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NEPHROLOGY

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Contents

"With plenty to offer, EMJ Nephrology 6.1 is sure to showcase fascinating content that will spark countless hours of intense debate and discussion..."

Spencer Gore, CEO

Editorial Board

VIEW IN FULL ←

Aims and Scope

The European Medical Journal (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.

EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

EMJ is published quarterly and comprises review articles, case reports, practice guides, theoretical discussions, and original research.

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- Peer review, which is conducted by EMJ's Peer Review Panel as well as other experts appointed due to their knowledge of a specific topic.
- An experienced team of editors and technical editors.

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Front cover and contents photograph: Copenhagen, Denmark home of the ERA–EDTA 2018. © Marinv / 123rf.com

EMJ Nephrol.

EMJ Innovations 2.1

The European Medical Journal is bringing the New Year in with a bang with the publication of *EMJ Innovations 2.1*. This edition is packed with all the most exciting upcoming...

VIEW ALL JOURNALS ←

Welcome

I am pleased to welcome you to the 2018 edition of *EMJ Nephrology*, within which you can relive the very best moments from the 55th European Renal Association–European Dialysis and Transplant Association (ERA–EDTA) Congress 2018. Find inside a comprehensive review of the event, as well as an array of peer-reviewed articles, abstract reviews direct from ERA–EDTA itself, and interviews with our esteemed *EMJ Nephrology* Editorial Board.

As usual, the ERA–EDTA annual congress exceeded all expectations and here we bring you some of the hottest research topics straight from the congress itself. Discover the latest biomarkers for kidney disease, improvements in care for pre-eclampsia patients, and recommendations for improving mineral metabolism, before turning to the gripping Abstract Review section. Penned by the presenters themselves, this section includes a real variety of research topics, such as the factors that affect urothelial cancer risk in chronic kidney disease patients, Twitter as a learning tool for nephrologists, and renal management strategies in tuberous sclerosis. To complement this extensive congress coverage, we bring you insights into the careers and lives of some of the *EMJ Nephrology* Editorial Board members. Find out about their unique perspectives on the world of nephrology in this distinctive section of the journal.

Building on the hottest topics of the year, this edition's peer-reviewed articles form the pinnacle of nephrology research. This year's Editor's Pick, by Chakera et al., discusses the most up-to-date developments in microbiological techniques for the diagnosis of peritonitis in peritoneal dialysis. The authors provide substantial evidence to improve the confidence of clinicians to continue using peritoneal dialysis, without the risk of infection. There is also an emphasis on antibiotic susceptibility testing: a topic of major importance in the current medical world. Another article of interest is that by Salvadori and Tsalouchos, which focusses on the nephrologist's view of induction therapy in antineutrophil cytoplasmic antibody-associated vasculitis with renal involvement. This in-depth review discusses the challenges faced by the nephrologist in induction therapy, as well as the future implications for the technique. Read these articles and many more in this exciting section.

We hope you enjoy reading all the content on offer within this eJournal as much as we have enjoyed creating and collating it for you. We are certain that it will inspire further research and spark discussion that will last for months to come. We are looking forward to next year's ERA–EDTA Congress in Budapest, Hungary, and hope to see you there.

