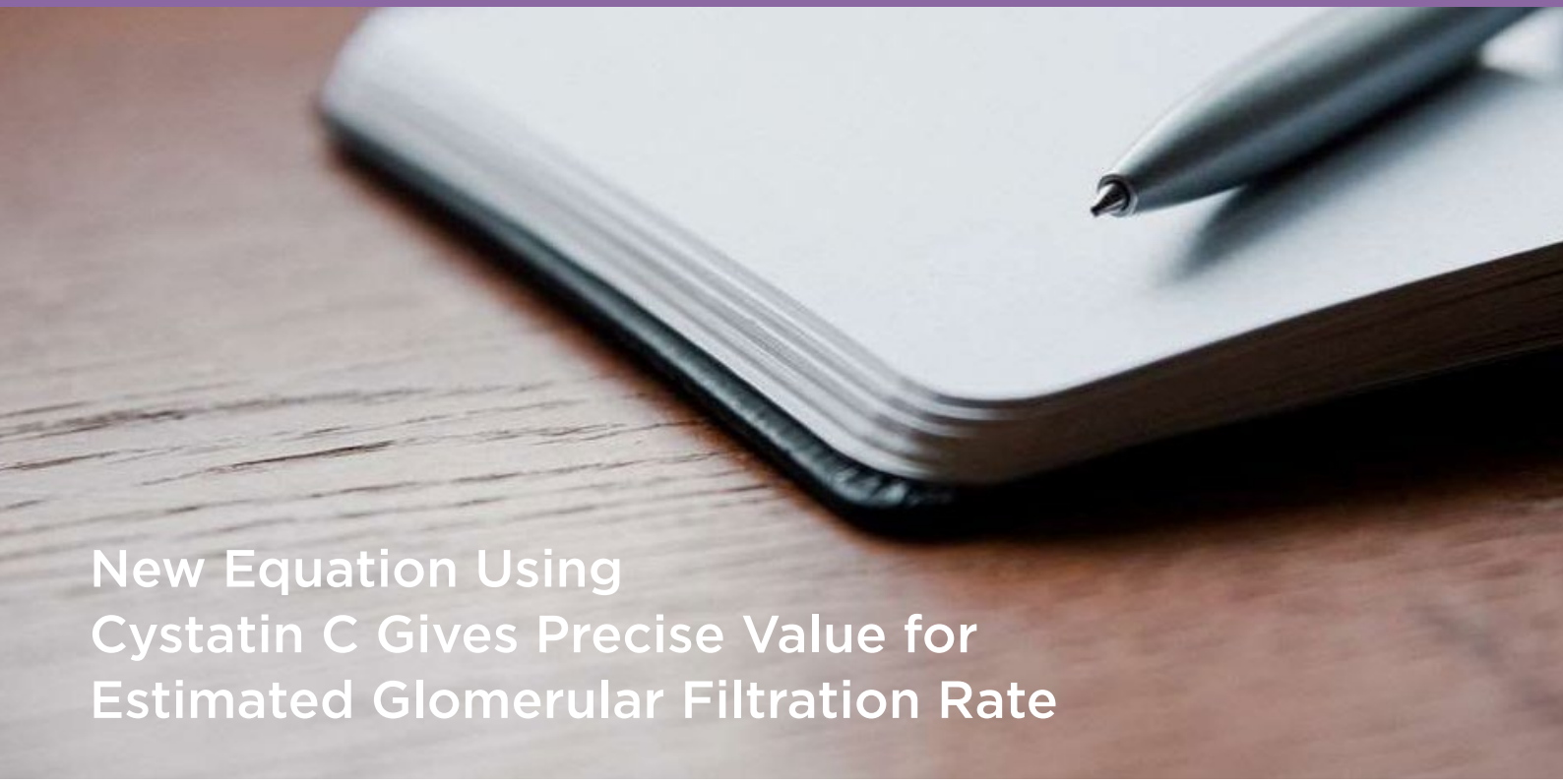
AVACOPAN is an orally administered drug which has been shown to be beneficial in achieving remission in ANCA-associated vasculitis (AAV). This is according to findings from the ADVOCATE study presented at the 57th ERA-EDTA Virtual Congress 2020 in a press release dated 7th June 2020. The ADVOCATE study was a Phase III trial spanning 52 weeks to assess the efficacy and safety of avacopan, formerly CCX168, in the treatment of AAV.

AAV is a systemic disease involving the formation of autoantibodies causing inflammation of small blood vessels and may result in severe injury of the kidneys, potentially causing harm to the lungs, upper respiratory tract, heart, skin, and nervous system, even causing death. Modern immunosuppression therapy, such as rituximab, is available and works by blocking parts of the immune system, unlike corticosteroids which work by blocking the entire immune system. This can, however, lead to infection. Prof David Jayne, Cambridge, UK, explained: "AAV must be treated with immunosuppressants. However, the side effects of these substances can be severe – especially at higher corticosteroid doses." Complement component C5a plays a role in the pathogenesis of AAV. Avacopan is a novel orally selective C5aR antagonist which has been investigated in two clinical Phase II trials to show its effect on the inhibition of activation of immune cells induced by C5a, reducing inflammation.

Patients enrolled in the trial (n=330) were randomised 1:1 to receive prednisone (n=164) or avacopan (n=166), combined with either cyclophosphamide then azathioprine, or rituximab. The patients were confirmed to have achieved sustained remission if they did not relapse between Week 26 and 52. At Week 26, remission was present in 72.3% of patients in the avacopan group compared to 70.1% in the prednisone group. At Week 52, 65.7% of patients were in remission in the avacopan group compared to 54.9% in the prednisolone group. Dr Maria Jose Soler Romeo, Chair of the Paper Selection Committee of the 2020 ERA-EDTA Congress, from Barcelona, Spain, commented on the significance of research such as this: "This is so important, because potentially life-threatening diseases such as AAV often require treatments that themselves pose risks – new immunosuppressive, specifically targeting substances are therefore urgently needed in order to improve therapies further and avoid the high dose steroids side effects."

"AAV must be treated with immunosuppressants. However, the side effects of these substances can be severe – especially at higher corticosteroid doses."





New Equation Using Cystatin C Gives Precise Value for Estimated Glomerular Filtration Rate

GLOMERULAR filtration rate (GFR) can be accurately and precisely calculated with new methods. This is according to a study presented at the 57th ERA-EDTA Virtual Congress 2020 in a press release dated 9th June 2020.

GFR is measured by the volume of blood filtered per minute by the kidneys (mL/min/1.73 m^2) and is an indicator of renal function calculated using the laboratory parameter serum creatinine (estimated GFR [eGFR]). Creatinine is a nonprotein nitrogenous substance and its production is a breakdown product of muscle metabolism excreted in the urine affected by age, sex, and muscle mass. Impaired kidney function is apparent when eGFR decreases and serum creatinine increases; the significance of creatinine-based eGFR (eGFRcr) is a prevalent topic in the nephrology field.

Cystatin C (Cys-C) is an endogenous protein released by most body cells' metabolism and according to this new study could be a more appropriate maker of eGFR than serum creatinine. The volume of Cys-C is independent of age, sex, and muscle mass, and potential confounding factors in cystatin-based eGFR estimation (eGFRcys) include inflammation, cancer, thyroid dysfunction, or steroid therapy. Furthermore, Cys-C is not universally available in laboratories and proves to be a more expensive test than creatinine.

A new equation involving both eGFRcr and eGFRcys has been formulated (eGFRcr-cys) and provides what may be the most accurate way of determining a true value for eGFR. As early as possible in the disease course, it is paramount to establish kidney function as precisely as possible to aid with drug dosage, study enrollment, and in cases of kidney donor requirement. Significantly, the new equation not only gives an accurate value of true GFR in early kidney diseases, but also in the later disease stages. The authors stated that the reason for this may be attributable to the confounding factors being independent of each other and playing a less significant role in the new equation.

This revelation may prove to be the new basis upon which eGFR is calculated, exclaimed Prof Denis Fouque, Editor-in-Chief of Nephrology Dialysis Transplantation, from Lyon, France: "Accurate measurement is needed for the early detection of chronic kidney disease [CKD]. The ERA-EDTA recommends that eGFRcys and eGFRcr-cys be implemented as the new standard."

"Accurate measurement is needed for the early detection of CKD. The ERA-EDTA recommends that eGFRcys and eGFRcr-cys be implemented as the new standard."

The Hidden Cost of Repair: Cancer Risk Following Kidney Injury

Katherine Colvin
Editorial Assistant

Citation: EMJ Nephrol. 2020;8[1]:25-27.

INJURY to renal cells can lead to the development of papillary renal cell carcinoma (RCC) via the kidney's own repair mechanisms. Leading nephrologist and renal scientist Prof Paola Romagnani, University of Florence and Anna Meyer University Children's Hospital, Florence, Italy, gave a 'Gold Plenary' presentation at the European Renal Association–European Dialysis and Transplant Association (ERA–EDTA) Virtual Congress 2020, outlining the past 15 years of renal science and experimental methods that have shaped understanding of kidney repair mechanisms. The yearly death rate of acute kidney injury (AKI) is greater than the yearly death rates of prostate cancer, breast cancer, heart failure, and diabetes combined. The role of renal progenitor cells in both glomerular and tubular repair improves survival following AKI, however, these repair processes themselves increase patients' risk of developing papillary RCC.

GLOMERULAR REPAIR MECHANISMS

The repair mechanism of renal glomeruli following AKI has been studied in depth, to reveal a regenerative capability beyond hypertrophy. This regenerative capability is accounted for by the discovery of resident renal cells with the functional properties of stem cells that can undergo self-renewal and differentiation into different nephron epithelial cell types. These stem cell-like cells have been named renal progenitors. Glomerular podocytes, critical components of the glomerular filtration barrier lining the capillaries, are unable to regenerate, likely because of their complex cytoskeleton structure. This structure affords the ability to withstand filtration pressures, but undergoing mitosis and cell division would disrupt this cytoskeleton and compromise function. As a result, podocytes can only undergo DNA synthesis and hypertrophy to increase renal function.

Renal progenitors are capable of differentiation into podocytes following renal injury, as demonstrated in an experimental *in vivo* model where cell labelling for the *PAX2* marker traced the duplication and differentiation of these progenitor cells into new, replacement podocytes, displaying the full podocyte phenotype as revealed by step microscopy. Retinoic acid promotes the differentiation of renal progenitors to podocytes, but the presence of excess albumin can lead to loss of retinoic acid in the urine, impairing progenitor differentiation into podocytes and leading to glomerulosclerosis and chronic kidney disease. Mouse models supported this process, where mice with remission of proteinuria were found to have greater numbers of integrated podocytes following kidney

injury compared to those with persistent, severe proteinuria and progression, which Prof Romagnani suggested that: "podocyte regeneration by renal progenitors can determine disease outcome."

TUBULAR REPAIR MECHANISMS

Renal tubules have long been thought to have a greater regenerative capability than glomeruli, with only recent re-evaluation of the current scientific understanding that apparent tubular recovery matches clinical recovery from AKI. The fact that all patients are at risk of developing chronic kidney disease (CKD) over the longer term following an episode of AKI, with risk being proportional to the severity of the AKI, suggests what Prof Romagnani termed an "inefficient repair response to AKI." Following injury, only a small subset of tubular cells regenerates; these regenerated cells arise from renal progenitor cells, as demonstrated by mouse studies by Prof Romagnani, in which labelling of tubular epithelial cells traced the repair of the renal tubules following AKI. The repair behaviours of renal tubules were hypothesised by Prof Romagnani's team to follow two mechanisms: "renal progenitors proliferate, while other tubular cells endocycle." The endocycle is a limited cell cycle where mitosis is not completed and cells hypertrophy; the majority of differentiated tubular epithelial cells undergoing endoreplication were located in the S2 segment in the cell-labelling study. Endocycling and hypertrophy improves survival in AKI, as an absence of endocycling by renal tubular cells leads to hyperkalaemia; however, excessive endocycling is profibrotic and promotes the development of CKD.

"The yearly death rate of acute kidney injury (AKI) is greater than the yearly death rates of prostate cancer, breast cancer, heart failure, and diabetes combined."

"Prof Romagnani's work to elucidate the detail of these repair pathways and their clinical outcomes helps clinicians to appreciate the importance of avoiding kidney injury during any illness or treatment..."

A further mechanism for regeneration of renal tubules following AKI is the overactivation of the Notch pathway. The notch pathway plays a crucial role in the promotion of progenitor cell proliferation, both of renal progenitors and in other stem cell systems. Prof Romagnani's team undertook studies in mice where they induced overexpression of the Notch pathway. In these mice, renal tumours developed following the classical pathway of progression from adenoma to carcinoma, which were found to be of the papillary histotype. Cell labelling of these tumours showed they were composed of thousands of cells from a single cellular origin; that is, the tumours were in fact of monoclonal origin.

RISK OF PAPILLARY RENAL CELL CARCINOMA

Papillary RCC represents 15% of all RCC and occurs more frequently in patients with autosomal-dominant polycystic kidney disease, end-stage kidney disease, or renal transplant. This affiliation with other kidney disorders suggests a role for AKI directly contributing to the development of papillary adenomas, with some of these adenomas transforming to RCC. Studying the clonal origin of papillary RCC tumours suggests that the tumours are derived from a cell subset with a high proliferative capacity, as is seen in renal progenitor cells. Cell-labelling studies of mice reveal that both notch-induced and AKI-induced papillary RCC are derived from renal progenitors, with notch-induced changes still reflective of AKI, as notch overexpression can be triggered by AKI as a repair pathway. Notch overexpression induces tumour-like growth of human renal progenitors, as seen in a tubule-on-a-chip study.

These findings, that AKI directly contributes to the development of papillary RCC, are supported by two patient cohort studies. A Danish registry of patients with AKI found that the incidence ratio of RCC following AKI was 4.4 (95% confidence interval: 1.7–9.0), whilst a study in Florence, Italy found that in a cohort of patients with RCC the incidence ratio of a previous AKI episode was 3.2 (95% confidence interval: 2.6–4.1). This Italian study, combined with an Italian Society of Urology (SIU) multicentre study, then performed a further multivariable analysis of RCC cases of the papillary histotype, using age, sex, and presence of CKD or diabetes as covariates, and found that AKI was the most significant risk factor for development of papillary RCC. The Italian study also analysed patients with RCC undergoing tumour removal surgery and found that those patients who experienced an AKI with their surgery admission had an increased risk of tumour relapse. These different analyses each demonstrate a direct link between AKI and the development of papillary RCC.

CONCLUSION

A clearer understanding of the processes of renal repair has led to a better appreciation of long-term risk for patients following AKI, for both CKD and papillary RCC. It may be that targeted interventions to promote repair mechanisms, such as increased expression of the Notch pathway, may be utilised for future management of kidney injury, however there is a clear need to balance this with long-term CKD risk. Prof Romagnani's work to elucidate the detail of these repair pathways and their clinical outcomes helps clinicians to appreciate the importance of avoiding kidney injury during any illness or treatment, and outlines a need to monitor patients following kidney injury over the longer term for the development of papillary RCC.

During the ERA–EDTA 2020 Virtual Congress, Prof Romagnani received the ERA–EDTA Award for Outstanding Basic Science Contributions to Nephrology.

Chronic Kidney Disease Classification: Past, Present, and Future

Lenos Archer-Diaby
Editorial Assistant

Citation: EMJ Nephrol. 2020;8[1]:28-30.

CHRONIC kidney disease (CKD), a long-term condition resulting in the gradual loss of kidney function, is surrounded by debate regarding validity of observations and definitions of terminology and classifications. This subject drove the "Chronic Kidney Disease: Two Decades of Progress and Challenges for The Future" session held on the 7th June during the ERA-EDTA Virtual Congress 2020.

HISTORY

The session was hosted by honorary ERA-EDTA member Prof Andrew Levey, Tufts Medical Center, Boston, Massachusetts, USA, a widely recognised authority on clinical practice guidelines in CKD, who showcased the evolution of our understanding of the disease.

Prof Levey started by providing a history of the advances made in the field of CKD management and treatment. This began in 1886, when Max Jaffe developed an assay for creatinine concentration determination; it is one of the most commonly used assays in clinical laboratories today.

Following this, it was Dr Homer Smith who, in 1935, discovered that inulin fulfils the necessary criteria for an ideal filtration marker to measure clearance. Prof Levey himself was the Principal Nephrologist Co-investigator for the Modification of Diet and Renal Disease (MDRD) Study, the largest randomised clinical trial to test the hypothesis that protein restrictions slow the progression of renal disease. The results of this study, presented in 1994, failed to demonstrate a beneficial effect of protein restriction.

This led to the 1999 MDRD Study equation aiming to estimate glomerular filtration rate from serum creatinine, which ultimately transformed clinical evaluation of kidney function and led to the subsequent founding of the CKD-EPI equation based on creatinine, cystatin C, and other filtration markers. Other important breakthroughs in the field include Richard Bright's discovery of the association between total urine protein and oedema and CKD as observed in post-mortem studies, and Hermann Senator's studies of urine albuminuria, which disproved the then held notion that albuminuria was a definitive sign of CKD.

Prof Levey then described further observations from various studies and noted that although recognition of these observations about kidney disease measures were beneficial, translating them into routine clinical practice required standardisation of laboratory methods.

GUIDELINES AND CLASSIFICATION

CKD was first defined and classified in the National Kidney Federation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines

of 2002, which were updated in 2012 by the Kidney Disease Improving Global Outcomes (KDIGO). The guidelines aimed to provide a conceptual principle for CKD with kidney failure as the end stage. CKD was defined as displaying markers for kidney damage or GFR <60, while kidney failure was defined as GFR <15 or requiring treatment by dialysis for a duration greater than 3 months.

However, following controversies regarding the definition, classification, and prognosis of CKD, a major impetus for the 2012 guidelines, KDIGO stated that the classification should revolve around patient prognosis. The 2009 KDIGO Chronic Kidney Disease: Definition, Classification and Prognosis Conference reached a consensus on revisions to the classification of CKD based on prognosis but did not propose to change the definition of CKD. As a result, the classification was changed from five stages by KDOQI to six GFR categories and three albuminuria categories by KDIGO. Furthermore, GFR, albuminuria, and cause of disease were emphasised as part of the classification.

RISK FACTORS FOR CARDIOVASCULAR DISEASE

Although only added to the classification in 2012, these risk factors had been noted far earlier. As early as 1974, a study observed accelerated sclerosis among patients treated with prolonged maintenance haemodialysis. Furthermore, in 1998 the NKF Task Force on Cardiovascular Disease, led by Prof Levey, found evidence for kidney failure leading to cardiovascular death, but also showed decreased GFR as well as albuminuria and proteinuria in earlier stages of CKD.

A 2010 study found that lower estimated glomerular filtration rate (eGFR) and albuminuria are independent risk factors for all-cause and cardiovascular mortality in the general population. Similar findings were reported in other cardiovascular disease outcomes including coronary heart disease, stroke, peripheral artery disease, and leg amputation. Recently, in 2017, the Global Burden of Disease study (GBD) and Chronic Kidney Disease Prognosis Consortium (CKD-PC) estimated global cardiovascular and renal outcomes of reduced GFR and found that in 2013 reduced GFR was associated with 4% of the deaths worldwide (2.2 million), and more than half were cardiovascular deaths (1.0 million) compared to end-stage renal disease (0.9 million).

"...although recognition of these observations about kidney disease measures were beneficial, translating them into routine clinical practice required standardisation of laboratory methods"

Following the 2009 conference, controversies persisted regarding the application of GFR and albuminuria thresholds to different risk groups. Therefore, the CKD-PC proposed the following question: "Are the eGFR and albuminuria risk thresholds for the CKD definition consistent across subgroups defined by hypertension, diabetes, age, gender, and ethnicity?"

Using 46 cohorts, the CKD-PC published a series of papers to address this question, which showed a higher absolute risk in high-risk subgroups and a similar, or higher, relative risk in low-risk subgroups. These findings indicate that both lower eGFR and higher albuminuria are important in both low-risk and high-risk groups. Therefore, lower eGFR and higher albuminuria cannot be considered 'normal' in any subgroup including older age.

CHRONIC KIDNEY DISEASE CLINICAL ENDPOINT

For many years, the number of randomised controlled trials in kidney disease has lagged behind other specialties. This is in part because it is harder to conduct clinical trials in kidney disease, because the hard-clinical endpoint of kidney failure (GFR <15) occurs many years after the onset of the disease. GFR decline occurs before the onset of kidney failure; proteinuria or albuminuria arise before the stage of GFR decline.

With this in mind, and with support from NKF, CKD-EPI and CKD-PC collaborated with the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to assess the validity of proteinuria and albuminuria as

surrogate endpoints. The agencies have now accepted that doubling of serum creatine is a valid surrogate endpoint for the clinical endpoint of kidney failure.

Prof Levey then presented two current models for the use of GFR and albuminuria in predictive instruments that he believes are ready for clinical use.

FUTURE OUTLOOK

In his concluding remarks, Prof. Levey commented that there are still controversies regarding CKD definition and classifications, overdiagnosis, methods, threshold values, and nomenclature. However, he added: "In each case we feel that debate has been beneficial. It has forced us to think more clearly, perform more analyses, and make appropriate revisions."

Looking towards the future, Prof Levey emphasised that eGFR and urine albumin creatinine ratio should be used more frequently in clinical practice, research, and public health settings, because they are powerful measures that are easy to obtain for the detection and staging of acute CKD, and are markers for risk and prediction of heart and vascular disease.

In his closing remarks Dr Levey reiterated that: "It is time to move forward from debate about validity of the observation and semantics of the definition and classification to the challenges of improving clinical practice, seeking explanations for high prevalence and poor prognosis, and testing strategies for prevention and treatment of CKD."

"...in 2013 reduced GFR was associated with 4% of the deaths worldwide (2.2 million), and more than half were cardiovascular deaths (1.0 million) compared to end-stage renal disease (0.9 million)."

Abstract Reviews

Hot off the press from the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Virtual Congress 2020, we present abstract summaries of those presented at the congress.

The Association Between Cystatin C and Arterial Stiffness in Non-Chronic Kidney Disease Patients

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Keywords: Arterial stiffness, atherosclerosis, cystatin C (cysC).

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BACKGROUND AND AIM

Serum cystatin C (cysC) is a protease inhibitor with a low molecular weight, which is produced by all nucleated cells at a constant rate. It is freely filtered by the glomerulus, then reabsorbed and metabolised in the proximal tubule. Extrarenal clearance of cysC is low.[1] Compared to serum creatinine, it is influenced less by age, sex, and muscle mass; additionally, it is not affected by inflammation or fever. However, thyroid dysfunction, certain malignancies, and corticosteroid therapy can alter cysC levels.[2] Despite some of its drawbacks, it is an important marker in detecting renal impairment, especially in early stages of chronic kidney disease (CKD).[3,4]

Increased arterial stiffness is a hallmark of atherosclerosis and is associated with increased morbidity and mortality because of cardiovascular causes. It is a consequence of structural and functional vascular changes.[5,6] Studies have shown that in patients with CKD, cysC correlates with increased arterial stiffness.[7] However, the data on the connection between cysC and arterial stiffness in patients without CKD are sparse.

METHODS

The study was a cross-section, single-centre evaluation of arterial stiffness parameters in patients without CKD. It was performed at the University Medical Centre Maribor, Maribor, Slovenia, between 1st October 2018 and 1st January 2020. Basic demographic and laboratory data of enrolled patients were recorded. The CKD Epidemiology (CKD-EPI) creatinine-based equation was used to estimate glomerular filtration rate (eGFR). Patients with active malignancies, previously diagnosed CKD, and/or eGFR ≤60 mL/min/1.73m^2 at the time of admission were excluded from the study. None of the included patients had a history of thyroid disease and none of them were treated with corticosteroids at the time of inclusion in the study. Arterial stiffness was measured with applanation tonometry (SphygmoCor®, AtCor Medical, Sydney, Australia). Carotid-femoral pulse wave velocity (cfPWV) was used as the gold standard of central arterial stiffness[8] and subendocardial viability ratio (SEVR) was used as the marker of myocardial perfusion.[9] SPSS® (IBM, Armonk, New York, USA) version 22 was used for statistical analysis and results with p<0.05 were deemed as statistically significant.

RESULTS

In the study, 111 patients (65.8% male; median age: 64.3±9.4 years) were included. The most common comorbidities were arterial hypertension (n=86; 77.5%), hyperlipidaemia (n=64; 57.7%), and diabetes (n=22; 19.8%). Mean creatinine value was 77.7±13.8 µmol/L (range: 49–108 µmol/L), mean eGFR was 81.3±9.4 mL/min/1.73m2 (range: 62–90 mL/min/1.73m^2), and mean value of cysC was 0.94±0.18 mg/L (range: 0.67–1.63 mg/L). Mean cfPWV value was 10.1±2.4 m/s (range: 6.2–16.8 m/s) and mean SEVR value was 165.7±36.1% (range: 92.0–299.0%). Significant correlation was found between cysC and SEVR (Pearson's correlation coefficient [r]=-0.316; p<0.001) and between cysC and cfPWV (r=0.472; p<0.001). Multiple regression analysis, with SEVR and cfPWV as dependent variables and cysC, age, sex, diabetes, arterial hypertension, eGFR, and hyperlipidaemia as independent variables, showed statistically significant association between cysC and SEVR (β coefficient [β]=-0.278; p=0.017) and between cysC and cfPWV (β=0.220; p=0.038).

CONCLUSION

Serum cysC was independently associated with increased arterial stiffness, reduced myocardial perfusion, and increased cardiovascular risk in the cohort of patients without CKD. This research shows the potentially important role of cysC in cardiovascular risk assessment in all patients, even in those with normal kidney function.

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Digital Education for Patients with Chronic Kidney Disease: The Renal Health Project Experience

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Keywords: Chronic kidney disease (CKD), education, internet, social networking.

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Chronic kidney disease (CKD) is a growing problem in many parts of the world, with >700 million people affected.[1] One of the main challenges in the management of patients with CKD is adherence to treatment, which greatly depends on patient education.[2] Evidence from recent studies reveals that adherence to treatment, in the context of CKD, is associated with better outcomes, including decreased mortality.[3] The authors started the Renal Health project in 2015, aiming to increase awareness of CKD in the general population and increase adherence to treatment for patients with CKD through digital education. This review presents strategies for patients' health education using technology.

The first tool the authors created was an application for smartphones named Renal Health,[4] which is now freely available for Android and iOS in English, Spanish, and Portuguese.

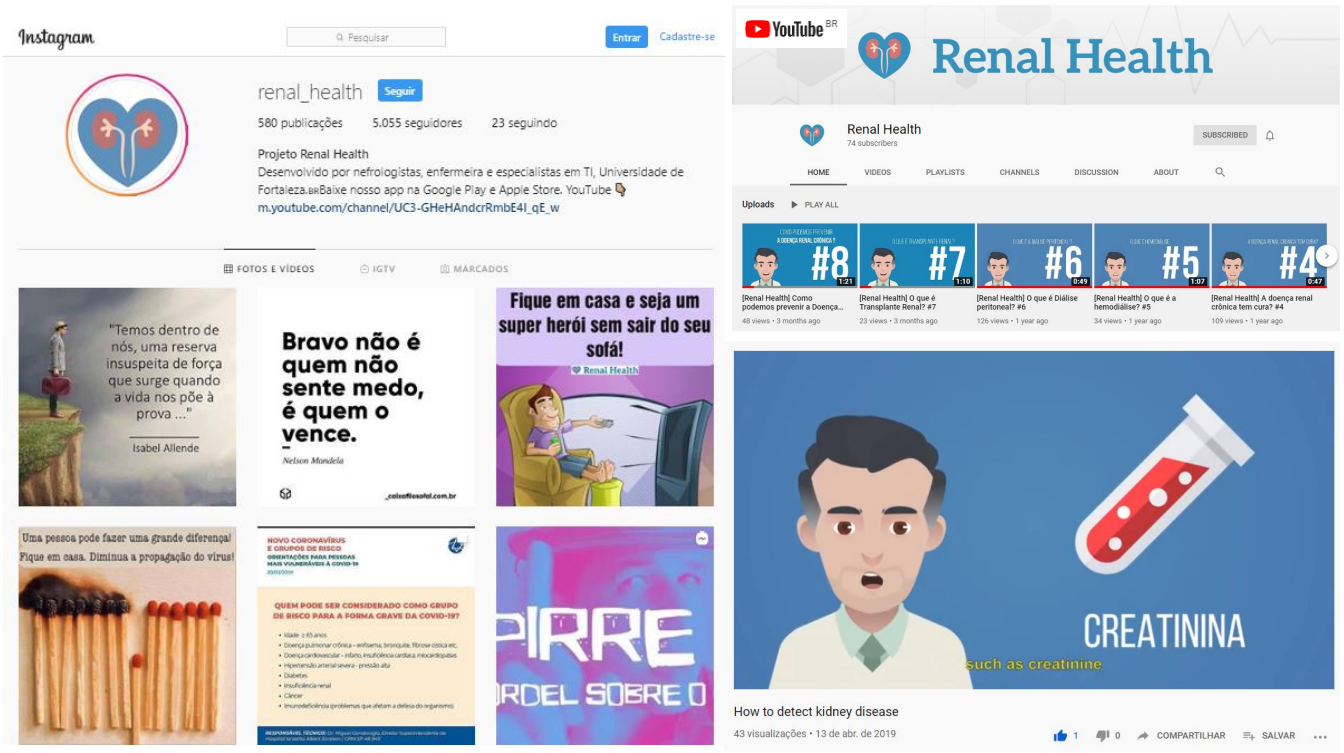

Figure 1: A) The Renal Health Instagram profile;[6] and **B)** YouTube channel.[7]

This app is intended to help patients undergoing dialysis or renal transplant to better understand their disease, organise their treatment, and control their laboratory tests, diet, and all aspects of treatment. With better understanding, patients can achieve an improved adherence level to treatment.

The other strategies in the Renal Health project provide health education through social networks and via the internet, periodically updated by renowned health professionals, to increase patients' knowledge of all aspects of their kidney diseases, from its risk factors, causes, and prevention to treatment, dialysis, and transplantation.[5] In 2018, the project launched a profile on Instagram[6] and a channel on YouTube[7] (Figure 1). After 18 months, the project achieved >5,000 followers on its Instagram profile, and evaluation of received feedback is currently ongoing (almost all of which was positive, supporting a good impact in patients' lives by improving their lifestyle). Regarding the YouTube channel, the intention was to provide short videos with information about different aspects of kidney diseases, from prevention to specific parts of treatment. At time of writing, eight videos have been published and have >500 views.

The next steps of this project are to test the Renal Health application with a large number of patients on dialysis and patients having undergone renal transplant, to investigate the impact on clinical outcomes and to evaluate the impact of digital health education. This will be achieved by first identifying the project's audience, and then assessing if it is effective in slowing the progression of CKD for those in conservative treatment or reducing complications for those in dialysis or post-transplantation.

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Mepolizumab Therapy in Eosinophilic Granulomatosis with Polyangiitis: 1-Year Follow-Up Study Using Anti-IL-5 as a Steroid Sparing Therapeutic Approach

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Keywords: Anti-IL-5 therapy, eosinophilic granulomatosis with polyangiitis (EGPA), vasculitis.

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BACKGROUND

Eosinophilic granulomatosis with polyangiitis (EGPA) is a small vessel vasculitis characterised by the presence of tissue eosinophilia, necrotising vasculitis, and granulomatous inflammation.[1] Typically, a prodromal asthmatic phase, leads to an eosinophilic stage, which can evolve to include the presence of vasculitis with renal manifestations.[2,3] In the recent randomised, placebo-controlled MIRRA trial for relapsing and refractory EGPA, adjuvant therapy with the anti-IL-5 monoclonal antibody, mepolizumab (MEPO), at 300 mg subcutaneously (SC) monthly, resulted in a longer remission period, reduced steroid exposure, and reduced relapse rates.[4,5]

AIMS

The aim of this study was to analyse the response and outcome for EGPA patients who received MEPO monthly for a minimum of 52 weeks, with particular focus on the steroid minimisation benefits. This retrospective, descriptive study analysed 13 EGPA patients, who received 100 mg SC monthly MEPO therapy under the eosinophilic asthma care pathway. Time points of assessment included MEPO commencement (M0) and 12 months (M12).

Table 1: Eosinophilic granulomatosis with polyangiitis patients receiving mepolizumab therapy for 1 year (100 mg subcutaneously).

Demographics	**N=13**
Sex ratio (M/F)	4M:9F
ANCA (positive/negative)	3 Myeloperoxidase (MPO) ANCA, 1 Proteinase (PR3) ANCA, 9 ANCA negative
Age of diagnosis of asthma	35 years (IQR 28.5–40.0)
Age of diagnosis of EGPA	47 years (IQR 43.5–53.5)
Median age	51 years (IQR 47.5–60.5)
EGPA disease characteristics	**N=13 (%)**
Asthma	13 (100.0)
Serum eosinophilia or biopsy evidence (n=12)	12 (100.0)
Pulmonary infiltrates, non-fixed	8 (61.5)
Mono-/polyneuropathy	4 (30.7)
Sinonasal abnormality	12 (92.3)
Glomerulonephritis	3 (23.0)
Cardiovascular	4 (30.7)
Prior immunosuppressants	**N=13 (%)**
Steroids	13 (100)
Cyclophosphamide	6 (46)
Rituximab	6 (46)
Azathioprine	10 (77)
Mycophenolate mofetil	8 (62)
Methotrexate	4 (31)
Alemtuzumab	1 (8)

Table 1 continued.

Response to therapy	MEPO commencement M0 (%)	Post MEPO Month 12 (M12) (%)
Prednisolone dose (N=13) Mean ±SD	18.925 mg ±11.440	10.575 mg ±5.850
Eosinophil count x10^9/L (N=13) Mean ±SD	0.415 mg ±0.250	0.035 mg ±0.039
Asthma Control Questionnaire (ACQ) (n=5) Mean ±SD	2.92±1.270	1.31±0.790
BVAS (N=13) Mean ±SD	7.307±6.290	2.2307±1.690
Creatinine (n=9) Mean ±SD	68.44 µmol/L ±15.030	69.11 µmol/L ±17.840
Continuation of anti-IL-5 therapy (N=13)	12/13 (92.3)	
Long term plan >12 months (N=13)	**Current months**	**Adjuvant therapy 12 months**
1 Continue	15	Azathioprine
2 Switched to benralizumab	26	MMF (+), IVIG (-)
3 Continue	18	
4 Switched to benralizumab	14	
5 Discontinued rituximab	12	MTX
6 Continue	14	
7 Continue	24	MMF reduced
8 Continue	18	MTX commenced
9 Continue	15	MMF stopped
10 Continue	14	
11 Continue	13	Rituximab
12 Continue	13	Azathioprine
13 Continue	12	

ACQ: Asthma Control Questionnaire; ANCA: Anti-neutrophil cytoplasm antibodies; BVAS: Birmingham Vasculitis Activity Score; EGPA: eosinophilic granulomatosis with polyangiitis; F: female; IQR: interquartile range; IVIG: intravenous immunoglobulin; M: male; MMF: mycophenolate mofetil, MTX: methotrexate; SD: standard deviation.

RESULTS

This study demonstrated that anti-IL-5 therapy serves as a favourable model with steroid minimisation, improvement in the Asthma Control Questionnaire (ACQ), reduction in the Birmingham Vasculitis Activity Score (BVAS) and eosinophil counts at 100 mg SC dosage (Table 1). Anti-neutrophil cytoplasm antibody positive serology normalised in all four patients, independent of subtype. MEPO was well tolerated, and demonstrated considerable clinical benefit, with 12 patients (92.3%) continuing anti-IL-5 therapy beyond 12 months.[6,7] One patient had MEPO switched to rituximab to treat both EGPA and new onset rheumatoid arthritis. Adjuvant therapy with conventional immunosuppressants was well tolerated and renal function was preserved.

CONCLUSION

The relapsing nature of EGPA places a potential dependency of therapy on steroids for asthmatic and vasculitic flares.[8] This underscores the importance of pathway targeted biologic therapy to minimise steroid exposure, prevent tissue damage accrual, and ensure early response to treatment.[9,10]

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Use of Rituximab for Glomerular Diseases Indicated Versus Off-Label: Clinical Perspective

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Keywords: Glomerulonephritis (GN), Kuwait, lupus nephritis (LN), membranous nephropathy (MN), minimal change disease (MCD), rituximab (RTX).

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BACKGROUND AND AIMS

Rituximab (RTX) is used worldwide for the treatment of glomerulonephritis (GN), including membranous glomerulopathy (MN), minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), and ANCA-mediated vasculitis.[1-5] However, its role in IgA nephropathy (IgAN), lupus nephritis (LN), and C3 glomerulonephritis (C3GN) is still not clear.[6-9] The authors hypothesised that RTX is used by Kuwait nephrologists for all immune-mediated glomerular disease as salvage therapy to induce remission, despite a lack of established indication for use; that is, off-label use. This study reviewed and assessed the indications for use of RTX and compared these to the available established literature and review outcomes.

Table 1: Baseline characteristics of patients studied, and outcomes following treatment with rituximab.

Glomerular diseases	MN	MCD	LN	IgG4-related	FSGS	C3 GN	IgA vasculitis	ANCA-mediated GN
Number of patients (N=69)	11 (16%)	9 (13%)	27 (39%)	5 (7%)	5 (7%)	2 (3%)	2 (3%)	6 (9%)
Mean age (years)	45	25	34	43	37	42	29	41
Sex								
Male	7	6	4	1	3	2	2	5
Female	4	3	23	4	2	0	0	1
Mean baseline eGFR	70	98	69	57	33	35	17	41
Mean 24-hour UP (g/day)	8.8	7.5	4.1	2.2	8.4	5.2	2.9	3.0
ACEI/ARB	11	2	17	3	3	1	0	2
Other immune therapy								
Prednisolone	11	5	25	4	4	2	2	5
CNI	9	1	6	1	3	0	0	0
MMF	2	3	23	3	4	1	2	2
Cyclophosphamide	1	0	1	0	0	0	0	1
RTX alone	0	0	0	1	0	0	0	0
RTX as add-on therapy	11	4	27	4	5	2	2	6
RTX switch	0	5	0	0	0	0	0	0
RTX dose								
375 mg x 4	7	7	22	3	2	2	2	3
1 g x 2	4	2	5	2	3	0	0	3
Outcome								
Partial remission	8	4	11	2	2	0	-	-
Complete remission	2	5	6	1	0	0	-	-
Total remission	10	9	17	3	2	0	0	1
Mean final eGFR (mL/min/1.73m^2)	72	100	76	60	28	16	7	75
Mean final 24-hour UP (g/day)	1.5	0.4	1.5	1.2	5.9	7.8	-	-
Indication supported by literature?	Supported	Supported	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Insufficient data	Supported

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CNI: calcineurin inhibitor; eGFR: estimated glomerular filtration rate; FSGS: focal segmental glomerulosclerosis; GN: glomerulonephritis; IgAN: IgA nephropathy; LN: lupus nephritis; MCD: minimal change disease; MMF: mycophenolate mofetil; MN: membranous nephropathy; RTX: rituximab; UP: urinary protein.

MATERIALS AND METHODS

Data for patients with GN aged ≥18 years who had received RTX treatment by a nephrologist were collected from three public hospitals in Kuwait between January 2014 and January 2018. The indication to administer RTX was solely determined by the nephrologist in charge.

Patients were separated based on their original GN subtype. For analysis purposes, MN and MCD were categorised into a disease group with data supporting RTX use, based on the literature available. In comparison, the remaining cases were categorised into a group with insufficient data to support RTX use (i.e., an off-label group), which included FSGS, LN, IgA nephropathy, IgG4-related disease, C3 GN, and membranoproliferative GN. Clinical remission was assessed 6 months after receiving RTX.

Statistical analysis was performed using Stata version 16 (StataCorp, College Station, Texas, USA). Statistical tests comparing categorical variables were performed as chi-squared tests. A logistic regression model was used to assess the probability of remission.

RESULTS

A total of 67 cases of glomerular diseases were reviewed. Three patients were excluded because of missing outcome data, and three for refusal of biopsy (two with LN, and one with presumed MCD). A total of 61 cases were included in the final analysis (Table 1). No major side-effects were reported. RTX was an add-on therapy in most cases.

The remission rate was 95% in diseases with data supporting the use of RTX (MCD and MN), compared to 56% in the off-label group (p value=0.002). The crude odds ratio for remission in the diseases supporting the use of RTX was 15 (confidence interval: 1.2–152), while the crude odds ratio for remission in the off-label group was 0.07 (confidence interval: 0.008–0.55; p value=0.012). For the MN patients, anti-PLA2R antibody testing was not performed on serum samples, but was positive in all of the biopsies. In the off-label group, patients with LN had a reasonable mean initial estimated glomerular filtration rate.

All five patients with Class III LN achieved remission with RTX, and 11 of the 21 patients with Class IV LN achieved remission. There was one further patient with Class V LN, who achieved remission. The patients with FSGS had a low mean initial estimated glomerular filtration rate that did not improve, and only two out of the five patients showed partial resolution of proteinuria. Not included in the table is a case of membranoproliferative GN that showed no response, and a case of IgAN that showed partial remission.