Spencer Gore

Chief Executive Officer, European Medical Group

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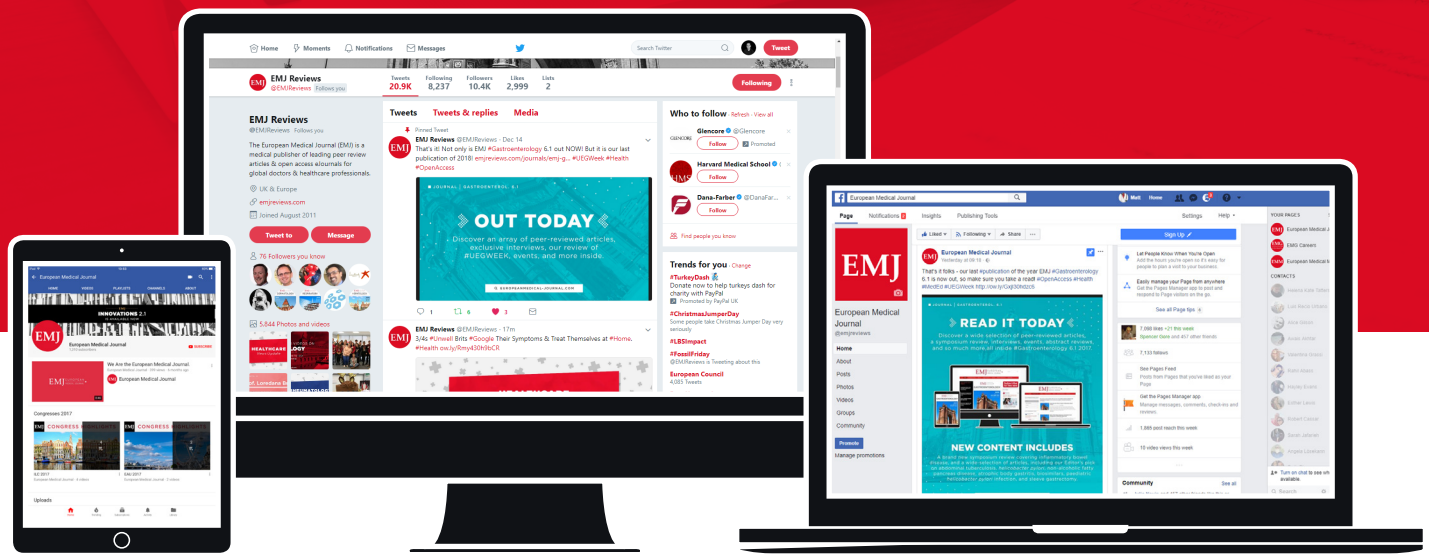

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Foreword

Dear colleagues,

I take great pleasure in being able to introduce to you the latest issue of *EMJ Nephrology*. With a complete review of the excellent European Renal Association–European Dialysis and Transplant Association (ERA–EDTA) 2018 Congress and a host of peer-reviewed articles, I am sure everyone will find something to enjoy and learn from in this eJournal.

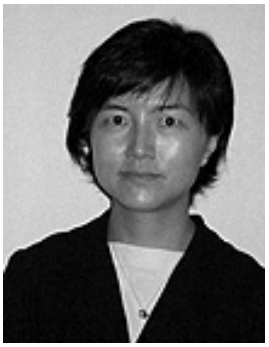
The 55th ERA–EDTA Congress in Copenhagen, Denmark, was attended by more delegates than ever before, creating a bustling atmosphere perfect for the revelation of key research. A hand-picked selection of the latest breakthroughs was on show throughout the 3-day event, garnering much attention both at the event itself as well as on social media. This eJournal's Congress Review section includes all of the pivotal highlights, including key details from the vast array of poster presentations and discussion sessions. Whether you had the pleasure of attending the event yourself or were sadly absent this year, I advise you to head to the Abstract Reviews section, where a collection of these presentations are succinctly summarised by the authors themselves.

Interviews with my colleagues on the Editorial Board will be of great interest to aspiring nephrologists; the interviews detail their career trajectories, how they arrived at their current specialities, and their thoughts on the future of the field. In a digital age full of instantaneous communication, it is all too easy to forget the patients' emotions, but these interviews demonstrate the unsung importance of personality and integrity for all medical professionals, particularly in their interactions with patients.

The latter half of this eJournal contains a broad selection of wonderful peer-reviewed articles, which I hope all will enjoy. The Editor's Pick for this edition is 'Peritonitis in Peritoneal Dialysis Patients: The Case for Rapid Diagnosis, Targeted Treatment, and Monitoring to Improve Outcomes', by Chakera et al., a paper that argues the importance of increasing our currently poor understanding of host–microbe interactions in the peritoneal cavity. These papers superbly complement the Congress Review, providing a breadth of knowledge to benefit all readers on areas including renal transplant, glomerulonephritis, and peritoneal dialysis.

I would like to thank everyone who contributed to the creation of this exciting issue of *EMJ Nephrology* and hope to see all of you at the ERA–EDTA Congress next year in Budapest, Hungary.

Kind regards,



Dr Angela Yee-Moon Wang
University of Hong Kong, Hong Kong

Available now.

Featured inside:

Congress Review

+ Review of the EAU Copenhagen, Denmark, 16th–20th March 2018

Abstract Reviews

Articles

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+ Aetiology and Evaluation of Men with Urethral Stricture and the Current Role of Urethroplasty in the Treatment of Anterior Urethral Strictures
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  Roderick Clark

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Congress Review

Review of the 55th European Renal Association–European Dialysis and Transplant Association (ERA–EDTA) Congress 2018

Location: Copenhagen, Denmark – Bella Center

Date: 24.05.18–27.05.18

Citation: EMJ Nephrol. 2018;6[1]:12-24. Congress Review.

This year's host of the annual ERA–EDTA Congress was the Danish capital of Copenhagen, labelled the happiest city in the world and home to Hans Christian Andersen's Little Mermaid. As thousands of researchers, physicians, experts, and novices flocked to the Bella Center, Copenhagen prepared for Europe's flagship nephrology event, a 4-day spectacular packed with a bounty of the latest nephrological studies, results, and news.

The excitement was audible as the packed congress hall awaited Prof Bo Feldt-Rasmussen, ERA–EDTA President, University of Copenhagen, Copenhagen, Denmark, to take to the stage. ERA–EDTA returned to Copenhagen for the first time since 2002 and Prof Feldt-Rasmussen explained that with 6,547 delegates in attendance and >2,000 abstracts and posters being presented during the event, the ERA–EDTA Congress was back, bigger and better than ever before.

Attention quickly moved to the spectacular scientific programme masterminded by the organising committee. Modern medicine, specifically nephrology, faces a number of new challenges that inspired the theme of this year's congress: 'kidney disease: new paradigms, new challenges, new opportunities'. The congress brought this theme to life with something for everyone to enjoy, detailing the newest techniques and methodologies, including gene editing, molecular biology, and big data. "All of this is crucial in our ongoing search for better treatment for our patients," summarised Prof Feldt-Rasmussen. In a nephrology celebration packed with unmissable symposia, late-breaking clinical trial sessions, and presentations, ERA–EDTA 2018 attempted to look at the field from a new direction, innovatively tackling the problems faced by the field.

With mounting pressure on governments and industry, ERA–EDTA turned the spotlight away from the operating table and towards the environment. The impact of medicine on the environment made the ERA–EDTA Congress agenda for the first time this year: "At the global level, the healthcare sector also has a clear negative impact on the environment," explained Prof Peter Blankestijn, University Medical Center Utrecht, Utrecht, Netherlands. Prof Blankestijn highlighted the key areas of dialysis and home healthcare that could be changed to decrease the effect nephrology has on the environment. The inclusion of the environmental impact of medicine at such a high-profile event will surely induce a domino effect, triggering other specialities to consider the impact of their profession on the environment.

This year's host of the annual ERA–EDTA Congress was the Danish capital of Copenhagen, labelled the happiest city in the world…

For some, there was an additional triumph to celebrate this year, as the annual ERA–EDTA awards were presented. Prof Jürgen Floege (Germany) was recognised for his outstanding clinical contribution to nephrology; Prof Hans-Joachim Anders (Germany) was awarded for his outstanding basic science contributions to nephrology; Prof Andrzej Więcek (Poland) was presented the award for outstanding contributions to ERA–EDTA; and, last but not least, Dr Shrikant Ramesh Mulay (Germany) was presented with the ERA–EDTA 2018 Young Investigators Award.