Independently, eight cases of vasculitis were reviewed (six cases of pauci-immune ANCA-related vasculitis and two cases of IgA vasculitis) that received RTX during the same period but were not included in the above analysis. Remission was achieved in only two of the patients with pauci-immune vasculitis, and in none of the patients with IgA vasculitis.

CONCLUSION

These data are in line with the literature supporting RTX use in resistant MCD and MN. However, RTX off-label use in other GN subtypes is still not clear, despite some successes in LN and IgG4-related disease. Because of the small number of patients with vasculitis, this study cannot comment on the effectiveness of RTX in this group. Overall, this study provided significant insight on RTX use for GN in Kuwait.

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Chronic Interstitial Nephritis in Agricultural Communities: A Toxin-Induced Proximal Tubular Nephropathy

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Keywords: Chronic kidney disease (CKD), environmental toxins, lysosomes.

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INTRODUCTION

In the early 1990s, clinicians in Central America and Sri Lanka noticed an upsurge of chronic kidney disease (CKD) in agricultural communities, predominantly amongst sugarcane workers and paddy farmers. Clinically, these patients did not present traditional causes of CKD such as glomerulonephritis, polycystic kidney disease, and hypertension; the latter only as a late feature. Proteinuria was rare, but when present was of the tubular type. Ultrasound showed bilateral shrunken kidneys and renal biopsies revealed a chronic tubulointerstitial nephropathy. This condition is known under many names, including CKD of unknown aetiology/cause (CKDu) and Mesoamerican nephropathy (only in Central America); recently, chronic interstitial nephritis in agricultural communities (CINAC) has been suggested as an overarching name.[1] Because of recent increasing awareness, multiple similar regional epidemics of CKDu have been suspected around the globe (i.e., the Uddanam region of Andhra Pradesh in India, Egypt, Tunisia, Senegal, and Peru, probably with more to follow).[2] Up to now, there is no consensus on its aetiology. Heat stress or dehydration and toxic agrochemical exposure are the two major hypotheses. Also, there are no diagnostic criteria that can directly identify patients with CINAC.

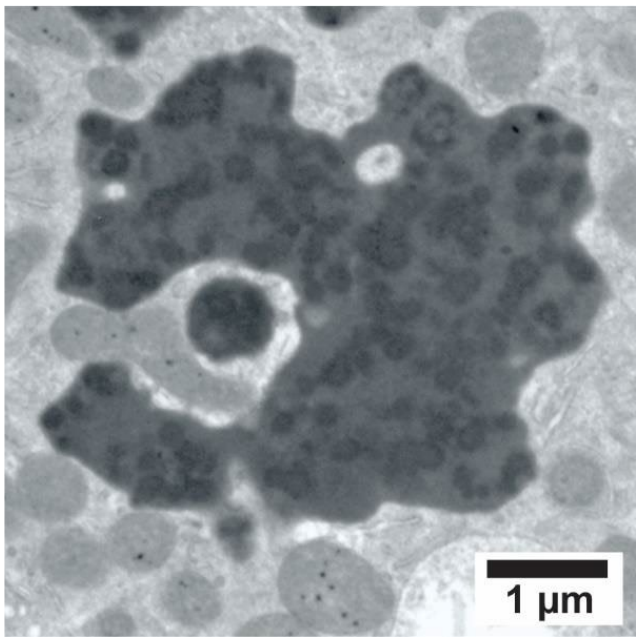

Figure 1: Enlarged dysmorphic lysosome containing dispersed electron-dense round to irregular aggregates as observed in a patient with chronic interstitial nephritis in an agricultural community.

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METHODS

To address these issues, the authors analysed renal biopsies by light and electron microscopy in CINAC patients (Sri Lanka: 18; El Salvador: 10; India: 1; France: 3), comparing patients to those with normal kidney function at implantation and after 6 and 12 months of calcineurin inhibitor (CNI) therapy, transplant patients on CNI with indication biopsies (n=24), proteinuric nephropathies (n=15), light-chain disease (n=4), several cases on nephrotoxic drugs (lomustine, clomiphene, lithium, tenofovir, cisplatinum), and patients with reduced renal function of various causes (n=20).[3] In addition, a rat study was conducted comparing the histopathology of heat stress or dehydration with cyclosporine nephrotoxicity.

RESULTS

In addition to previously described histopathological changes, there was a unique constellation of proximal tubular cell (PTC) lesions including cellular/tubular atrophy, cell fragment shedding, weak-to-nonproliferative capacity of the PTC, increased proliferation/hypertrophy of the distal tubules, and the presence of enlarged dysmorphic lysosomes with a light–medium electron-dense matrix containing dispersed dark electron-dense nonmembrane-bound round/irregular 'aggregates' (Figure 1).[3] Identical renal lesions were observed in 55–80% of renal transplant protocol biopsies taken after 6 and 12 months of CNI therapy as well as in indication biopsies, whereas in implantation biopsies the prevalence of the lesion was 10-fold lower. Moreover, several cases on nephrotoxic drugs (lomustine, clomiphene, lithium) and a subset of patients with light-chain disease, all conditions that can either directly or indirectly be linked to CNI, presented the same lesion. Control biopsies (n=66) of normal kidney, toxic nephropathies (tenofovir, cisplatinum), and overt proteinuric patients of different aetiology to some extent could demonstrate the tubular cell changes observed by light microscopy, but not or very rarely those that were observed by electron microscopy. Rats treated with cyclosporine for 4 weeks developed similar PTC alterations, which were absent in a dehydration group.

CONCLUSION

In conclusion, a sensitive constellation of renal PTC lesions was detected associated with CINAC and some toxin-induced nephropathies, amongst which was CNI nephrotoxicity. This indicates a toxin-induced aetiology for CINAC and suggests a pathomechanistic involvement of the calcineurin pathway, although involvement of other pathways cannot be excluded.

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Barriers to Home Haemodialysis in Saskatchewan Canada: Results from a Provincial Survey

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Keywords: Barriers, end-stage renal disease, home haemodialysis (HHD), in-centre haemodialysis, patients.

Citation: EMJ Nephrol. 2020;8[1]:42-43. Abstract Review No. AR6.

BACKGROUND

Despite clinical and lifestyle advantages of home haemodialysis (HHD) compared to in-centre hemodialysis,[1] it remains underutilised in the province of Saskatchewan, Canada. Only 2.5% of patients with end-stage renal disease utilise the modality,[2] which is far below that of other developed countries. The aim of the study was to explore the patients' perception and to identify the barriers to use of HHD in Saskatchewan, Canada.

METHODS

In this cross-sectional study, the authors approached all prevalent in-centre hemodialysis patients across Saskatchewan (two major centres [Regina and Saskatoon] and five associated satellite units attached to each centre) from June 2018 to January 2019. 398 patients agreed to participate in the study. For comparison of responses between main and satellite units, Chi square and Mann–Whitney U test were used, as appropriate.

RESULTS

Satisfaction with current dialysis care (91%), increase in utility bills (65%), fear of catastrophic events at home (59%), medicalisation of one's

home (54%), and knowledge deficits towards treatment modalities (54%) were the main barriers to HHD uptake. Compared to patients dialysing in the main units, satellite patients chose not to pursue HHD more frequently because they had greater satisfaction with their current dialysis unit care (97% versus 87%, respectively; p<0.001), felt more comfortable dialysing under the supervision of medical staff (95% versus 86%, respectively; p<0.007), could not afford additional utility costs (92% versus 45%, respectively; p<0.001), were unaware of the risks and benefits of HHD (83% versus 33%, respectively; p<0.001), had concerns over time commitments for training to HHD (69% versus 32%, respectively; p<0.001) and had concern for family burnout (60.8% versus 40.6%, respectively; p<0.001) (Figure 1).

CONCLUSIONS

Satisfaction with in-centre care; lack of awareness and education, specifically in the satellite population; concerns with family burnout; and expenses associated with utilities and training time will need to be addressed in order to increase the uptake of HHD. With identifying to utilising HHD, it is possible to better design centre-specific programmes to address the unique barriers leading to low utilisation of HHD. The findings will help healthcare decision or policy makers formulate well-informed decisions to address province specific barriers in order to increase the uptake of HHD.

Some of these issues can be addressed as a programme (education), but others will require policy level changes (reimbursement of costs borne by the patient).

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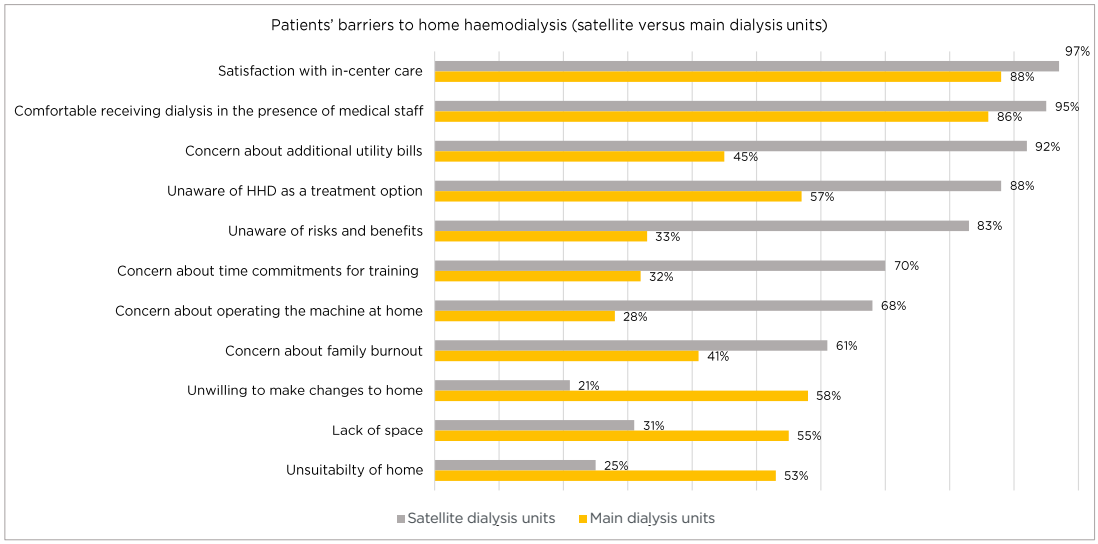

Figure 1: Patients' barriers to home haemodialysis (satellite versus main dialysis units).

HHD: home haemodialysis.

Interview

Prof Hamid Rabb

Professor of Medicine and Medical Director of the Johns Hopkins Kidney Transplant Program

Q1 Regarding the current COVID-19 pandemic, could you explain how the virus affects the kidneys, and the result this has in those infected?

Severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) can affect the kidneys in a number of ways: 1) patients with COVID-19 pneumonia have generalised inflammation and pro-coagulant status, which in turn causes kidney inflammation, injury, and decreased function; 2) patients with severe COVID-19 infections can have fluctuations and drops in blood pressure, impairing kidney blood flow and thus causing kidney dysfunction; 3) the SARS Co-V-2 can directly infect kidney tubular cells and podocytes, causing damage, white blood cell infiltration, and acute kidney injury.

Q2 Recent publications have discussed kidney transplant programmes during the pandemic. What are your thoughts on the potential safety concerns?

Patients who have undergone kidney transplant are at particular risk of worse outcomes after COVID-19, like other immunocompromised patients. During the early stage of transplant, immunosuppression needs to be very high, making the patient particularly vulnerable. There is also a risk that the patient can catch COVID-19 from a deceased or live donor, and aggressive testing of donors is being performed to reduce that risk. Furthermore, there is a risk that that the patient receiving a transplant can catch COVID-19 while hospitalised or during a follow-up visit. For these reasons, many programmes have temporarily suspended live donor kidney transplantation, and significantly reduced deceased donor kidney transplantation. Patients running out of dialysis access, those who are very highly human leukocyte antigen sensitised and might not get another transplant offer, and paediatric cases are some groups that continue to be transplanted in many programmes.

Q3 Could you summarise the major challenges that patients with kidney disease face when dealing with COVID-19, which you have examined in your recent viewpoint article 'Kidney diseases in the time of COVID-19: major challenges to patient care.'

Patients with kidney diseases are quite vulnerable to COVID-19 due to their comorbidities, often diabetes, hypertension, and other cardiovascular diseases. Those treated with in-centre dialysis need to go to dialysis centres, which despite the best precautions, may have difficulty with isolation. I have already mentioned the issues with kidney transplantation. Furthermore, when patients without kidney disease become ill with COVID-19

and then develop acute kidney injury (AKI), AKI is a multiplier that significantly increases risk of death. In many hospitals, there are so many patients with COVID-19-induced kidney complications needing dialysis that dialysis supplies are running out, and there are inadequate staff to carry out this highly skilled procedure. Furthermore, due to increased blood clotting in COVID-19 patients, continuous dialysis circuits can clot off which makes dialysis less efficient and further increases the need for dialysis supplies.

"Patients with kidney diseases are quite vulnerable to COVID-19 due to their comorbidities, often diabetes, hypertension, and other cardiovascular diseases. "

Q4 Following on from this, how do you suggest we address these challenges?

The COVID-19 pandemic has led to a surge of mainly clinical and some lab-based reports on how COVID-19 affects the kidney, how to reorganise dialysis and transplant programmes, and how to treat COVID-19 in patients with kidney diseases. However, research is in its infancy, and there is a great need to mobilise kidney researchers and resources to properly conduct research to improve outcomes in these patients.

Q5 As a nephrologist, could you comment on any other patient groups who are immunocompromised that are likely to be affected by COVID-19 and what advice you would give to their healthcare providers?

Kidney disease patients, either on dialysis or post-transplant, are closely followed by the health system and thus, there is an opportunity for other groups of vulnerable patients to learn from these experiences. Patients with cancers, rheumatologic diseases being treated with immunosuppression, and patients with other immunodeficiencies need to be followed particularly closely, practise even stricter social distancing than advised for the general population, may shed the virus for longer times than others, and need to rapidly contact their healthcare team at the outset of even minor symptoms. It also is possible that immunocompromised patients may have less overt symptoms such as fever due to a suppressed inflammatory response.

Q6 Johns Hopkins has been a stand-out institution during this time, offering the interactive map of infections and recoveries worldwide; how does it feel to be affiliated with an institution performing such seminal work?

I feel very fortunate to work with such talented and dedicated faculty, students, nursing, and staff. Johns Hopkins is a unique institution that was initially established to conduct research but also educate academic leaders and provide compassionate care. The warm collegiality and high density of committed individuals facilitates excellence for both local and international impact. I heard a half-joke from a senior faculty that Johns Hopkins Medicine's being located in a relatively underserved neighbourhood, plus fewer perks for faculty and trainees compared to private hospitals, actually "negatively selects" our members for more traditional values of medicine rather than more modern values like "work-life balance." During this crisis, the values and principles of the people at Johns Hopkins have really shone through and continued to distinguish the institution.

Q8 A research interest of yours is the molecular pathogenesis of kidney ischaemia/reperfusion recovery. How will the pandemic affect the development of treatment options for patients with this condition?

My team's research for the last 25 years has been to elucidate the mechanisms of how inflammation, particularly by white blood cells, leads to AKI and mediates repair. We have also pioneered the mechanistic concept of how the injured lung and kidney modify each other's function during critical illness. Coincidentally, both lines of research are front and centre during COVID-19 infections. We have started a series of studies, both at our institution and collaborating with others in the USA and Italy, evaluating the molecular aspects of COVID-19 effects on the kidney, and harnessing our understanding of these mechanisms to improve outcomes for COVID-19 patients. Of course, there are many challenges, which include how to develop the best experimental models for COVID-19-induced kidney disease, logistics of conducting discovery research during institutional and public restriction of activities, as well as a shift in attention of physician-scientists and resources towards direct care of infected patients.

New Aspects of Pathogenesis and Treatment of Membranous Glomerulopathy After the MENTOR Study

EDITOR'S PICK

The role of podocytes in membranous nephropathy (MN) has been recognised for several years and has led to innovations in treatment of MN, with drugs increasingly becoming more specific and efficacious. This timely review evaluates the latest clinical findings regarding the pathogenesis and treatment of MN, from supportive to immunosuppressive therapies. With 10,000 new cases a year in Europe, optimising the treatment pathway for patients with MN is imperative.

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Abstract

Membranous nephropathy (MN) is the major cause of nephrotic syndrome in adults, accounting for 20% of cases with an annual incidence of 1 per 100,000 population. In the past 10 years, the role of podocytes has been identified. Environmental triggers in genetically predisposed patients can activate podocytes to exhibit antigenic epitopes, including PLA2R, THBS1, and NELL1, which become targets of specific autoantibodies with subsequent complement activation. The discovery of these mechanisms has opened a new horizon in the treatment of MN, and novel drugs are available with more specific mechanisms of action. Rituximab, a monoclonal antibody directed against CD20 expressed on B lymphocytes, has been used in several trials and appears to induce remission of nephrotic syndrome in 60% of patients (GEMRITUX trial). The recently published results of the MENTOR trial documented the superior efficacy of rituximab in patients observed for up to 24 months. In MN, the concept of targeting disease control has introduced novel therapies with specific blocking mechanisms, such as belimumab; nonspecific blocking mechanisms, such as those against adrenocorticotropic hormone; and new therapeutic options, such as ofatumumab, bortezomib, and eculizumab, which have recognised the pathological processes involved in the glomerular diseases.

INTRODUCTION

Membranous nephropathy (MN) is the most frequent cause of nephrotic syndrome in adults and older patients. It accounts for 20% of nephrotic syndromes in adults and its annual incidence is 1 per 100,000 population. Overall in Europe, 10,000 new cases are diagnosed per year.[1] In the last 10 years, the pathogenetic mechanisms have been defined which has opened up new ways of treatment.

RESEARCH METHODOLOGY

This paper reviews the latest insights into the pathogenesis and treatment of MN. The authors analysed available papers on MN pathogenesis and MN therapy by performing a literature search using PubMed with the search terms "MN pathogenesis" and "MN therapy." Firstly, the papers published in the last 3 years were examined. Paper selection was made according to the relevance of the journal, the authors, the dimension of the study, and the novelty of the findings, with 20 recently published papers selected. The authors then looked to older publications, and studies previously published were also included. Currently ongoing studies were searched for in "https://clinicaltrials.gov/" and randomised controlled trials (RCT) that were active and enrolling patients were included. Those that had not started or were closed were not included. Overall, the story of MN is a very long one and it has not yet finished. This literature review covers from the first studies in 1995, up to the time of writing.

AETIOLOGY AND PATHOGENESIS

In recent years, MN has been found to be essentially a disease of the podocyte which, as a response to environmental triggers and on a genetic basis, exhibits antigen epitopes which bind antibodies that are then able to bind complement. The first antigen to be recognised was NEP by Debiec et al.[2] Later, a different podocyte protein, the M-type PLA2R, was identified as the antigen responsible for 70–80% of MN.[3] Because PLA2R is a normal molecule of the podocyte structure, MN may be regarded as an autoimmune disease, at least in those patients in whom anti-PLA2R antibodies may be found.[4] The discovery of M-type PLA2R as a major antigen in idiopathic MN (iMN) was a breakthrough in the understanding of the pathogenesis of this disease, establishing iMN as an autoimmune disease. Subsequent studies confirmed that circulating antibodies against PLA2R were detected in approximately 70% of incident iMN patients. Recently, it has been shown that the presence of PLA2R antibodies supported a diagnosis of iMN, changes in antibody levels were related to clinical disease activity, disappearance of antibodies preceded and predicted a subsequent decrease of proteinuria, and high titres of antibodies were associated with a low likelihood of spontaneous remission.[5] Recently, another podocyte antigen, THSD7A, has been found to be responsible for around 10% of MN.[6]

In a recent study of PLA2R-negative patients with MN, the technique of laser dissection of glomeruli followed by mass spectrometry allowed the identification of the presence of the protein NELL-1 that was also localised by immunohistochemistry.[7] The authors concluded that a subset of MN is associated with co-localisation of NELL-1 and IgG along the glomerular basement membrane. In these patients, anti-NELL antibodies were also found in the serum. Additionally, the antigens of aldose reductase and superoxide dismutase have been suggested in some cases of MN.[8] As a consequence of these findings, for a better understanding of the disease and of possible new therapies, studies are now looking for new podocyte markers that are able to activate the complement cascade and for cells that are able to produce the antibodies involved.[9,10]

The Toronto Glomerulonephritis Registry determined the Toronto Risk Score, dividing patients into those at low risk for progression, intermediate risk, and high risk, according to their proteinuria levels in the first 6 months.[11] van den Brand et al.[12] found markers predictive of evolution towards renal failure in a1 and b2 microglobulin excretions.[13] The best marker of the disease evolution and determinant for treatment is the titre of anti-PLA2R.[14-16]

TREATMENT

Supportive Treatment

In the first period of the disease, supportive treatment without the use of immunosuppressants is recommended by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines for all patients with MN and nephrotic syndrome.[17] Recommended treatment consists of restricting dietary sodium intake to <2 g/day and controlling blood pressure, hyperlipidaemia, and oedema. For all patients, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be the first-line therapy because of their antiproteinuric effect.[18] If the nephrotic syndrome persists, or patients have a recurrence of nephrotic syndrome in the first 6 months of treatment, immunosuppressive treatment should be considered.