In the following Congress Review, the key findings, studies, results, and trials are discussed, providing you with the highlights from the 55th ERA–EDTA annual congress. As ever, chronic kidney disease was of paramount importance, but this year the link between cardiovascular disease and chronic kidney disease was placed under the microscope as the results of three important studies were discussed. Furthermore, the ever-growing diabetes epidemic did not escape the attention of the globe's nephrologists, as the impact of the metabolic disorder on the kidneys was also a topic of great debate. For those of you who were not able to attend this year's congress, we are sure this review will capture the spirit of the occasion.

The 56th ERA–EDTA annual congress will be held next year in Budapest, Hungary. The Hungarian capital and pearl of the great Danube river, home to the historic thermal spas and birthplace of goulash, will welcome you for another celebration of kidney research, and we look forward to seeing you there.

Review Confirms Recommendation for Pre-Emptive Kidney Transplant

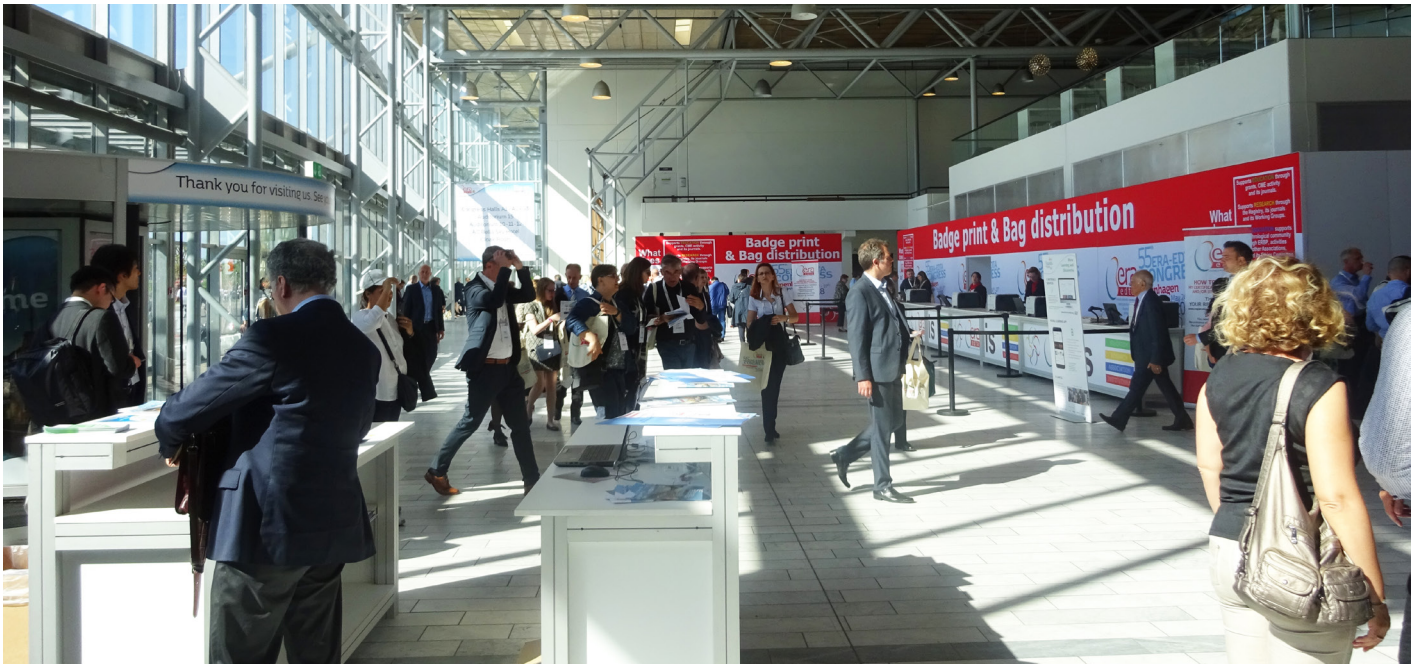
QUESTIONS about the best treatment strategy for patients with kidney failure have been explored in a review article published during ERA–EDTA 2018 and discussed in a ERA–EDTA press release dated 24th May 2018. This article provided supporting evidence that patients who received a kidney transplant prior to commencing dialysis would benefit from this procedure in terms of extended life.