Immunosuppressive Treatment

The combination of corticosteroids with cyclophosphamide or chlorambucil, given over 6 months, is best-known as 'Ponticelli's regimen.' Several studies have documented a remission rate of 70–80% with this treatment.[19-22] Cyclophosphamide and chlorambucil are equally effective in inducing remission, but one study[21] has documented a better tolerability profile for cyclophosphamide. A prophylactic treatment with trimethoprim sulfamethoxazole is recommended to avoid pneumocystis pneumonia.[23]

Anti-Calcineurin Drugs

Prospective, randomised studies have documented the efficacy of cyclosporine A (CsA) and tacrolimus (TAC) in the treatment of MN.[24-26] In addition to their immunosuppressive effect, CsA and TAC have an antiproteinuric effect because of their action on podocyte structure via interaction with synaptopodin.[27] The main drawbacks of CsA and TAC are their nephrotoxicity and the high rates of recurrence when the drugs are reduced.[28]

Mycophenolate Mofetil

Several observational studies have suggested that mycophenolate mofetil (MMF) is effective for the treatment of MN.[29] However, the only published controlled study did not document such efficacy.[30] For this reason, although the combination of MMF with a high dose of corticosteroids appears effective, the KDIGO guidelines do not recommend MMF as the first-line of treatment for patients with MN.[17]

Rituximab

Rituximab (RTX) is a monoclonal antibody directed against CD20 on the surface of B lymphocytes. In the case of MN, RTX is used to block the production of antibodies directed against the antigens that characterise the MN. Previous observational studies documented the efficacy of RTX in MN, with complete or partial remission of the nephrotic syndrome in 60% of patients.[31-34] No treatment-related serious adverse events were reported in either study. The RTX doses used in the different studies have principally been 375 mg/m^2/week for 4 weeks, or one or two 1g doses. More recently, a controlled, prospective, randomised trial commenced (GEMRITUX trial),[35] comparing two doses of 375 mg/m^2 with supportive treatment versus supportive treatment alone in 75 patients with MN. The study results at 17 months documented a remission rate for patients treated with RTX of 65% versus 34% in supportive treatment alone ($p<0.03$).

INSIGHTS FROM THE MENTOR STUDY

The recent publication of the first 24 months of data from the MENTOR study has allowed for better clarification of the role and relevance of RTX in the treatment of iMN.[36,37] The MENTOR study is a landmark investigator-initiated, open-label, randomised, noninferiority trial conducted in North America. In the study, 130 patients with primary MN, almost all positive for PLA2R, were randomised to receive RTX or CsA. The primary endpoint was complete remission or partial remission of proteinuria at 24 months post-randomisation.

Patients assigned to receive RTX were given a dose of 1 g on Day 1 and on Day 15. If complete remission was attained at 6 months, no additional RTX was given, but if proteinuria decreased by >25% from baseline at 6 months, a second course of RTX was given. When proteinuria did not decrease by >25% at 6 months, it was considered a treatment failure. Patients assigned to CsA were given 3.5 mg/kg/day in two equally

divided doses. If complete remission was attained at 6 months, CsA was stopped. If proteinuria decreased by >25% from baseline at 6 months, CsA was continued for an additional 6 months. A treatment failure was considered when proteinuria decreased <25% at 6 months. All patients were followed for 24 months.

The cumulative treatment failure for each treatment is shown in Table 1. The difference in favour of RTX is both high and significant, particularly at 24 months. Table 2 shows the response at 24 months according to baseline anti-PLA2R levels, and again documents a significant response in favour of RTX. Overall, the MENTOR study documented that RTX was not inferior to CsA in inducing complete or partial remission of proteinuria and was superior in maintaining proteinuria remission up to 24 months.

WHAT SHOULD BE THE INITIAL THERAPY FOR PRIMARY MEMBRANOUS NEPHROPATHY?

The first-line, initial therapy should be either RTX or cyclophosphamide (the latter according to Ponticelli's regimen). A cyclophosphamide regimen may be preferred for patients with very high levels of anti-PLA2R, even if the clinical response does not seem to be predicted by PLA2R at baseline. There is currently an Italian RCT underway, the RICYCLO trial,[38] comparing RTX to cyclophosphamide. CsA is now considered the second-line therapy for MN, with MMF, Acthar® gel, and plasma exchange as third-line therapies.

Table 1: MENTOR trial: cumulative treatment failure.

Time from randomisation (months)	Rituximab (n=65)	Cyclosporine A (n=65)	Risk difference
6	26%	29%	-3.1
12	26%	32%	-6.2
18	27%	74%	-46.0
24	40%	80%	-40.0

Table 2: MENTOR trial: baseline anti-PLA2R levels and response at 24 months.

Anti-PLA2R level at baseline	Rituximab (CR/PR)	Cyclosporine A (CR/PR)
≤40 U/mL	11/15 = 73%	7/19 = 37%
>40 U/mL	28/50 = 56%	6/46 = 13%
Total	39/65 = 60% (23 CR)	13/65 = 20% (0 CR)

CR: complete remission; PR: partial remission.

Box 1: Insights and unanswered questions from the MENTOR study.

Insights from MENTOR

- RTX is the preferred initial therapy of apparently primary MN (irrespective of anti-PLA2R levels) compared to CsA, after 24 months of observation.
- RTX is safe and well-tolerated over the short-term.
- A 40% failure rate at 24 months for RTX and an 80% failure rate of CsA at 24 months indicates that additional unmet needs exist in the treatment of primary MN, but may have been, in part, because of the trial design.

Unanswered questions from MENTOR

- What is the influence of spontaneous remissions on results? (no placebo control)
- What is the efficacy and safety of RTX in comparison to CyC-based regimens?
- What is the influence of anti-PLA2R positive/negative status on efficacy? (no stratification for anti-PLA2R levels)
- Is there any clinical value of monitoring CD19/20 B cells in circulation?
- Would more prolonged CsA therapy or more repeat dosing of RTX influence results?
- Will RTX therapy prevent ESRD?

CD: cluster of differentiation; CsA: cyclosporine A; CyC: cyclophosphamide; ESRD: end-stage renal disease; MN: membranous nephropathy; RTX: rituximab.

What Can Be Done to Augment the Response to RTX?

Higher doses of RTX can be used when anti-PLA2R levels are very high. Combination treatment of RTX with low-dose cyclophosphamide for 3–6 months may be considered, but a RCT is needed. Ofatumumab, obinutuzumab, or other drugs mentioned below may be used to augment the response to RTX but, again, an RCT is needed. Adjunctive plasma exchange or immunoadsorption[39] may also be considered, or combination therapy with sequential calcineurin inhibitors, as is undergoing testing in the STARMEN trial.[40]

How do Anti-PLA2R Antibody Levels Influence the Treatment of Primary MN?

This issue was not tested in the MENTOR study because no placebo control or stratification for anti-PLA2R levels was undertaken. However, from the available data, high PLA2R levels were associated with higher resistance to treatment, while low levels were associated with a high spontaneous remission rate. In addition, declining serum anti-PLA2R levels predicted clinical remission, while rising levels predicted relapse. However, CsA was much less effective in lowering anti-PLA2R antibody levels.

Unanswered Questions

The efficacy and safety of RTX in comparison to cyclophosphamide-based regimens is unanswered by the MENTOR study, but the RI-CYCLO trial aims to determine this. It is unclear from the MENTOR study what the influence of anti-PLA2R antibody status is on the efficacy of RTX because no stratification for anti-PLA2R levels was made. The study does not clarify if there is any clinical value in monitoring CD19/20 B cells in circulation. Finally, the study does not answer the question as to whether RTX therapy will prevent end-stage renal disease. Box 1 summarises the insights from the MENTOR Study, as well as the unanswered questions.

Ongoing Trials with Rituximab

There are several ongoing trials comparing RTX with cyclophosphamide or anti-calcineurin drugs, using different RTX doses. There are four ongoing RCT with RTX. The peptide GAM immunoadsorption therapy in autoimmune

membranous nephropathy (PRISM)[41] study is based on the understanding that iMN is an autoimmune disease characterised by the presence of IgG autoantibodies to M-type PLA2R. Immunoadsorption is a method of removing specific circulating immunoglobulins and has been shown to remove >80% of circulating IgG with a single session of 2.5 plasma volumes, with albumin and antithrombin III unaffected; with multiple sessions this can rise to >98%. The sequential treatment with TAC–RTX versus steroids plus cyclophosphamide in patients in the iMN(STARMEN) trial[40] will compare a TAC–RTX treatment with Ponticelli's regimen-treated groups. Rates of remission, relapse, and preservation of renal function will be evaluated at a 2-year follow-up.[42] Trial NCT00977977[43] compares RTX to CsA. The CsA group will withdraw CsA after 6 months and introduce RTX. The RI-CYCLO trial[38] is recruiting MN patients in Italy to compare the efficacy of RTX with Ponticelli's regimen.

ADRENOCORTICOTROPIC HORMONE

Adrenocorticotropic hormone (ACTH) stimulates the production of endogenous glucocorticoids and activates the melanocortin receptors, which perform several functions including immunomodulation, anti-inflammation, and modulation of exocrine functions.[44] In rodents, these receptors have been found in podocytes and glomerular endothelial, mesangial, and tubular epithelial cells. In animal models affected by iMN, the inhibition of melanocortin receptors reduces proteinuria and improves podocyte morphology.[45] After a first pilot study,[46] two studies[47,48] demonstrated the beneficial effects of natural ACTH in resistant glomerular diseases. Hladunewich et al.,[49] in a prospective open-label study, confirmed these beneficial results in 20 patients affected by iMN. To date, two ongoing studies are registered on clinicaltrials.gov.[50,51]

NEW EXPERIENCES

Ofatumumab

Ofatumumab is a new monoclonal antibody acting on CD20. It differs from RTX because it has different target epitopes. Ofatumumab, in addition to acting on the same epitope as is recognised by RTX, also acts on a second epitope localised on the small loop of CD20 and on a portion of the large, extracellular loop. Ofatumumab has been assessed as a RTX rescue therapy. Ruggenenti et al.[52] recently described two cases of clinical remission of iMN in patients who developed primary and secondary resistance to RTX. Resistance to RTX in these cases could be as a result of a change in the CD20 antigen conformation, which prevents B-cell–RTX binding and the consequent B-cell depletion.

Belimumab

As a monoclonal antibody, belimumab specifically targets the soluble form of B-lymphocyte stimulator that has a critical role in the differentiation and homeostasis of B lymphocytes. The effects of belimumab on proteinuria and anti-PLA2R antibody production have been evaluated in 14 patients with anti-PLA2R-positive MN. The treatment significantly reduced the antibody titre and proteinuria within 12 weeks.[53] Changes in proteinuria and in anti-PLA2R antibody titre after belimumab treatment seemed to parallel the changes observed after RTX, with a delay in onset. This may reflect the immediate B-cell lysis achieved by RTX, whereas the slower effect of belimumab might reflect the progressive 'exhaustion' of antibody-producing B cells secondary to B-lymphocyte stimulator binding and inhibition.

Targeting Memory Plasma Cells

The advanced stages of MN could be mediated primarily by autoreactive plasma cells, which are resistant to anti-CD20 monoclonal antibodies but sensitive to anti-CD38 antibodies or proteasome inhibitors.[52] Memory plasma cells survive RTX because they do not express the CD20 antigen; plasma cells express CD38.[54,55] These autoreactive plasma cells could be a target for anti-CD38 monoclonal antibodies, such as daratumumab and isatuximab. To date, these agents have been developed to kill malignant plasma cells.[55] Other molecules, such as the proteasome-inhibitor bortezomib, may effectively deplete plasma cells. Bortezomib acts by causing an intracellular accumulation of abnormal proteins with consequent plasma cell apoptosis. To date, bortezomib has been used in antineutrophil cytoplasmic antibody nephritis[56] and in resistant systemic lupus erythematosus.[57] Preliminary

data suggest it may be useful in the treatment of iMN that is resistant to other therapies.[58,59] The main drawback of bortezomib is its toxicity, which necessitates treatment interruption in most patients.

Targeting Complement

Complement inhibition by the anti-C5 monoclonal antibody eculizumab could be another avenue for treating iMN. In this approach, complement inhibition could prevent glomerular damage that occurs prior to the removal of antibodies.[60] To date, attempts to treat membranous nephropathy by eculizumab have failed and studies remain unpublished.

CONCLUSION

The discovery of anti-PLA2R antibodies and other antibodies involved in the pathogenesis of MN has revolutionised the treatment approach to this disease; for the first time, iMN may be considered an autoimmune disease in which podocytes play the initial and most important role. The possibility of monitoring anti-PLA2R antibodies represents an important tool for nephrologists to monitor the disease and to check the therapeutic effects. Other autoantibodies have been recognised as causative in iMN, including autoantibodies against THSD7A and NELL-1. Few iMN remain to be explained, but it is likely only a short time until other antigens and autoantibodies will be discovered.

After the publication of the first data of the MENTOR trial, RTX represents the most important drug in the treatment of iMN. Several relevant questions remain to be answered. What is the most appropriate dosage? What is the role of other immunosuppressants? What is the role of PLA2R or other autoantibodies at baseline? How should relapses be treated? Several ongoing RCT aim to answer these questions. Additionally, the pharmaceutical pipeline is filled with other new drugs which are all the subject of RCT. Ofatumumab for MN resistant to RTX, drugs targeting the memory plasma cells, and drugs affecting the complement pathway seem to be the most important therapies for future study and potential treatment of MN.

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Pharmacokinetics of Ceftriaxone During Prolonged Intermittent Renal Replacement Therapy in a Patient with Child–Pugh B Cirrhosis and Ascites

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Abstract

Prolonged intermittent renal replacement therapy (PIRRT) is emerging as an alternative to continuous renal replacement therapy as renal support for the critically ill. Unfortunately, dosing data are lacking for many antibiotics, including ceftriaxone. To allow clinicians to prescribe ceftriaxone effectively and safely in this setting, an understanding of the effects of PIRRT on the plasma pharmacokinetics (PK) of ceftriaxone is required. In this case, the authors describe the PK of ceftriaxone in a critically ill patient on PIRRT for the treatment of presumed spontaneous bacterial peritonitis. Blood samples were taken over two dosing intervals: one during PIRRT, and the other off PIRRT. A one-compartment PK model was used to describe ceftriaxone PK; little difference in clearance was noted with and without PIRRT. The authors suggest that ceftriaxone at a dose of 2g qd during PIRRT therapy is adequate to maintain serum levels above the minimum inhibitory concentrations for likely pathogens of non-central nervous system infections in critically ill patients.

INTRODUCTION

Continuous renal replacement therapy (CRRT) is the standard renal support for critically ill patients with acute kidney injury.[1] Prolonged intermittent renal replacement therapy (PIRRT) has emerged as an alternative to CRRT because it has lower operating costs while maintaining efficacy, patient safety, and mobility.[1] There are various data sources providing advice around antimicrobial dosing for patients receiving intermittent haemodialysis and CRRT, but data are limited for patients undergoing PIRRT and largely confined to case reports.[2-4] This increases the potential for inadequate or potentially toxic dosing of antimicrobial agents in critically ill patients receiving PIRRT.[2]

Ceftriaxone is a third-generation cephalosporin with a broad spectrum of antibacterial activity, suitable for the treatment of spontaneous bacterial peritonitis (SBP).[5] Optimal bactericidal activity is determined by the percentage of time unbound ceftriaxone concentration remains above the minimum inhibitory concentration (MIC) of the pathogen.[6] For patients with normal renal function, a daily dose of 2 g is able to maintain peritoneal concentrations above the MIC for common SBP causative isolates.[5] Cephalosporins are predominantly renally excreted and accumulate in patients with renal impairment; however ceftriaxone is an exception because of its high level of protein binding, hepatic metabolism, and biliary excretion.[5] Despite this, pharmacokinetic (PK) studies of ceftriaxone in patients with normal and impaired renal function have shown a prolonged half-life and decrease in urinary recovery for those with reducing renal function.[7] The reduction in drug elimination has a non-linear correlation with reducing renal function that may be related to elimination by both renal and non-renal pathways.[7]

Past studies have shown that the unbound concentration and volume of distribution of ceftriaxone is affected by critical illness, resulting in lower trough concentrations, and consideration for decreasing the dosing interval or changing to a continuous infusion were suggested.[7,8] However, it has been demonstrated that patients on ceftriaxone requiring CRRT therapy have an equivalent clearance to those with normal renal function and dose adjustments are not required for these patients.[9,10] Information to guide ceftriaxone dosing for critically ill patients undergoing PIRRT is lacking.

The aim of this report is to describe the PK of ceftriaxone in a patient with SBP undergoing PIRRT and to provide dosing advice for this setting.

METHODS AND RESULTS

Patient Characteristics

A 44-year-old male (height: 164 cm; weight: 148 kg) with a history of Child–Pugh B hepatic cirrhosis, ascites, congestive cardiac failure, atrial fibrillation, diabetes, and chronic kidney disease was diagnosed with SBP. He received an ascitic paracentesis for fluid overload, resulting in drainage of 14 L of fluid, which was complicated by acute-on-chronic renal impairment and was therefore transferred to an intensive care unit for dialysis and inotropic support. The ascitic fluid was negative in the bacterial culture and ceftriaxone was commenced empirically for SBP treatment. His serum albumin was 33 g/L on the day PIRRT commenced.

Antibiotic Dose and Administration

Because the recommendation from the literature is that patients on ceftriaxone requiring CRRT or intermittent haemodialysis therapy do not require dosage adjustments,[5-11] the patient received a dose of 2 g intravenously over 30 minutes qd for both PIRRT and non-PIRRT cycles.

Prolonged Intermittent Renal Replacement Therapy

PIRRT (Fresenius 5008, Fresenius, Sydney, Australia) was conducted as a 10-hour treatment in the haemodiafiltration mode with a heparinised circuit and a 1.4 m^2 filter (Ultraflux® AV600S, Fresenius), with the following renal replacement therapy settings: blood flow rate 200 mL/min; dialysate flow rate 200 mL/min; and ultrafiltration flow rate 250 mL/h, except for a 1-hour period where the ultrafiltration flow rate was 275 mL/h. The transmembrane pressures ranged from 50 to 135 mmHg. Fluid removal per ultrafiltration was 1,964 mL in 10 hours on the day of sampling. PIRRT was initiated on Day 1 of the study period for just under 10 hrs.

Blood Sampling

PIRRT was commenced after the patient received their first dose of ceftriaxone and blood was sampled at 4.5, 8.5, 11.5, and 16.5 hours after dosing for this PIRRT session. Blood samples were also taken at 2.0, 5.5, 9.0, and 12.0 hours after dosing for the non-PIRRT session which occurred after the patient's second dose of ceftriaxone. A total of eight samples were taken throughout a 2-day study period which included one PIRRT session. Of the four samples taken for the PIRRT session, PIRRT was active for the 4.5 hour and 8.5 hour samples, and was ceased prior to taking the remaining two samples. Samples were stored at -80°C prior to assay at Pathology Queensland Laboratories, Brisbane, Australia. The dialysate was not assayed to assess PIRRT clearance of ceftriaxone.

Drug Assay

Serum unbound ceftriaxone concentrations were measured by validated ultra performance liquid chromatography coupled with QDa mass detection (Waters Corporation, Milford, Massachusetts, USA) at Pathology Queensland. Unbound concentrations were separated using a validated ultrafiltration method with an Amicon® Ultra 0.5 mL 30,000-molecular-weight-cutoff centrifugal filter device (Merck Millipore, Sydney, Australia). The assay had a lower limit of quantification of 0.1 mg/L and the imprecision was <10% across three quality-control levels.

Pharmacokinetic Modelling

PK data was analysed using a non-parametric method with library package for R, Pmetrics™ (Laboratory of Applied Pharmacokinetics and Bioinformatics, Hollywood, California, USA) with testing of both one- and two-compartment models. A second clearance term representing the presence of PIRRT was tested and excluded due to mathematical insignificance. Both additive (λ) and multiplicative (γ) error models were tested. Inspection of the log-likelihood ratio and goodness-of-fit models was used to select the final model.

Consent

Informed consent was obtained to collect blood samples and report this case.

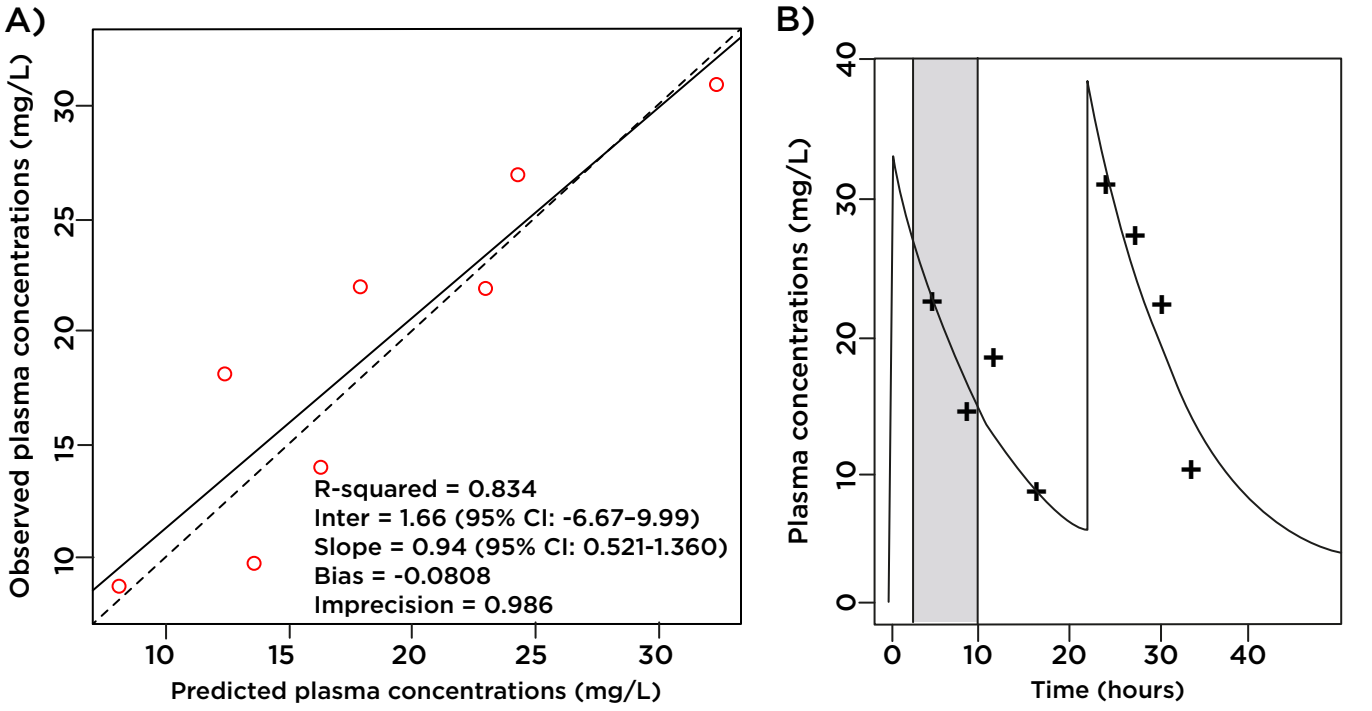

Figure 1: A) Observed-predicted plot for ceftriaxone plasma concentrations (mg/L); **B)** predicted unbound plasma concentration time profile versus observed data. Prolonged intermittent renal replacement therapy is shown in grey.

Pharmacokinetics and Pharmacodynamics

As both one- and two-compartment models produced similar parameters, the one-compartment model was selected on the principle of parsimony. The clearance of ceftriaxone was 5.23 L/hr for this patient and the estimated volume of distribution in the central compartment was 27.07 L. Because PIRRT did not have a clear effect on clearance there is no separate PIRRT clearance value. The intercompartmental rate constant from peripheral to central compartment (KPc) and central to peripheral compartment (KcP) were 6.95 h^{-1} and 8.24 h^{-1} respectively.

According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Clinical & Laboratory Standards Institute (CLSI), the MIC breakpoint for ceftriaxone for the treatment of *Enterobacteriaceae* is 1 mg/L.[12,13] As displayed in Figure 1, an intravenous dose of 2 g qd ensured unbound ceftriaxone plasma concentrations well above this breakpoint for the entire dosage interval while undergoing PIRRT.

Clinical Outcome

The patient was successfully discharged from the intensive care unit but subsequently died from respiratory failure due to ascites and fluid overload.

DISCUSSION

To the best of the authors' knowledge, this is the first report of the PK of ceftriaxone in a patient receiving PIRRT. Data are limited on describing the PK of antimicrobials, which are highly protein bound and predominantly nonrenally eliminated in patients receiving PIRRT.

Anidulafungin is a highly protein-bound (84%) echinocandin antifungal which is degraded in human plasma with minimal renal excretion of unchanged drug.[14] When given to an adult undergoing PIRRT, the PK data were comparable to those of healthy adults without renal dysfunction, suggesting that dose adjustment is unnecessary.[15]

The fluoroquinolone moxifloxacin has moderate protein binding of approximately 54%, is predominantly hepatically metabolised, and also has minimal urinary excretion.[16,17] In a study of moxifloxacin PK during PIRRT, the mean volume of distribution and half-life were similar in critically ill patients requiring PIRRT and in healthy subjects.[16] Standard dosing of 400 mg qd given post-PIRRT was recommended.[16]

The lincomycin clindamycin is also highly protein bound and hepatically cleared, and does not require dosage adjustment during CRRT.[7] Drug–protein complexes have a large molecular weight and are not removed by CRRT as readily as drugs with a low protein binding capacity.[7]

The above data suggest that for moderately to highly protein-bound drugs with predominantly nonrenal clearance, such as ceftriaxone, PIRRT also does not readily remove drug–protein complexes. This may explain the lack of change in ceftriaxone clearance in our patient in whom albumin levels were within the normal therapeutic range while on PIRRT despite having a history of Child–Pugh B cirrhosis and ascites, which could further alter ceftriaxone PK.

An increase in free ceftriaxone concentration after PIRRT was observed and may demonstrate a redistribution of ceftriaxone into the vascular system. This effect has been previously described during plasma exchange and would be expected to affect highly protein bound drugs.[18] Accumulation of ceftriaxone may result from multiple doses of ceftriaxone during PIRRT cycles, however this is an area that requires further research.

CONCLUSION

In this patient, the clearance of ceftriaxone was not substantially affected during PIRRT, and ceftriaxone dosage adjustments should not be required to achieve PK or pharmacodynamic targets for the treatment of SBP. The authors believe this to be the first reported case on the PK of ceftriaxone in a patient with Child–Pugh B hepatic cirrhosis, ascites, and chronic kidney disease requiring PIRRT, so further studies involving larger patient numbers are required to confirm this recommendation.

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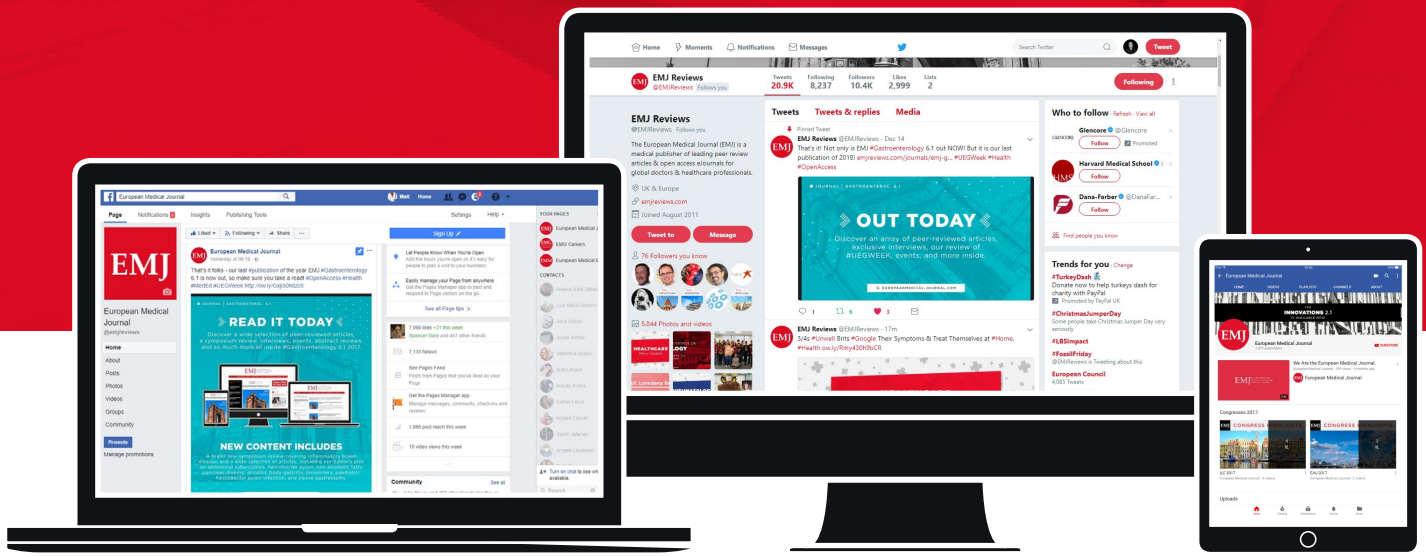

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Acute Kidney Injury: Risk Factors and Management Challenges in Low- and Middle-Income Countries

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Abstract

Acute kidney injury (AKI) is a major global health problem, occurring in >13 million people and responsible for >2.3 million deaths every year, 85% of which are in developing countries. Although the International Society of Nephrology (ISN) set a goal of eliminating preventable deaths by AKI by 2025, implementation of this program in developing countries presents major challenges for several reasons: there are few data on the epidemiology and causes of AKI in low- and middle-income countries (LMIC); health care resources to diagnose, manage, and treat AKI are often limited; and governments, institutions, and global health initiatives have not focussed sufficiently on the AKI problems. Thus, developing and implementing effective strategies to eliminate preventable deaths from AKI in LMIC have required efforts to better understand how to increase the awareness of AKI by health care workers and institutions.

INTRODUCTION

Acute kidney injury (AKI) is recognised worldwide as a major public health challenge, particularly in developing countries. Despite technological progress and preventive efforts, the AKI incidence remains high with >13 million cases globally per year, 85% of which are in developing countries, and can be attributed to >2.3 million deaths.[1-4]

Although AKI in high-income countries (HIC) with sophisticated medical infrastructure is predominantly a disease found in hospitalised, critically ill, and elderly patients, in low- and middle-income countries (LMIC), AKI is largely a community-acquired condition,[1-9] with dehydration and hypotension appearing to be the most common causes, as seen in recently published data.[10]

In LMIC, several cases of community-acquired AKI are due to causes that have the potential to be reversed with simple interventions.[5-10] Infectious diseases and obstetric complications are the leading causes of AKI, followed by animal venoms and natural herbal medicines. Although treating the underlying cause is of prime importance, death as a consequence of AKI may often be prevented by simple interventions such as oral rehydration or immediate temporary dialysis. However, in LMIC, acute renal replacement therapy (RRT) is available only in large cities, usually for the proportion of the population who

can pay for treatment. Thus, patients who develop AKI and are in need of dialysis often die.[3,9-13]

Given the potential reversibility of AKI with early intervention, early diagnosis is of particular importance. Acute Dialysis Quality Initiative recommendations for diagnosis of AKI in LMIC[11] include the estimation of urine output, measurement of serum creatinine levels by point-of-care tests (POCT), and thorough urinalysis. Dialysis might reduce mortality related to AKI in resource-limited settings. When RRT is available, peritoneal dialysis (PD) is used more commonly than intermittent haemodialysis, and these two techniques demonstrate equivalent outcomes.[14]

The International Society of Nephrology (ISN) AKI initiative aims to prevent all avoidable deaths by AKI by 2025 (0by25). In the context of the ISN 0by25 initiative, this report aims to revise the risk factors for AKI and its management challenges in low- and middle-income countries, focussing on barriers to early diagnosis and adequate treatment.

EPIDEMIOLOGY, AETIOLOGY AND RISK FACTORS

Despite the high burden of AKI,[1,4,6-10] reliable information on AKI incidence in LMIC has been slow to be produced due to limitations in the quantity, quality, and availability of data. In the 2013 meta-analysis,[2] nearly 84% of the included studies were from HIC, two studies were from Africa, and none were from Asia. In the 2015 meta-analysis,[4] which included >77 million AKI patients and multiple reports from Africa and Asia, the AKI incidence in LMIC had increased and approached that seen in HIC: it ocurred in 21% of hospitalised patients, which is very similar to worldwide AKI incidence.[2,4,7] However, the proportion of AKI patients requiring RRT in LMIC was lower than in HIC: 2% versus 11% of all AKI patients.

The aetiology of AKI in LMIC is often different from that seen in HIC and also differs between urban and rural areas. Rural, community-acquired AKI is associated with severe gastroenteritis; acute glomerulonephritis; envenomation; intoxication from traditional remedies; complications of endemic infections such as malaria, AIDS, leptospirosis, and dengue; obstetric complications including septic abortion; and use of nephrotoxic drugs and agentes. Conversely, aetiologies of AKI in large urban centres is similar to those in HIC[2-4,10-11] (Table 1).

The two most common causes of AKI in the 0by25 Global Snapshot[10] were hypotension and dehydration occurring in 40% and 38% of patients, respectively. In this study, risk factors such as infection, sepsis, and use of nephrotoxic drugs were common to all countries. Several risk factors for AKI present in LMIC are modifiable, such as nephrotoxin exposure, dehydration, hypotension, anaemia. Other risk factors are non-modifiable, such as comorbidities (chronic kidney disease, diabetes, cancer and/or heart disease) and demographic factors (age, sex), and other factors are related to environmental and infrastructure risks such as inadequate sanitation, insufficient clean water, and inadequate control of parasites or infection carrying vectors. Nevertheless, the high incidence of community-acquired AKI caused by modifiable factors provides an opportunity to combat the problem at an early stage and consequently avoid disease progression.[12,13]

Given the limited health care investment in LMIC, which severely hinders the availability of RRT and intensive care, the focus in LMIC is to decrease AKI incidence by targeting modifiable risk factors, which are of importance in decreasing incidence, severity, and costs.

BARRIERS TO CARE: DIAGNOSIS AND TREATMENT

AKI has the potential to be treatable and reversible. However, early recognition failure is associated with its progression, which requires complex therapies, and leads to delayed or impaired recovery and high mortality.[11,14] There are major challenges involved in developing strategies to establish an early AKI diagnosis and provide appropriate treatment in LMIC, such as the lack of laboratory supplies, necessary therapeutics, adequate medical infrastructure, and personnel.[14,15] Additionally, limited education about kidney disease and inadequate access to basic health care in LMIC hinder the early recognition of AKI and delay intervention.[2,14]

Another barrier to AKI care regards the shortage of healthcare workers in areas such as Africa because of the brain drain to western countries.

Table 1: The contrasting characteristics of acute kidney injury around the world.

Characteristic	High-income countries[A]	Low- to middle-income countries[B]
Occurrence	Predominantly in ICU	In rural health centres and hospitals, as well as in large urban hospitals
Disease	Associated with multiple organ failure	Often caused by a single disease; multiple organ failure is uncommon
Demographics	A disease of elderly populations	A disease of otherwise healthy children and young persons
Incidence	Increasing	Increasingly recognised as high
Reporting	Adequately reported	Severely under-reported
Prevention	Difficult to prevent	Preventable, generally with public health initiatives
Cost	Very expensive to treat	Inexpensive to treat at early stages; unaffordable at severe stages
Main exposures	Sepsis and septic shock Trauma Marjor surgery Nephrotoxic drugs Burns	Diarrhoea and endemic infections Obstetric complications Animal venoms Prolonged physically demanding work in an unhealthy environment
Mortality	High	Similar to, or even higher than, high-income countries

ICU: intensive care unit.

[A] Includes World Bank upper-middle-income ($3,956–12,235 USD) and high-income (>$12,236 USD) categories.[7]

[B] Includes World Bank low-income (<$1,005 USD) and lower-middle-income ($1,006–3,955 USD) categories.[7]

As a result, patients often spend days with worsening and untreated AKI.[13] In sub-Saharan Africa, delays of up to 3 weeks between onset of symptoms and presentation to hospital were described in adults with AKI,[13] whereas delays in presentation to hospital (mean 6 days) and treatment initiation were present in 50–80% of children with AKI.[13]

The problem of late AKI recognition has also been investigated by the 0by25 Global Snapshot.[10] In LMIC, patients are rarely or never seen by a nephrologist and are rarely seen by a physician; rather, their first contact with the health care system occurs in the community dispensary, where unspecialist health care providers are the only available resource. Given the constraints, efforts to educate individuals about AKI in LMIC must focus on the most basic levels of the health care system.

Acute Dialysis Quality Initiative recommendations for diagnosis of AKI in LMIC[11] include the estimation of urine output, measurement of serum creatinine levels by point-of-care tests (POCT), and thorough urinalysis. Recently, serum urea nitrogen levels, measured using a dipstick, has been studied in AKI; it is very cheap (<$1 USD) and the AUC was >0.75.[16-18]

To better understand the barriers to improving awareness of AKI in LMIC, a questionnaire was developed by a group of 20 nephrologists during

the 2014 International Society of Peritoneal Dialysis Meeting in Madrid.[14] These nephrologists included physicians from Africa, Asia, and North and South America. More than 80% of respondents indicated that the diagnosis of AKI in this setting is mostly based on clinical judgment, reflecting the limited availability of laboratory services. Only 60% of respondents indicated that these rural health centres have intravenous fluids and only 52% stated that they have appropriate antibiotic therapy to treat infection-related AKI. Antivenom therapy is generally not available in rural communities.[18] All district health centres had oral rehydration solutions and 96% indicated that intravenous fluids and antimalarial drugs are readily available, 72% indicated that antibiotics are available, and 63% indicated that laboratory support is available to diagnose AKI. No respondents indicated that dialysis therapies were available.[14]

This shortcoming is highlighted in the study by Olowu et al.,[13] which was performed in 13 countries in sub-Saharan Africa. In 3,340 patients admitted to hospital with AKI, the indications for dialysis was 66% in children and 70% in adults. However, only half of the children and one-third of adults received dialysis when required.

In LMIC, RRT are available only in large cities, usually for the proportion of the population who can pay for treatment. Thus, patients who develop AKI and are in need of dialysis often die. Dialysis might reduce mortality related to AKI in resource-limited settings. When RRT is available, PD is used more commonly than intermittent haemodialysis, and these two techniques demonstrate equivalent outcomes.[19-24] By contrast, gravity-driven PD is a more realistic option because RRT can be delivered without machines and electricity, relying only on consumable supplies, reducing costs and complexity in low resources settings.[9,20] Although particularly useful in areas with fragile health infrastructure, PD is underused in most parts of the world, despite advantages such as reasonable costs (as little as $150 USD to save one life).[24] This approach appears feasible, as documented by the encouraging results from PD programs for AKI in centres in Africa, Brazil, and Asia.[5,19-27]

THE SAVING YOUNG LIVES PROGRAM

The ISN 0by25 initiative, led by Ravindra Mehta and started in 2012,[2] aims to eliminate or at least decrease preventable AKI-related deaths around the world by 2025, with a focus on low- and middle-income countries in Africa, Asia, and Latin America. Based on previous studies, avoidable deaths from AKI are known to happen as a result of three different situations: secondary public health problems such as diarrhea, endemic infections, and unclean water; late or no recognition; lack of access to laboratory studies or inadequate response to clinical treatment; and lack of acute RRT to treat life threatening fluid overload, acidosis, and hyperkalemia.[2]

Although knowledge of AKI epidemiology has greatly improved since the use of a standardised AKI classification system, few studies have focussed on community-acquired AKI in LMIC. In the meta-analysis by the 0by25 initiative, the main issues regarding AKI epidemiology were raised.[2] Information was presented regarding the increasing associated mortality of even mild AKI, the effects of an AKI episode on long-term outcomes, and early detection and treatment of AKI in outpatient and low-resource settings. However, to reduce AKI related mortality and morbidity, knowledge of the factors that affect AKI outcomes is key to implementing initiatives.