"This recommendation is, however, reasonable for patients of all ages based on currently available observational studies if we take their limitations into account."

Kidney transplantation is a cost-effective, long-term procedure and demonstrates improvements in quality of life; therefore, it is logical that patients should receive a kidney transplant before beginning dialysis, a treatment plan that was encouraged by all current clinical guidelines. However, this recommendation is not based on gold-standard evidence, as the study's lead author, Prof Rainer Oberbauer, Medical University of Vienna, Vienna, Austria, explained: "There are no randomised controlled trials proving that pre-emptive kidney transplantation is the preferred treatment for eligible patients with end-stage renal failure." Furthermore, the existing evidence base does not resolve the question of whether dialysis vintage negatively affected graft and patient survival post transplantation.

This review synthesised the most recent studies investigating pre-emptive transplantation and the link between dialysis vintage and outcomes. The strongest evidence suggested an association between pre-emptive transplantation and a lower risk of actual graft loss (including death) when compared with non-pre-emptive transplantation. The results also showed that the latest studies, conducted within the last decade, did not indicate an association with dialysis vintage and graft survival, unlike older studies. While the majority of the recently published studies demonstrated a grade association between patient survival and dialysis vintage, any impact on functioning graft survival was not clear. The authors also highlighted an association between dialysis vintage and death post transplantation that varied by country; they suggested the reasons for this variance were likely the differences in national waiting times for a kidney transplant and in median dialysis duration of those on the transplant waiting list.

Based on their results, the study authors were confident that pre-emptive kidney transplantation was the most suitable recommendation for patients, with Prof Oberbauer noting: "This recommendation is, however, reasonable for patients of all ages based on currently available observational studies if we take their limitations into account."



DKK3: A new Biomarker for Kidney Disease Progression

CHRONIC kidney disease (CKD) patients at risk of disease progression could be identified earlier, regardless of the cause of kidney injury, with the use of a new biomarker, DKK3. According to a ERA–EDTA press release dated 25th May 2018, this newly discovered biomarker could allow physicians to better manage CKD patients and alleviate the future burden of the disease.

The pathologic model for renal progression and kidney damage is advancing tubulointerstitial fibrosis. Cytokines that control the regenerative process are released by damaged cells in renal tubules, but they can also lead to the tubulointerstitial fibrosis by continuous activation for the Wnt signalling pathway. Dickkopt-related (DKK) proteins are modulators of the Wnt signalling pathway and, as such, urinary DKK3 could be used to indicate tubular stress and the progression to tubulointerstitial fibrosis, indicating which CKD patients are becoming progressive rather than stable.

Results from a prospective cohort study of 575 patients with various CKD aetiologies were presented at ERA–EDTA 2018. The median urinary DKK3 and creatinine concentrations were found to be significantly higher in patients with CKD compared to the general population (33 pg/mg versus 431 pg/mg; p<0.0001). DKK3 concentrations were significantly associated with CKD progression; urinary DKK3 >1,000 pg/mg creatinine and >4,000 pg/mg creatinine were associated with a mean annual estimated glomerular filtration rate reduction of 2.4% (95% confidence interval: -4.6–[-0.2]%; p=0.007) and 7.6% (95% confidence interval: -10.9–[-4.2]%; p<0.001), respectively, independent of estimated glomerular filtration rate and albuminuria.

"These findings show that urinary DKK3 identifies CKD patients at risk for kidney disease progression, regardless of the cause of kidney injury."

Study co-author Prof Danilo Fliser, Universitätsklinikum des Saarlandes, Homburg, Germany, summarised the impact of the study: "These findings show that urinary DKK3 identifies CKD patients at risk for kidney disease progression, regardless of the cause of kidney injury. Therefore, urinary DKK3 might represent a novel diagnostic toll to improve the management of CKD patients and thereby to prevent the major burden of CKD." These results have enabled a new test to be developed that can identify DKK3 within 1 mL of spot urine using a newly developed DKK3-ELISA test. This ease of detection could allow patients at risk of progressive CKD to be identified and treated accordingly, allowing better management of symptoms and lessening the burden of CKD.

Chronic Kidney Disease, Diabetes, and the Heart

CHRONIC kidney disease (CKD) affects 10–15% of the entire global population; these patients have a poor prognosis due to the associated high risk of cardiovascular adverse events, including sudden cardiac death, stoke, and heart attack. Type 2 diabetes mellitus (T2DM) has also been associated with an increased risk of cardiovascular disease and, despite recent advances, T2DM patients who present with kidney disease have a poor prognosis. In the results of a hotly anticipated study, published in a ERA–EDTA press release dated 25th May 2018, the combined effect of CKD and T2DM on the risk of cardiovascular diseases was discussed.

In this study, carried out by Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, 496 CKD patients were enrolled. The patients were divided into four groups based on their diabetic status: no diabetes, known T2DM, unknown T2DM, and prediabetes (classified as a fasting blood sugar level of 6.0–6.9 mmol/L). The participants were interviewed and medically examined before analysis of blood and 24-hour urine samples was carried out.

The analysis revealed that diabetes had a significant impact on the risk of cardiovascular disease in CKD patients. Of the patients in the known T2DM group, >1 in 2 had developed cardiovascular disease, which is higher than the risk observed in the unknown T2DM and prediabetes patients, where 1 in 3 patients were affected by cardiovascular disease. All three diabetes groups presented with a greater cardiovascular disease risk than the nondiabetic kidney disease group, in which 1 in 4 patients had cardiovascular disease.

"We have to do everything we can to prevent CKD patients from developing diabetes mellitus…"

Discussing the results, study leader and ERA–EDTA President Prof Bo Feldt-Rasmussen, Rigshospitalet, University of Copenhagen, stated: "CKD patients who also have diabetes mellitus are seriously ill, high-risk patients. They have a worse prognosis than many cancer patients. We have to do everything we can to prevent CKD patients from developing diabetes mellitus and to raise kidney patients' awareness of preventive measures." The identification of the elevated risk of cardiovascular disease development as a result of T2DM and CKD poses an important question for the medical community. The reality that kidney damage is often triggered by diabetic disease must be taken into consideration and diabetes treatment must be improved to reduce the risk of kidney and cardiovascular disease.

Collaborative Care Required for Women with Pre-Eclampsia

GREATER collaboration has been called for between nephrologists, midwives, and obstetricians in the deliverance of post-partum care for women who present with pre-eclampsia. When discussing the nationwide Danish cohort study investigating chronic kidney disease (CKD) and pre-eclampsia, which was detailed in a ERA–EDTA press release dated 24th May 2018, Dr Mette Brimnes Damholt, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, declared: "The findings show that pre-eclampsia increases the risk of kidney disease significantly and is associated with several types of CKD in later life."

In light of previous associations between later end-stage renal disease and pre-eclampsia, the researchers set out to investigate associations between pre-eclampsia and incidence of post-partum CKD. Following a search of the Danish national health registers, 1,072,330 women with pregnancies lasting ≥20 weeks were identified. These pregnancies took place from 1978–2015 and the average follow-up time was 18.6 years.