The AKI meta-analysis published in 2015 by Mehta et al.[2] included 499 papers, 266 of which were based on Kidney Disease: Improving Global Outcomes (KDIGO) or equivalent AKI definitions.[2] The AKI incidence, according to KDIGO stages, in >4.5 million patients was 20.9%, and AKI affected 3,000–5,000 patients per 1 million of the population per year. Recent studies have described an incidence as high as 15,000 per 1 million of the population per year. Even so, AKI incidence in LMIC is still unkown and some studies have showed lower levels than in HIC. Additionally, epidemiological data from LMIC are difficult to interpret as there are heterogeneous cohorts and different methods of reporting involved, as well as huge variations in ability to diagnose and treat AKI.[2]

Another factor to consider is the high incidence of AKI in hospitalised patients in areas with more resources, in contrast to community-acquired AKI and patients in rural areas, where AKI is

often not detected.[28-31] Nonetheless, AKI in this population is often avoidable and reversible, affecting healthy and young individuals, and might be secondary to animal venoms, complications during pregnancy including septic abortion, use of herbal medicine, infectious diarrhoea, and other infectious diseases (Table 1).

ISN has collaborated with the Institute of Health Metrics and Evaluation (IHME), who have coordinated with the Global Burden of Disease Study (GBD) to include AKI in future GBD reports, which will envolve determining the relationship between AKI and disability or death. The main goal is to add strength to the concept that a high proportion of cases of AKI in LMIC are avoidable, demonstrating that investment in early recognition can reduce mortality and improve outcomes. As most studies on AKI are from developed countries and mainly focus on intensive care unit (ICU) populations, the 0by25 initiative developed two projects to assess how AKI contributes to the global burden of health loss: the AKI Global Snapshot (GSN) study, and the Pilot Study.

The GSN is a prospective observational cohort study, comparing aetiologies, risk factors, diagnoses, treatment, and AKI outcomes. The GSN was performed in 2014 and included >600 participating centres in 93 countries.[10,32] Patients were classified as having community-acquired or hospital-acquired AKI and countries were classified into HIC, upper-middle-income countries (UMIC), and LMIC according to their 2014 GNI per capita, using thresholds defined by the World Bank Atlas method.[33] In LMIC, 79% of AKI cases occurred in the community. Almost 50% of patients were hospitalised when AKI diagnosis occurred, with similar rates across all country categories. Hypotension and shock were the most prevalent causes in HIC and UMIC, while dehydration was the most frequent risk factor for AKI in LMIC. Most dehydration episodes were majoritively associated with inadequate oral intake (60%), followed by vomiting (44%). There was a higher number of patients with Stage 3 AKI in LMIC than in HIC and UMIC (58%, versus 47% and 41%, respectively). However, more patients in LMIC experienced recovery from AKI than patients from HIC and UMIC. The large proportion of patients presenting with Stage 3 AKI has important implications on higher mortality rate, longer hospital stay, and no recovery of kidney function [10].

In a separate analysis of children, the main risk factors for AKI in HIC were hypotension (30%), postsurgical complications (27%), and dehydration (26%). In contrast, dehydration was the most common risk factor in LMIC (43.5%) and UMIC (30.6%).[34] Mortality in community-acquired AKI was higher in LMIC (11% versus 9% in HIC). In the paediatric population, this difference was higher: 3% in HIC and 20% in LMIC. In LMIC, mortality was higher among ICU patients (21%), in comparison to HIC (13%). AKI recovery was more often complete in LMIC (39%) than in HIC (33%) or UMIC (28%). Recovery rates from community- versus hospital-acquired AKI were very similar in HIC and UMIC. In LMIC, recovery occurred in 79% of patients with community-acquired AKI and in only 20% of patients with hospital-acquired AKI.

The results of the GSN underline the need to raise awareness of AKI, in order to increase the detection of patients who present with earlier stages of AKI. The study also indicates that the main causes of AKI in LMIC are dehydration, infection, and sepsis. The strategies to reduce the burden of AKI need to be based on the identification of patients at risk, implementation of preventative actions, application of diagnostic methods, and timely referral for specialist care.[34,35] Development of educational and training tools for raising awareness and standardising the care of AKI cases is also essential.

The Pilot Study, not yet published, involves a prospective cohort of patients at high risk of community-acquired AKI in three different countries: Malawi, Nepal, and Bolivia.[36,37] The primary aim was to evaluate the feasibility of implementing an education and training program to optimise care of AKI, based on a protocol-driven approach in rural areas. Patients were selected for signs or symptoms associated with a high risk of developing AKI. AKI was confirmed within 7 days by a serum creatinine concentration test, according to KDIGO criteria.

The results of the pilot study will provide an assessment of the diagnosis and management of AKI in community health centres and will identify barriers to optimal care of patients. It is expected to show the effect of simple interventions, such as education and provision of POCT, on the outcomes of patients with a high risk of developing AKI. The 0by25 initiative developed partnerships with the governments

of participating countries to establish the best approaches to decrease avoidable deaths from AKI.

NEXT STEPS AND CONCLUSION

AKI has been associated with high mortality rates; however, it is likely that a significant number of deaths associated with AKI could be avoided. In the 0by25 initiative, the ISN has challenged both the nephrology community and the broader health care community to work collaboratively to develop effective programs to treat AKI in developing countries. Additionally, the governments of low- and middle-income countries need to be aware of the importance of sanitation, pure water supply, and basic health education, to have a chance of eradicating AKI in the foreseeable future.

The ISN 0by25 initiative has offered an opportunity to help improve education, training, care delivery, and the implementation of diagnostic and intervention studies in AKI. Additional key elements include improvement in health care and diagnostic tool availability and provision of acute RRT for those in need. The worldwide heterogeneity in the cause, setting, and progressional course of AKI demands an integrative approach.

The Saving Young Lives initiative[5,24] has shown that providing assistance with and promoting the development of local resources can help to generate local RRT programmes in LMIC. However, given the lack of investment and resources in LMIC, the delivery of affordable RRT to all patients with AKI in LMIC remains limited.[5,22] The 0by25 initiative would like to develop a sustainable infrastructure to enable 'need-driven' approaches for education and training, care delivery, and measurable outcomes. This approach will be tested in future studies in selected centres in developing countries with the aim of rapidly scaling up the lessons learned for broader adoption at national and regional levels. The program was implemented according to five strategic components representing the 5R framework: Risk assessment, Recognition, Response, Renal support, and Rehabilitation approach, as detailed in Figure 1.

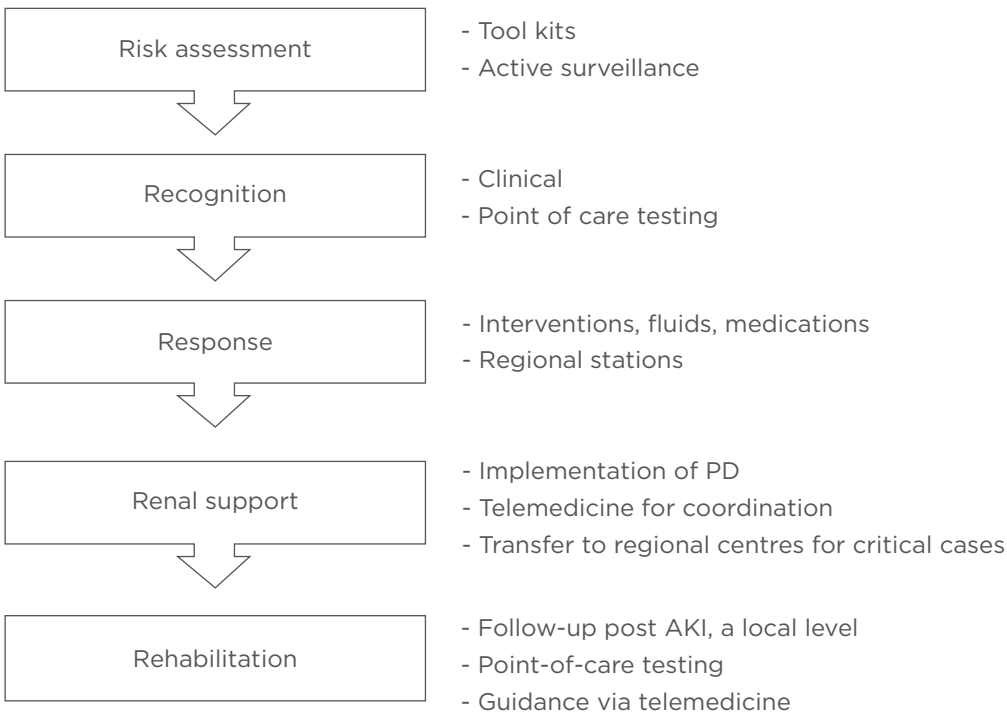

Figure 1: The 5R approach for a sustainable AKI programme by the ISN 0by25 initiative.[10]

AKI: acute kidney injury; ISN: International Society of Nephrology; PD: peritoneal dialysis.

Table 2: Commercially available intravenous fluids.

Type of fluid	Na^+	K^+	Ca^{2+}	Mg	Cl^-	HCO^{3-}	Lactate	pH	Osmoles
Ringer's lactate	131	5	1.8		112		28	6.5	279
PlasmaLyte	130	4	0.0	1.5	110	27		7.4	273
½ Normal Saline	77				77			5.0	154

Ca^{2+}: calcium ion; Cl^-: chloride ion; HCO^{3-}: bicarbonate; K^+: potassium ion; Mg: magnesium; Na^+: sodium ion.

The Saving Young Lives program was started in 2012 and has been providing financial and educational support to develop PD therapy for patients with AKI in developing countries.[5,20-28] In these settings, the advantages of PD over HD include medical and technical simplicity and the lack of need for electricity, machinery, and pure water, among other factors.

Fluids can be a barrier to PD use for AKI treatment in LMIC. Commercially produced solutions are produced to high standards with strict aseptic technique and careful monitoring of bacterial and endotoxin contamination. Locally prepared solutions carry the potential risks of contamination and mixing errors which may be life-threatening. Commercial solutions often have closed drainage systems to prevent accidental contamination. However, the disadvantage of commercial solutions is the financial cost, which may limit utilisation in low resource settings, particularly if patients are paying for their own care. This includes both the cost of purchasing the solutions and the cost of transportation to sites providing the treatment, as well as costs such as taxes and bureaucratic assessments. However, the costs of peritonitis due to contaminated, locally produced fluid must also be considered when making decisions based on financial grounds.

The ISPD recommend the following types of fluid, in order of preference:[27]

- Commercially prepared solutions.
- Locally prepared fluid made in an approved and certified aseptic unit/pharmacy. These products have a limited expiry date, as approved by the manufacturing unit.
- Solutions prepared in a clean environment, with the minimum number of punctures and least number of steps. This fluid should be used immediately.

In situations where dialysis fluids are not available or are unaffordable, dialysis fluids can be prepared using available intravenous fluids. Table 2 shows some examples of intravenous fluids that can be converted into dialysis fluids. By adding glucose and/or bicarbonate to these fluids, solutions can be developed that are similar in composition to standard dialysis solutions.

Importantly, excellent outcomes have been observed when using PD to treat patients with AKI.[20-23] As a team effort, the international societies have helped to provide supplies, and education, training, and support for health care workers. To date, successful programs have been developed at 10 sites in eight countries, with three additional sites in development as of late 2015.

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Diabetic Kidney Disease in Childhood and Adolescence: Conventional and Novel Renoprotective Strategies

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Abstract

Diabetic kidney disease (DKD) is defined as a clinical syndrome consisting of persistent macroalbuminuria, progressive decline in glomerular filtration rate (GFR), hypertension, increased cardiovascular disease events, and the associated mortality of these conditions. The disease evolves from the microvascular complications of poorly controlled Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM). The pathogenic pathways comprise renal haemodynamic changes, ischaemia and inflammation, and overactive renin–angiotensin–aldosterone system (RAAS), through which several events cascade down from hyperglycaemia to renal fibrosis. Conventional and novel renoprotective strategies target modifiable DKD risk factors and specific stages of the pathogenic pathways, respectively. Although these strategies may slow DKD progression to end-stage kidney disease (ESKD), novel drugs are still undergoing trials for validation in human participants. This narrative review appraises these renoprotective strategies and highlights the current clinical staging and pathogenesis of the disease.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is predominant in childhood and adolescence whereas Type 2 diabetes mellitus (T2DM) is more common in adulthood. Nevertheless, the prevalence of T2DM is rising in children and adolescents as well.[1] The major predisposing factor in both developed and developing countries is the increase in cases of paediatric obesity and metabolic syndrome.[2] Both types of diabetes are associated with long-term microvascular complications following poor glycaemic control, as defined by glycosylated haemoglobin or haemoglobin A1c (HbA1c) level of >7.5%.[3] These complications include diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy.

Diabetic nephropathy progresses to chronic kidney disease (CKD) over 10–20 years.[4] Microalbuminuria (urine albumin excretion rate of 30–299 mg/day or albumin/creatinine ratio of 30-299 mg/g creatinine) is the first biomarker to appear. It may regress to normoalbuminuria or progress to macroalbuminuria (urine albumin excretion rate of >300 mg/day or albumin/creatinine ratio of >300 mg/g creatinine).

Macroalbuminuria signals the development of overt diabetic kidney disease (DKD), which is characterised by a progressive reduction in the estimated glomerular filtration rate (eGFR) to <60 mL/minute/1.73 m^2, resulting in end-stage kidney disease (ESKD). Thus, DKD is defined as a clinical syndrome comprising persistent macroalbuminuria (noted at least twice within a 3–6-month interval), progressive decline in eGFR, hypertension, increased cardiovascular disease events, and the associated mortality of these conditions.[5,6]

DKD represents a significant cause of morbidity and mortality in patients with diabetes, and is the leading cause of ESKD on a global scale.[7,8] Although advanced DKD takes decades to develop, its structural lesions may manifest within 1.5–5 years in child and adult patients.[9] The structural lesions in diabetic children and adults with normoalbuminuric DKD are similar. Patients with T1DM may present with albuminuria without changes in eGFR. In contrast, adults with T2DM and micro- or macroalbuminuria progressively manifest typical DKD structural lesions as the eGFR declines.[9] The classical stages of DKD in T1DM are absent in adults with T2DM, given their frequent comorbidity with hypertension, albuminuria, and kidney failure at diagnosis. Conventional renoprotective strategies target modifiable DKD risk factors in diabetic children and adolescents, identified as diabetes duration,[10] hypertension,[11] dyslipidaemia,[12] obesity,[13] and smoking.[14] These factors are linked to microalbuminuria; however, none of these renoprotective strategies can stop or reverse DKD progression.[15] More importantly, some of them at best can retard the rate of decline in renal function. Given the transition of 25% of normoalbuminuric diabetic patients to CKD,[16,17] decline in renal function remains the most critical target of renoprotection.[18] The diverse pathophysiologic mechanisms of renal injury in diabetes are still unfolding. Thus, novel drugs for DKD are emerging and are still undergoing clinical trials. This narrative review appraises the renoprotective strategies for DKD in childhood and adolescence. Additionally, it highlights the current clinical staging and pathophysiologic mechanisms of the disease.

CLINICAL STAGING AND PATHOPHYSIOLOGIC MECHANISMS OF DIABETIC KIDNEY DISEASE

Different hypotheses on the pathophysiologic mechanisms of DKD have been advanced.[19-21] It is now believed that renal fibrosis constitutes the final common pathway arising from hyperglycaemia-induced renal haemodynamic changes, oxidative stress, inflammation, hypoxia, and overactive renin–angiotensin–aldosterone system (RAAS).[6] In fact, DKD is defined by the changes in renal structure and function in diabetes. The structural changes include mesangial expansion, basement membrane thickening of the glomeruli and tubules, and glomerulosclerosis. The functional changes affect urine albumin excretion, eGFR, and blood pressure. Thus, the clinical stages consist of glomerular hyperfiltration, normoalbuminuria, microalbuminuria, and ESKD.[22] Stage 1 is characterised by glomerular hyperfiltration, increased eGFR, increased urine albumin excretion rate, and normal blood pressure. In Stage 2, thickened glomerular basement membrane and mesangial expansion, normal eGFR, normoalbuminuria, and normal blood pressure occur. Stage 3 presents with microalbuminuria, declining eGFR, and hypertension, whereas Stage 4 presents with macroalbuminuria, further reduction in eGFR to <60 mL/minute/1.73 m^2, and hypertension. Stage 5 is marked by ESKD, decreasing albumin excretion rate, and hypertension. Nevertheless, a recent proposal described the clinical stages as follows: Stage 1 (from diabetes onset to 5 years) is characterised by borderline eGFR, no albuminuria or hypertension, a 20% increase in renal size, and elevated renal plasma flow.[23] Stage 2 (from 2 years after onset) is identified by normal eGFR and no clinical symptoms.[23] In Stage 3 (5–10 years after onset), glomerular damage and microalbuminuria occur with or without hypertension, whereas in Stage 4, irreversible proteinuria, sustained hypertension, and eGFR <60 mL/minute/1.73 m^2 are seen.[23] Stage 5 refers to ESKD with eGFR <15 mL/minute/1.73m^2.[23] This staging is not different from the previous staging, underscoring the current unanimity in its categorisation. DKD is a complex disease linking haemodynamic and metabolic pathways with oxidative stress and systemic inflammation.[22] The pathways (renal haemodynamic changes,

ischaemia and inflammation, and overactive RAAS) through which several events cascade down from hyperglycaemia to renal fibrosis are shown in a schematic diagram (Figure 1). The novel DKD drugs target specific stages of these pathways. Firstly, the renal haemodynamic pathway comprises the following sequence of events: hyperglycaemia induces the release of vasoactive mediators (insulin-like growth factor-1 [IGF-1], glucagon, nitric oxide [NO], prostaglandin, and vascular endothelial growth factor [VEGF]) which cause the dilatation of the glomerular afferent arterioles.[6] Additionally, the high filtered glucose load from hyperglycaemia triggers the upregulation of sodium-glucose transporter-2 (SGLT2), leading to increased tubular reabsorption of glucose and sodium chloride. Consequently, reduced availability of sodium chloride at the macula densa occurs; afferent arteriolar dilatation from tubuloglomerular feedback and efferent arteriolar constriction from elevated local angiotensin II levels both contribute to glomerular hypertension.[23] Insulin resistance, hyperinsulinaemia, and hyperglycaemia independently lead to endothelial dysfunction by producing reactive oxygen species (ROS), activation of protein kinase C, and proinflammatory signalling from advanced glycated end-products. Specifically, compensatory hyperinsulinaemia increases endothelin-1 secretion, which causes vasoconstriction and vascular dysfunction.[24] In summary, renal endothelin-1 A receptor activation leads to vasoconstriction, podocytopathy, oxidative stress, inflammation, and fibrosis.[25]

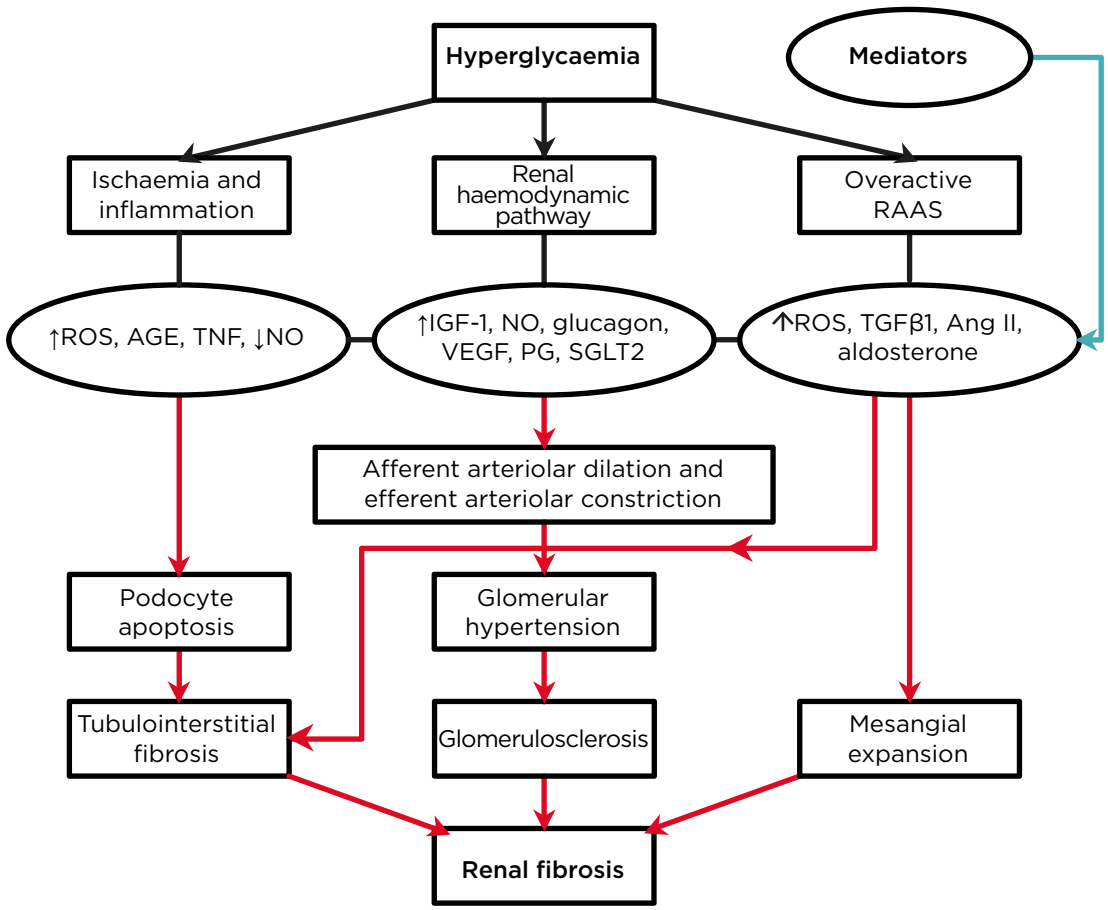

Figure 1: A schematic diagram of the major pathophysiologic mechanisms in diabetic kidney disease.