The results showed increased rates of post-partum CKD in women with pre-eclampsia when compared with women who had no history of pre-eclampsia and who delivered in the same gestational age interval. Additionally, the research team identified:

- Women who had a history of early pre-term pre-eclampsia had an almost four-fold increased risk of developing kidney disease (hazard ratio [HR]: 3.93).
- Women with a history of late, pre-term pre-eclampsia had an almost three-fold increased risk (HR: 2.81).
- Women with a history of term pre-eclampsia had a two-fold increased risk (HR: 2.27).

"The findings show that pre-eclampsia increases the risk of kidney disease significantly and is associated with several types of CKD in later life."

Additionally, it was noted that the strongest associations between pre-eclampsia and unspecified impairment and glomerular disease were within 5 years of pregnancy, whereas associations with chronic tubulointerstitial nephritis were not time-bound. These results highlight the need for multidisciplinary, collaborative care for patients with pre-eclampsia.

Lowering Urate Levels Reduces Cardiovascular Risk for Chronic Kidney Disease Patients

ALLOPURINOL, a well-established drug used to lower elevated levels of serum urate, could offer an effective treatment against cardiovascular risk

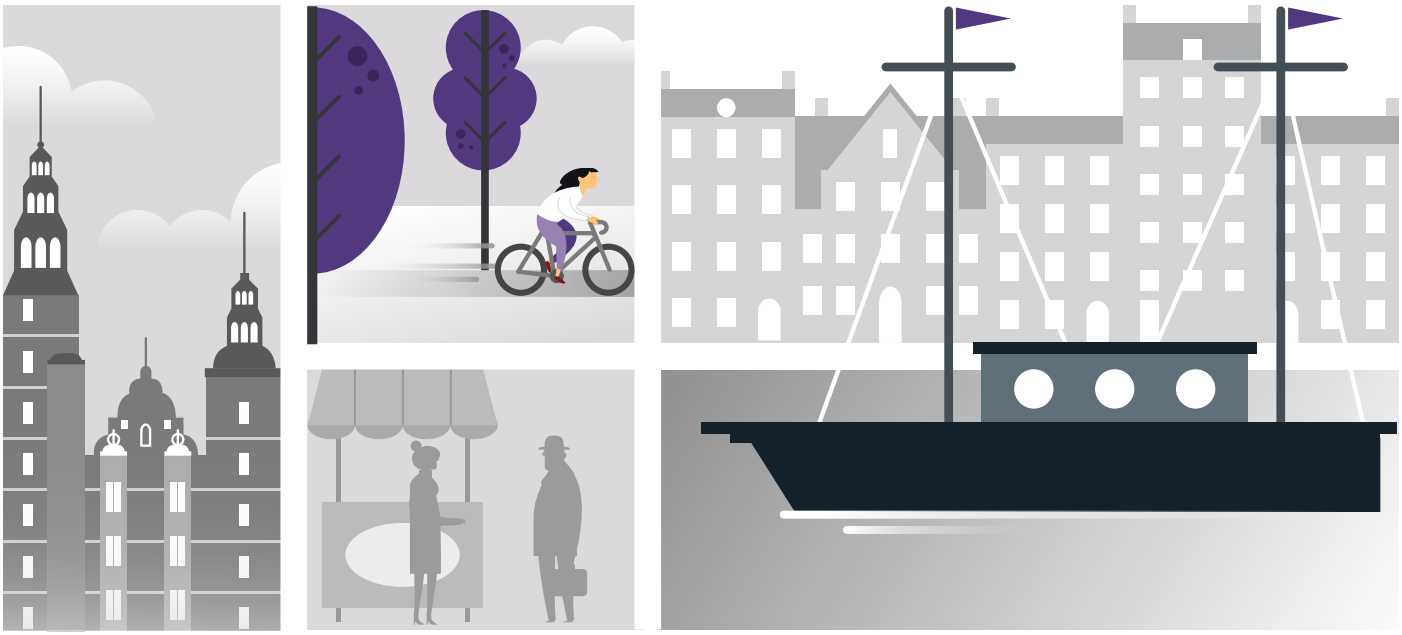
factors for chronic kidney disease (CKD) patients, according to results presented at ERA–EDTA 2018. The thought-provoking results from a study assessing the effect for allopurinol on serum urate levels and left ventricular hypertrophy (LVH) in haemodialysis patients were presented in a ERA–EDTA 2018 press release dated 25th May 2018.