AGE: advanced glycated end-products; Ang II: angiotensin II; IGF-1: insulin-like growth factor-1; NO: nitric oxide; PG: prostaglandin; RAAS: renin-angiotensin-aldosterone system; ROS: reactive oxygen species; SGLT2: sodium-glucose transporter-2; TGFβ1: transforming growth factor β1; VEGF: vascular endothelial growth factor.

Secondly, the events in the 'ischaemia and inflammation' pathway are triggered by the direct and indirect effects of hyperglycaemia.[6] Hyperglycaemia directly triggers the production of ROS, which contributes to podocyte apoptosis. Also, hyperglycaemia-induced cellular stress leads to proinflammatory responses and the activation of NF-kB by ROS and TNF. NF-kB is linked to proteinuria and infiltration of inflammatory cells into the renal interstitium.[26] Again, the glomerulosclerosis in DKD is associated with renal medullary hypoxia. Advanced DKD leads to reduced intrarenal production of NO.[27] Failure to supply the compensatory increase in oxygen demand by residual functional nephrons results in the generation of nephrotoxic free radicals. Hyperglycaemia also impairs the stability of the reactively increased hypoxia-inducible factor meant to ameliorate the hypoxic state, and thus promotes renal tissue fibrosis.

Thirdly, hyperglycaemia and advanced glycated end-products trigger the renal expression of renin and angiotensinogen through ROS, as well as the kidney-specific G protein-coupled metabolic receptor GPR91.[28,29] Overactivity of RAAS worsens DKD deterioration via mediators such as transforming growth factor-β1 (TGFβ1), angiotensin II, and aldosterone, which are all associated with renal tissue fibrosis.[30,31] In fact, inhibition of RAAS retards the progression of DKD;[32] a finding which supports the role of overactive RAAS in disease pathogenesis.

BIOMARKERS IN DIABETIC KIDNEY DISEASE

To achieve effective renoprotection, DKD should be identified early enough with biomarkers. The traditional biomarkers of glomerular injury such as albumin/creatinine ratio and eGFR can predict DKD. However, both biomarkers may lack specificity and sensitivity for the following reasons. Firstly, not all patients with microalbuminuric T1DM and T2DM will progress to the late stages of DKD because many of them may have normoalbuminuric DKD. Secondly, glomerular biomarkers (e.g., TNF-α, transferrin, Type IV collagen, and lipocalin-type prostaglandin D synthase) and tubular biomarkers (e.g., neutrophil gelatinase-associated lipocalin, nephrin, N-acetyl-β-D-glucosaminidase, and liver-type fatty-acid binding protein) appear before microalbuminuria,[33] which suggests that albumin/creatinine ratio can only predict the late stages of DKD. Moreover, tubulointerstitial lesions occur earlier than glomerular injury in diabetic nephropathy, showing that tubular biomarkers are more sensitive.

In fact, there are disadvantages in using microalbuminuria and eGFR as measures of renal function decline. For instance, there is a daily variation in urine albumin/creatinine ratio and eGFR values may be affected by the patient's haemodynamics, diet, and hydration status, and become more sensitive only in advanced DKD.[34] Predicting DKD at an early stage when renoprotective strategies would make a difference remains a diagnostic challenge. Thus, the limitations of albumin/creatinine ratio have resulted in a paradigm shift to novel molecular biomarkers which have higher sensitivity and specificity for earlier prediction of DKD. Using the 'multi-omics' methods (transcriptomics, proteomics, lipidomics, and metabolomics) to profile patients' bio-specimens (renal biopsy, plasma, and urine samples) has led to the recent identification of candidate biomarkers.[34]

RENOPROTECTION IN DIABETIC KIDNEY DISEASE

Renoprotection in DKD involves risk-specific interventions against disease progression. Despite its drawbacks, albuminuria remains the most important prognostic biomarker for the progression of CKD.[15] There are modifiable and nonmodifiable risk factors for microalbuminuria and its progression to macroalbuminuria in children and adolescents with T1DM. The risk factors for microalbuminuria include female sex, hypertension, duration of diabetes, high normal urine albumin excretion, elevated low-density lipoprotein-cholesterol (LDL-C) and triglycerides, high BMI, and smoking.[10-14] On the other hand, the risk factors for macroalbuminuria comprise male sex, elevated HbA1c, high serum uric acid, and smoking.[35-38] Adolescents with T2DM present a different picture regarding DKD risk factors. These factors appear more prevalent and less amenable to control in T2DM compared to T1DM. For instance, hypertension, dyslipidaemia, and obesity are more common in patients with T2DM than in their T1DM counterparts.[39-41]

Table 1: Some conventional and novel renoprotective strategies in diabetic kidney disease.

Renoprotective strategies	Mechanism of action	Outcomes in DKD
Conventional strategies		
- Strict glycaemic control†	- Reduces the incidence of microalbuminuria and macroalbuminuria	- Reduction of risk of progression to DKD
- Control of hypertension‡	- Blockade of RAAS and reduction of the frequency of microalbuminuria in hypertensive normoalbuminuric patients	- Retards DKD progression
• ACEI • ARB		
- Treatment of dyslipidaemia	- Lowers LDL-C levels and ameliorates albuminuria in patients on RAAS inhibitors	- Reduces cardiovascular disease events in DKD
• Statin therapy		
- Lifestyle modifications	- Reduces albuminuria in diabetic patients with comorbid obesity	- Reduces DKD risk
• Weight reduction		
• Cessation of smoking	- Smoking is an independent risk factor for DKD	- Reduces DKD risk or progression
• Dietary protein restriction*	- Retards loss of renal function in diabetics	- Reduces DKD risk
Novel strategies		
- Uric acid antagonist	- Reduces albuminuria in T2DM and urinary TGFβ in DKD	- Reduces DKD risk or progression
• Allopurinol		
- Vitamin D analogues	- Reduces albuminuria in diabetics	- Retards DKD progression
• Paricalcitol • Calcitriol		
- Endothelin receptor antagonists	- Reduces residual albuminuria in DKD	- Retards DKD progression
• Atrasentan • Avosentan		
- Glucose-lowering agents	- Inhibition of SGLT2	- Retards DKD progression
• Empagliflozin	- Inhibition of SGLT2	
• Canagliflozin	- Stimulates insulin secretion as GLP-1 analogue	- Improves glycaemic control and reduces DKD risk or progression
• Liraglutide • Semaglutide	- Stimulates insulin secretion as GLP-1 analogue	

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; DKD: diabetic kidney disease; GLP-1: glucagon-like peptide-1; HbA1c: haemoglobin A1c; KDIGO: Kidney Diseases Improving Global Outcomes; LDL-C: low-density lipoprotein-cholesterol; NKF: National Kidney Foundation; RAAS: renin-angiotensin-aldosterone system; SGLT2: sodium-glucose transporter 2; TGFβ: transforming growth factor β.

†Maintaining HbA1c level at 7%

‡Calcium-channel blockers (CCB) may be used alone or in combination with ACEI/ARB

*KDIGO/NKF recommend a target protein intake of 0.8 g/kg/day for patients with diabetes

Interventional measures in DKD consist of correcting hyperglycaemia, hypertension, and dyslipidaemia, as well as lifestyle modification.[42] Primary renoprevention circumvents the progression of normoalbuminuria to microalbuminuria. Secondary renoprevention involves the prevention of macroalbuminuria from microalbuminuria. Thus, conventional renoprotective strategies are mainly directed against the modifiable risk factors for microalbuminuria and its progression to macroalbuminuria. Also, novel drugs with different mechanisms of action are emerging as effective treatment strategies (Table 1). Additionally, multiple interventions like strict glycaemic control, blood pressure control, correction of dyslipidaemia, and lifestyle change (such as smoking cessation) led to an improvement in the prognosis of cardiovascular disease events and retarded the progression of macroalbuminuria in patients with T2DM and DKD.[43]

CONVENTIONAL RENOPROTECTIVE STRATEGIES

Strict Glycaemic Control

The efficacy of strict glycaemic control as a renoprotective strategy depends on the severity of DKD given its non-beneficial effect in advanced stages of the disease. In studies of patients with T1DM, strict glycaemic control (maintaining HbA1c level at 7%) substantially reduced the incidence of microalbuminuria and macroalbuminuria.[44,45] A meta-analysis also indicated that strict glycaemic control in patients with T1DM for 8–60 months decreases DKD progression risk.[46] In patients with T2DM, the same strategy resulted in a lower risk of microvascular complications compared to dietary treatment[47] and delayed the onset of microalbuminuria and macroalbuminuria, despite failing to reduce the incidence of ESKD.[48] Other strategies are thus required in synergy with strict glycaemic control to reduce the burden of DKD. Concurrent medical control of hyperglycaemia, hypertension, dyslipidaemia, and microalbuminuria significantly delayed progression to overt DKD, retinopathy, and ESKD in microalbuminuric patients with T2DM.[42,49] Thus, glycaemic control should be individualised according to the patient's comorbidities, such as underlying CKD and cardiovascular disease status. Although the Kidney Disease Outcomes Quality Initiative (KDOQI) recommends that strict glycaemic control should keep the HbA1c level to <7% in patients with T1DM and T2DM, a HbA1c level of >7% is suggested as the target for those with multiple comorbidities and risks of hypoglycaemia episodes.[50] Regarding response to glycaemic control, children and adolescents with T2DM appear to differ from adults with T2DM. For instance, the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study suggested that T2DM and its complications may be much more severe and resistant to glycaemic control in children and adolescents compared to their adult counterparts.[51] This multicentre trial specifically showed failure of glycaemic control in 46% of paediatric trial participants despite adequate compliance with metformin alone, metformin and rosiglitazone, or metformin and intensive lifestyle management.

Control of Hypertension

Blood pressure control is effective in retarding DKD progression, reducing cardiovascular disease events, and preventing early mortality in patients with T1DM and T2DM.[22] It reduces microalbuminuria and delays the onset of DKD.[52] RAAS blockade reduces the frequency of microalbuminuria in hypertensive normoalbuminuric patients. This reduction does not occur in normotensive patients because intrarenal RAAS is enhanced in hypertensive patients but not in normotensive patients.[6] There is a direct relationship between hypertension and the degree of albuminuria in T2DM.[53] Thus, RAAS blockade confers benefits extending beyond mere blood pressure control in hypertensive patients with diabetes. Angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-receptor blockers (ARB) are recommended as first-line antihypertensive drugs, especially in patients with albuminuria. A study group reported that ACEI reduced the risk of DKD in patients with T1DM with persistent microalbuminuria.[54] A similar therapy in normotensive and normoalbuminuric patients with T1DM failed to slow the progression to DKD.[55] Besides ACEI/ARB, calcium-channel blockers can serve as an alternative antihypertensive therapy, either alone or in

combination with RAAS blockers. Again, findings from the TODAY study indicate that blood pressure control was more difficult in children and adolescents with T2DM compared to their adult cohorts. Elevated blood pressure in the former was less amenable to treatment, requiring multiple drugs in >33% of trial participants who were initially on monotherapy.[56] However, clinical trials have revealed some therapeutic challenges in adults. The Veterans Affair Nephron Diabetes study reported no significant difference between ACEI/ARB combination therapy and ACEI or ARB monotherapy, as risks of hyperkalaemia and acute kidney injury could increase with the combination therapy.[57] Additionally, the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) showed that combination therapy with telmisartan and ramipril reduced macroalbuminuria to normoalbuminuria but resulted in renal function decline, increased requirements for renal replacement therapy, and increased mortality risk.[58]

Treatment of Dyslipidaemia

Statin therapy may ameliorate albuminuria and reduce cardiovascular disease risk in patients with DKD. For instance, in a trial of atorvastatin versus rosuvastatin, the former showed more renoprotective effects than the latter in reducing albuminuria in patients with DKD receiving RAAS blockers.[59] Additionally, the KDOQI guideline suggests that patients with DKD should receive statin-based medications to lower the levels of LDL-C and reduce the risks of cardiovascular disease events.[50] Nevertheless, a comparison between the response of adult and paediatric patients with T2DM to hypolipidemic therapy suggests a difference in treatment outcomes. In the TODAY study, sustained elevation in inflammatory markers was noted over time and dyslipidaemia increased from 4.5 to 10.7% in paediatric patients over 3 years of follow-up, despite hypolipidemic therapy.[60]

Lifestyle Modifications

Weight reduction, smoking cessation, and dietary restriction of sodium and protein constitute the bedrock of lifestyle modifications. Weight reduction in patients with diabetes with comorbid obesity led to a marked reduction in albuminuria.[61] The Kidney Disease Improving Global Outcomes (KDIGO) guideline recommends the avoidance or cessation of smoking for patients who have DKD or are at risk of DKD because it is deemed an independent disease risk factor.[62] Dietary modification is also useful for retarding the progression of DKD. Although the optimal sodium intake in DKD remains unresolved, its restriction reduces blood pressure and albuminuria.[63] Finally, protein restriction retards the progressive loss of renal function in T1DM and T2DM.[64] The KDIGO and the National Kidney Foundation (NKF) recommend a target dietary protein intake of 0.8 g/kg/day for people with diabetes and those with reduced eGFR.[65] Furthermore, adequate exercise can help to reduce DKD risk and cardiovascular disease events in diabetic adolescent and adult patients in whom improvements in blood pressure, lipid profile, insulin sensitivity, and cardiovascular disease outcomes were reported.[66,67]

NOVEL RENOPROTECTIVE STRATEGIES

Uric Acid Antagonist

Allopurinol, a uric acid antagonist, is effective in reducing albuminuria in T2DM.[68] The mediatory role of uric acid in the pathogenesis of DKD is the basis for using this agent as a renoprotective intervention. Hyperuricaemia leads to glomerular endothelial dysfunction, overactive RAAS, and induction of inflammatory pathways, which all contribute to the renal lesion in DKD.[69] Thus, it is not surprising that allopurinol also improves endothelial dysfunction and reduces urinary TGF-β1 in DKD.[70]

Vitamin D Analogues

The pleiotropic effects of vitamin D receptor activation underscore the potential usefulness of vitamin D analogues in DKD. Given the presence of vitamin D receptors on podocytes, podocyte modulation with these metabolites is thought to affect proteinuria. In some clinical trials, paricalcitol reduced albuminuria in patients with diabetes, and retarded the progression of DKD.[71,72] Vitamin D metabolites may also be renoprotective by inhibiting RAAS and preventing glomerulosclerosis.

Endothelin-Receptor Antagonists or Inhibitors

Endothelins modulate hypertension and CKD through the mechanisms of cell injury, vasoconstriction, endothelial dysfunction, and albuminuria. Two endothelin receptors are involved: endothelin-1 A and endothelin B receptors. The latter mediates proximal tubular sodium excretion. Endothelin receptor antagonists such as atrasentan and avosentan have undergone trials and were found to reduce albuminuria in DKD.[25,73] Avosentan was, however, associated with cardiovascular adverse events, possibly because it blocked both endothelin A and B receptors, unlike atrasentan that selectively inhibited endothelin-1 A receptors and was associated with minimal fluid retention.

Glucose-Lowering Agents

Apart from glycaemic control, some novel glucose-lowering agents may be renoprotective as well. For instance, several recent clinical trials indicated that SGLT2 inhibitors (empagliflozin and canagliflozin) may be associated with slower progression of DKD in T2DM patients.[74,75] Similarly, glucagon-like peptide-1 (GLP-1) analogues (liraglutide and semaglutide) resulted in the same renal outcomes in patients with diabetes.[6] GLP-1 can trigger insulin secretion and mediate glycaemic control. Importantly, its level is reduced in patients with T2DM. Thus, its analogues are beneficial in improving disease morbidity especially in adult patients with T2DM.

Other glucose-lowering agents with their specific therapeutic targets include linagliptin and saxagliptin (dipeptidyl peptidase 4 inhibitors which preserve the glucagon-like peptide effect), and rosiglitazone (thiazolidinediones which activate peroxisome proliferators-activated receptor-γ to increase tissue insulin sensitivity).[6] These drugs reduced albuminuria in macroalbuminuric patients with T2DM.[76-78]

FUTURE RESEARCH DIRECTIONS

Proteomics and metabolomics have identified potential biomarkers to monitor DKD and its progression and provided information on disease pathophysiologic mechanisms.[79-82] More research on these 'multi-omics' methods will provide clinicians with the best approach to manage DKD in the future. Finally, bioinformatics have enabled the identification of noncoding RNA as potential biomarkers and therapeutic targets given their important role in DKD progression.[83] Investigating the regulatory network of these noncoding RNA will open a new outlook for understanding the molecular mechanisms in DKD and how the transcriptomes can act as novel biomarkers and potential therapeutic targets for DKD.[83]

CONCLUSIONS

DKD evolves from diabetic nephropathy, a critical microvascular complication of T1DM and T2DM. Although the late stages of DKD rarely occur in the paediatric age group, structural changes suggestive of the disease may manifest as early as 1.5–5.0 years after the onset of diabetes in both child and adult patients. Thus, conventional and novel renoprotective strategies may help to retard the progression of DKD to ESKD in children and adolescents. Despite the evidence-based successes reported with most of these strategies, some of the novel therapeutic agents are still undergoing trials to validate their use in human participants.

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Pharmacokinetics of Amoxicillin and Cefepime During Prolonged Intermittent Renal Replacement Therapy: A Case Report

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Abstract

Prolonged intermittent renal replacement therapy (PIRRT) is an emerging form of renal replacement therapy in critically ill patients, but dosing data for antibiotics such as amoxicillin and cefepime are scarce and limited. This case report describes the effect of PIRRT on the plasma pharmacokinetics of amoxicillin and cefepime in a 69-year-old, critically ill patient with a polymicrobial intra-abdominal infection. Blood samples taken over 2 days, including a 7-hour PIRRT session, were analysed and a two-compartment model was used to describe cefepime and amoxicillin clearance and dosing requirements during PIRRT and off-PIRRT in this patient. Based on these data, an off-PIRRT dose of 1 g amoxicillin 12-hourly and cefepime 2 g daily with an on-PIRRT dose of 1 g amoxicillin 8-hourly and cefepime 2 g 12-hourly was deemed appropriate.

INTRODUCTION

Acute kidney injury and severe infections are common contributing factors to higher mortality in critically ill patients.[1] For this patient population, continuous renal replacement therapy (CRRT) has traditionally been used as the form of renal replacement therapy (RRT). However, prolonged

intermittent renal replacement therapy (PIRRT) is an emerging modality of RRT in the intensive care unit.[2] PIRRT utilises conventional dialysis machines but runs over a longer time period with lower dialysate and blood flow rates which provides more stable haemodynamics and minimal solute disequilibrium compared to conventional intermittent haemodialysis.[1] The advantages of PIRRT over CRRT include lower operating costs, decreased workload requirements and risk of infection because of the lack of bag handling, and increased patient mobility and participation in physical and occupational therapy.[1,3,4] CRRT, however, has higher clearance rates of small and large solutes and the use of antimicrobials during CRRT has published references with dosing recommendations.[1,4] Optimising antimicrobial dosing in critically ill patients is complex due to pathophysiological changes that can alter pharmacokinetics (PK) and pharmacodynamic properties of antimicrobials.[1] Current antimicrobial PK data during PIRRT are largely limited to case reports or *in silico* dosing simulation studies. This is further complicated by the variability of PIRRT settings (e.g., blood flow, dialysate, ultrafiltration rates) and haemofilter characteristics, which all contribute to the challenge of antimicrobial therapy optimisation.[2,5,6]

The aim of this report is to describe the PK of amoxicillin and cefepime in a patient with polymicrobial intra-abdominal infection undergoing PIRRT and to provide dosing guidance in this setting.

MATERIALS AND METHODS

Patient Characteristics

A 69-year-old, 160 cm, 90 kg male presented with perforated sigmoid diverticulitis with faecal peritonitis. He underwent an emergency Hartmann's procedure with formation of an end-colostomy. The patient had a complicated surgical admission; he underwent a further five laparotomies because of ongoing purulent/faecal collections which culminated into a further large bowel resection and stoma relocation. Initial intraoperative samples grew *Escherichia coli*, *Streptococcus anginosus*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, and mixed anaerobic bacteria. A further intraoperative sample taken 10 days later grew *E. faecalis* and *P. aeruginosa* which was reported to be resistant to piperacillin-tazobactam and meropenem. Wound dehiscence was noted after final surgical closure and swabs of the wound also cultured *E. faecalis*.

The patient sustained an acute kidney injury upon admission to hospital which temporarily required haemodialysis. Recovery of kidney function occurred 2 months into the patient's hospital admission. During the PK sampling period, the patient was oliguric, with a urine output ranging between 0 and 20 mL/hour.

Antibiotic Dose and Administration

According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) interpretive criteria for amoxicillin against *E. faecalis* and *E.coli*, clinical isolates are considered susceptible if the minimum inhibitory concentration (MIC) is ≤4 mg/L and ≤8 mg/L, respectively, and considered resistant when the MIC is >8 mg/L for both organisms.[7] Amoxicillin against *S. anginosus* is inferred from benzylpenicillin, for which clinical isolates are considered susceptible if the MIC is ≤0.25 mg/L and resistant if the MIC is >0.25 mg/L.[7] Lastly, for cefepime against *P. aeruginosa* and *E. coli*, clinical isolates are considered susceptible if the MIC is ≤0.001 mg/L and ≤1 mg/L, respectively, and resistant when the MIC is >8 mg/L and >4 mg/L, respectively.[7]

The patient was commenced on empirical intravenous (IV) antimicrobials for peritonitis on admission, followed by pathogen-directed therapy once intraoperative microbiology became available. During the PIRRT sampling period, the patient was prescribed IV amoxicillin 2 g over 30 minutes every 8 hours and IV cefepime 2 g over 30 minutes every 12 hours. Metronidazole 500 mg given intravenously every 12 hours was also administered in addition to this regimen.

Prolonged Intermittent Renal Replacement Therapy

PIRRT, using a Fresenius 5008 (Fresenius, Sydney, Australia), was conducted as a 7-hour treatment in the haemodiafiltration mode with a heparinised circuit and a 1.4m^2 filter (Ultraflux® AV6700S, Fresenius), a blood flow rate of 200 mL/minute, dialysate flow rate of 240 mL/minute, and an approximate ultrafiltration rate of 233 mL/hour.

Blood Sampling

The patient had a total of eight samples taken over a 2-day period, which included one PIRRT session. Off-PIRRT, blood samples were taken at 0.0, 1.0, 3.5, and 6.0 hours post an amoxicillin dose, which also corresponded to a 6.0, 7.0, 9.5, and 12.0-hour (trough) post-cefepime dose. On-PIRRT, blood samples were taken at 0.0, 1.0, 3.0, and 6.0 hours post an amoxicillin dose, which also corresponded to a 3.0, 4.0, 6.0, and 9.0-hour post-cefepime dose. Samples were stored at -80˚C prior to assay at Pathology Queensland, Brisbane, Australia.

Drug Assay

Serum amoxicillin and cefepime concentrations were measured by validated high-performance liquid chromatography mass spectrometry at Pathology Queensland. Both analytes were linear from 0.1 to 2.5 mg/L, with an intra- and inter-run precision of <10%.

Pharmacokinetics Modelling

PK data were analysed by a nonparametric method with library package for R and for Pmetrics (Laboratory of Applied Pharmacokinetics, Los Angeles, California, USA) with testing of both one- and two-compartment models. An addition of a second clearance term was included to represent the dialytic clearance from PIRRT, which was tested and included. Both additive (λ) and multiplicative (γ) error models were tested for both drugs. Inspection of the log-likelihood ratio and goodness-of-fit plot was used to select the final models.

Consent

Informed consent was obtained to collect blood samples and to report this case.

RESULTS

Pharmacokinetic Results

The concentrations of amoxicillin during the entire sampling period were at least 5–10-fold higher than the breakpoint MIC of *E. coli* (8 mg/L) and *E. faecalis* (4 mg/L).[7] Cefepime concentrations during the sampling were at least 29-fold higher than the breakpoint MIC of *P. aeuroginosa* (0.001 mg/L) and *E. Coli* (1 mg/L).[7] A two-compartment model with clearance terms describing PIRRT clearance and non-PIRRT clearance adequately described the data.

Table 1 describes the mean PK parameters of amoxicillin and cefepime. Figures 1 and 2 provide a graphical representation of the model goodness of fit of amoxicillin and cefepime, respectively, and confirm the adequacy of the model.

Table 1: Mean pharmacokinetic parameters of amoxicillin and cefepime in the patient.

	Amoxicillin	Cefepime
$Cl_{non\text{-}PIRRT}$ (L/hour)	8.45	5.57
Cl_{PIRRT} (L/hour)	0.66	1.16
Cl_{total} (L/hour)	9.11	6.73
V_C (L)	12.58	7.10
K_{PC} ($hour^{-1}$)	0.45	0.52
K_{CP} ($hour^{-1}$)	0.47	1.01
Error model	L=0.2 (additive)	L=0.2 (additive)

$Cl_{non\text{-}PIRRT}$: clearance of drug without prolonged intermittent renal replacement therapy; Cl_{PIRRT}: clearance of drug with prolonged intermittent renal replacement therapy; Cl_{total}: clearance of drug during prolonged intermittent renal replacement therapy with native renal function; K_{CP}: intercompartmental rate constant from central compartment to peripheral compartment; K_{PC}: intercompartmental rate constant from peripheral compartment to central compartment; V_C: volume of distribution of central compartment.

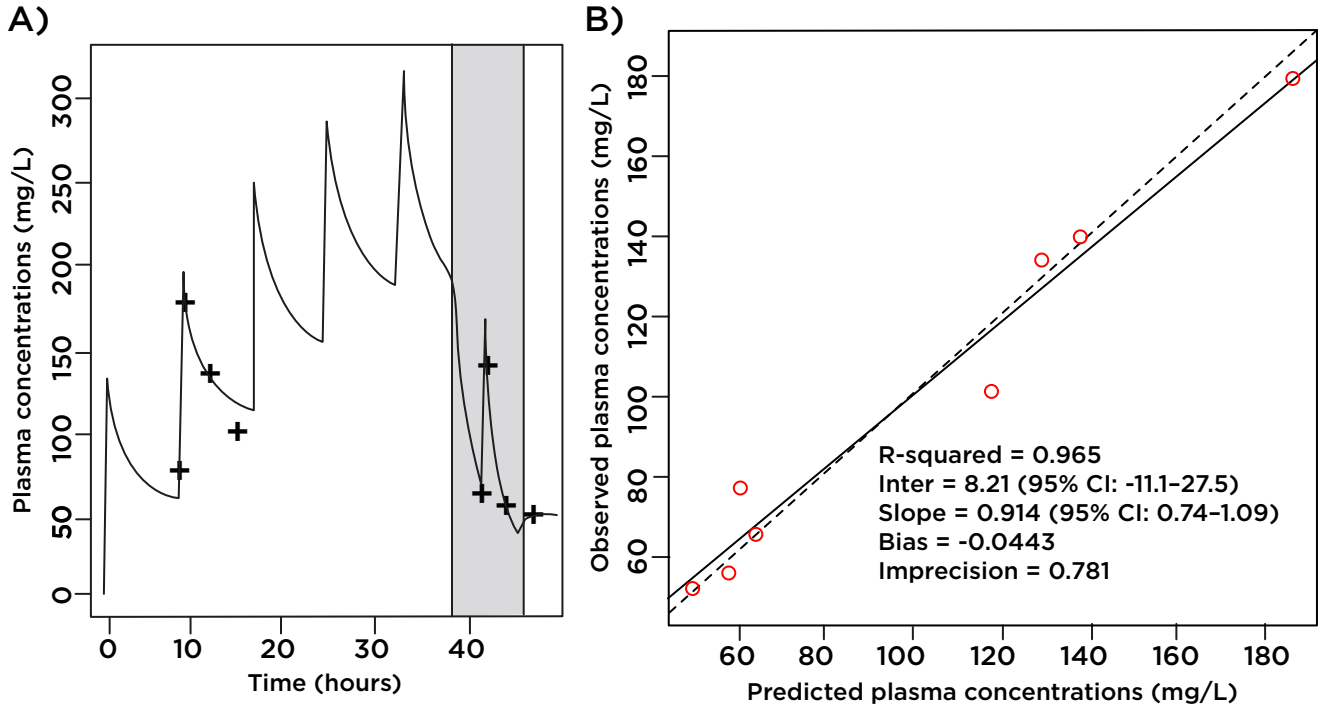

Figure 1: A) The predicted amoxicillin unbound plasma concentration time-profile versus observed data point, with PIRRT therapy shaded in grey. **B)** Observed-predicted plot for population and individual patient amoxicillin plasma concentrations.

CI: confidence interval; PIRRT: prolonged intermittent renal replacement therapy.

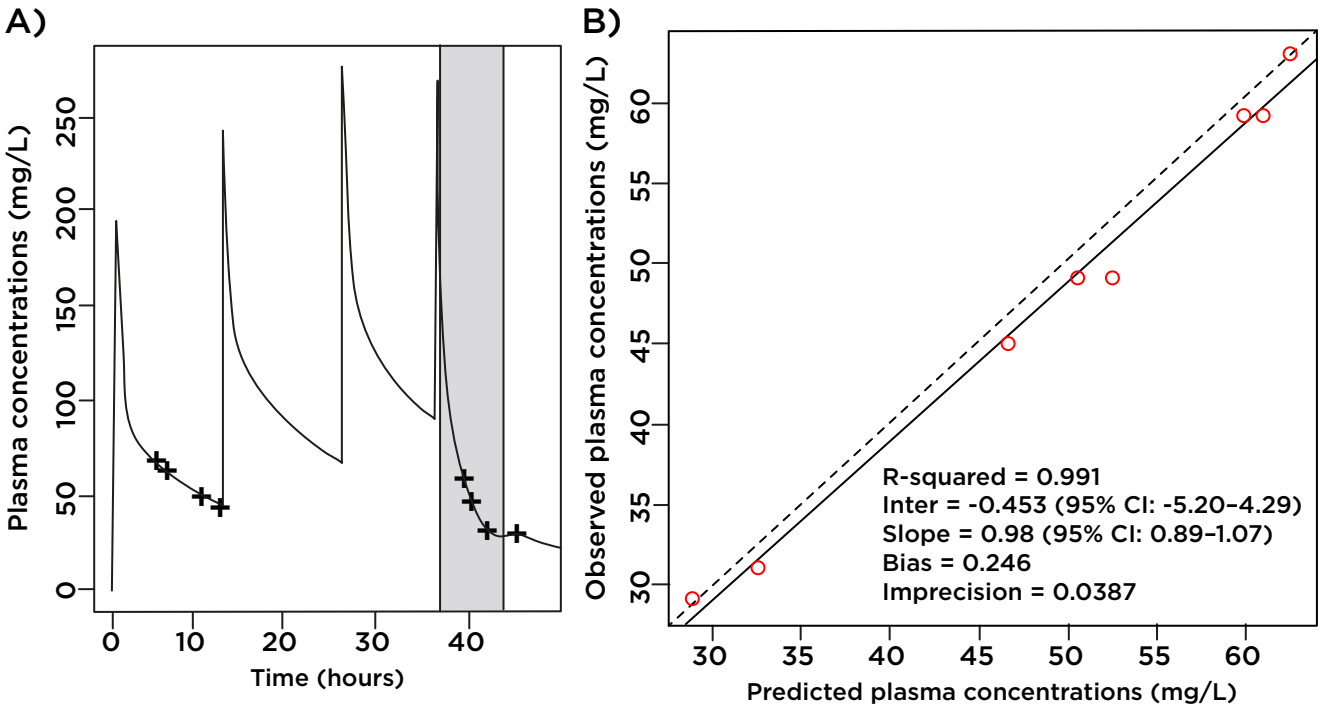

Figure 2: A) The predicted cefepime unbound plasma concentration time-profile versus observed data point, with PIRRT therapy shaded in grey. **B)** Observed-predicted plot for population and individual patient cefepime plasma concentrations.

CI: confidence interval; PIRRT: prolonged intermittent renal replacement therapy.

Clinical Outcomes

Around the sampling period, the patient exhibited signs of encephalopathy which treating clinicians suspected may have been because of cefepime toxicity. Because of this, ciprofloxacin was substituted for cefepime until antibiotics were subsequently ceased after a total of 6 weeks, with clinical, biochemical, and radiological resolution. The patient was successfully discharged from the intensive care unit after 38 days but remained in hospital to undergo medical treatment, followed by rehabilitation, for a further 6.5 months. He was discharged from hospital to transitional care to await placement in a rehabilitation facility for ongoing care.

DISCUSSION

To the authors' knowledge, this is the first report describing the effect of PIRRT on amoxicillin PK. Amoxicillin is a β-lactam antibiotic which is predominantly renally cleared and has been documented to be removed by most forms of RRT. However, dosing recommendations for other RRT modalities cannot be readily transferred to patients undergoing PIRRT.[8-13] β-lactams exhibit time-dependent pharmacodynamics, meaning the free drug concentration (∫) should be maintained over the causative organism's MIC for the maximum amount of time (T>MIC) to maximise bacterial killing.[14] Experimental studies recommend a minimum 50%∫T>MIC should be targeted, although higher targets, as high as 100%∫T>4-5xMIC, have been suggested in critically ill patients with severe infections.[4,15-17] In this patient, PIRRT significantly increased amoxicillin clearance compared with periods when PIRRT was not used (9.11 versus 0.66 L/hour). Because of the high amoxicillin clearance during PIRRT, inadequate amoxicillin dosing while a patient is on PIRRT could potentially lead to antimicrobial resistance or treatment failure.[18] However, in the sampling period the patient received an amoxicillin dose of 2 g every 8 hours on both PIRRT and non-PIRRT days, providing sufficient free drug levels to achieve 100%∫T>5xMIC. Given the low amoxicillin clearance when the patient was not on PIRRT and the high plasma levels achieved during the sampling period despite RRT, a dose of 1 g every 8 hours on PIRRT and 1 g every 12 hours on non-PIRRT days would be recommended.

Cefepime is a fourth-generation cephalosporin, with antimicrobial activity against Gram-positive and Gram-negative bacteria including *P. aeruginosa*, and is known to be removed by RRT.[19] Like other β-lactams, cefepime exhibits time-dependent bactericidal activity with studies suggesting similar targets ranging from 60–70%∫T>MIC to 100%∫T>4-5xMIC.[19,20] There have been various dosing schedules suggested for patients receiving PIRRT, including a Monte Carlo simulation study which recommended a cefepime 2 g loading dose with 1 g every 6 hours while on PIRRT or cefepime 2 g at commencement of PIRRT and 3 g at the end of PIRRT.[21] In this patient, PIRRT increased the cefepime clearance significantly (5.57 versus 1.16 L/hour). In spite of the higher clearance, a therapeutic target of 100%∫T5xMIC was easily achieved during the sample period. The use of cefepime in patients with renal impairment, in the intensive care unit, or of older age has been associated with an increased risk of neurotoxicity which can present as confusion, impaired consciousness, hallucinations, myoclonus, seizures, and encephalopathy.[19-24] This neurotoxicity is attributed to an ability to cross the blood–brain barrier and exhibit concentration-dependent GABA antagonism.[23,24] Because this effect is concentration dependent, some studies suggest that a cefepime trough level of 36 mg/L is a highly accurate and sensitive threshold marker for cefepime-induced neurotoxicity, although this could be as low as 23 mg/L.[23,24] Supratherapeutic cefepime concentrations could have contributed to the encephalopathy in this case, especially as no dosage adjustments were made when the patient was not being dialysed. A dose reduction to 2 g every 24 hours when not receiving PIRRT to reduce accumulation of cefepime is suggested.

The rate of diffusion, the principle mechanism of drug removal in PIRRT, is proportional to the surface area of the dialyser used. In this study, a dialyser with a surface area of 1.4 m^2 was used. Using larger or smaller dialysers would result in proportionally different drug clearances.[1]

CONCLUSION

In conclusion, amoxicillin 2 g every 8 hours and cefepime 2 g every 12 hours both on PIRRT and off PIRRT resulted in concentrations well in excess of the MIC but at levels that could potentially

be toxic in this patient. The authors recommend giving 1 g of the amoxicillin dose every 12 hours and 2 g of the cefepime dose every 24 hours during non-PIRRT periods because of the lower clearance when not on PIRRT. Given individual patient and PIRRT variabilities, however, further data are required to provide dosing recommendations for extrapolation to the rest of the patient population. The impact of PIRRT on metronidazole clearance was not available to be described in this paper.

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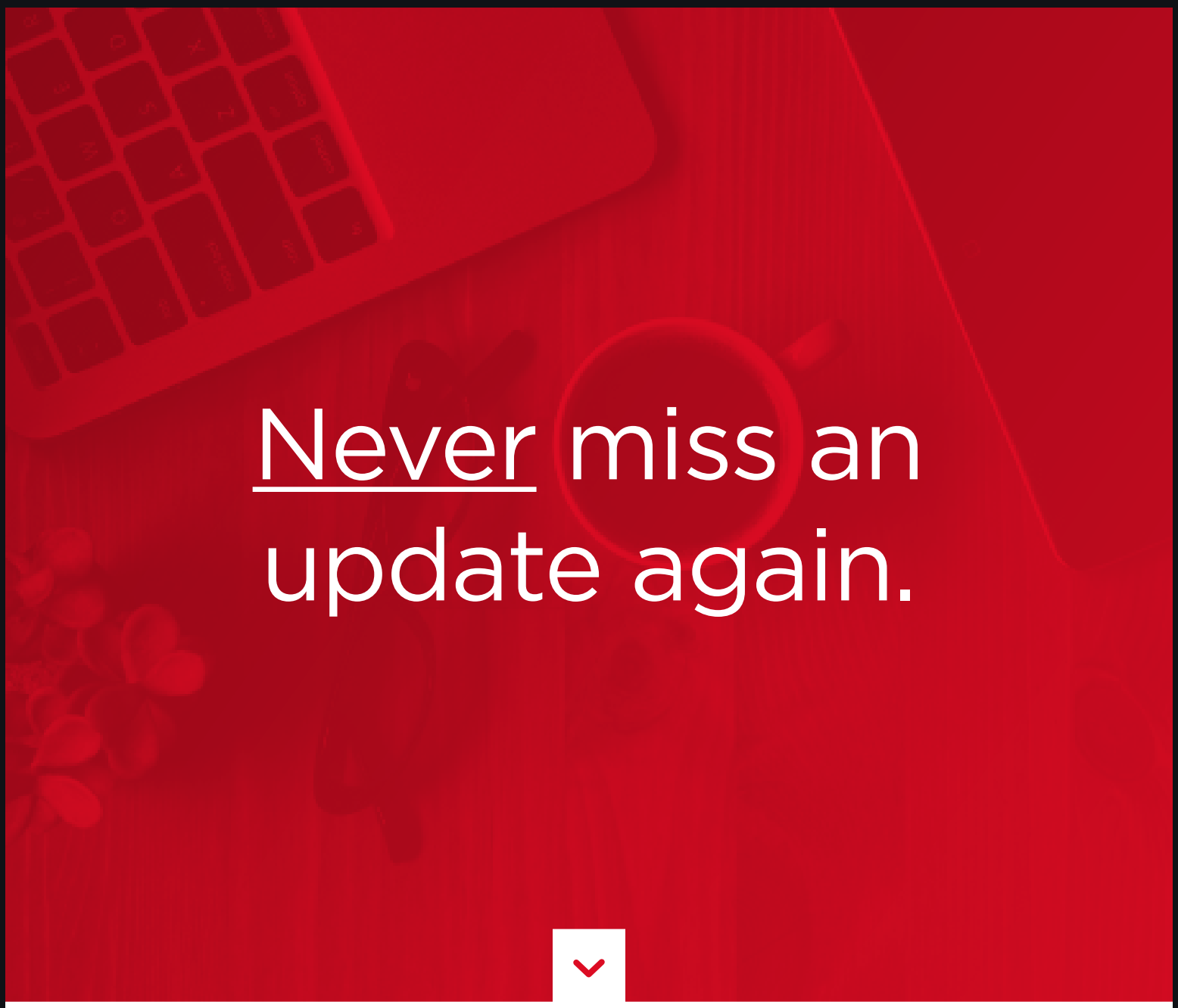

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