Dr Elaine Rutherford, University of Glasgow, Glasgow, UK, lead investigator of the study, explained the reasoning behind the initiation of the study: "In allopurinol we have a well-known, generally well-tolerated and inexpensive medication which may also be able, beyond its usual indications, to reduce the risk of cardiac arrest, not only in many cardiac patients but also, or especially, in renal patients."

The randomised control trial included 80 haemodialysis patients who received either 300 mg allopurinol or placebo after each dialysis session for 1 year. Both groups had similar urate levels at the beginning of the trial (average 365 µmol/L) and LVM was measured by magnetic resonance imaging (MRI) before and after the study. A total of 53 patients were evaluated at the end of the study. A significant reduction in serum urate levels was found in those treated with allopurinol (-44±84 µmol/L), whereas in the placebo group, the levels increased (+21±100 µmol/L). Allopurinol was not initially shown to have a significant effect on LVM; however, subanalysis of patients whose urate levels fell by ≥20% showed a significant decrease in LVM (-2.9±7 g/m^2, compared to +3.6±10.4 g/m^2 under placebo).

"In allopurinol we have a well-known, generally well-tolerated and inexpensive medication which may also be able, beyond its usual indications, to reduce the risk of cardiac arrest, not only in many cardiac patients but also, or especially, in renal patients."

Commenting on the study results Dr Rutherford said: "[...] there seems to be a link between reduced LVH and the efficacy of urate reduction, and thus a potential dependence on the allopurinol dose required by each individual. This now needs to be investigated in a study on cardiovascular outcomes among haemodialysis patients, specifically among those who respond to allopurinol with sufficient lowering of urate level, which needs to be discovered in a run-in phase."



Treatment Options for Severe Anti-Neutrophil Cytoplasm Antibodies-Associated Vasculitis

EVIDENCE detailing two treatment options for anti-neutrophil cytoplasm antibodies (ANCA)-associated vasculitis was provided by the results of a recently published study highlighted in a ERA–EDTA press release dated 25th May 2018. The researchers set out to answer two questions:

- Does a lower dose of oral glucocorticoids ameliorate the risk of infection without resulting in an increased risk of end-stage renal disease (ESRD) or death in patients with ANCA-associated vasculitis?
- Does plasma exchange reduce the risk of ESRD or death in patients with ANCA-associated vasculitis?

To answer these questions, the researchers designed and conducted a two-by-two factorial randomised controlled trial; this trial examined the impact of plasma exchange and two distinct regimens of oral glucocorticoids (standard regimen or a reduced-dose regimen) in a cohort of 702 patients with severe ANCA-associated vasculitis. The primary outcome assessed was a composite outcome of death from any cause or ESRD. Patients were followed for up to 7 years and all patients received immunosuppressive treatment. Patients were randomly assigned to either receive seven treatments of plasma exchange or no plasma exchange; furthermore, patients were additionally assigned to receive a standard oral glucocorticoid treatment regimen or a reduced-dose oral glucocorticoid treatment regimen (<60% of the cumulative dose).

...a reduced dose of oral glucocorticoids resulted in fewer serious infections than the standard dose and did not substantially increase the risk of ESRD or death.

The results did not demonstrate a statistically significant difference in the primary outcome between patients allocated to plasma exchange (28%) and patients not allocated to plasma exchange (31%) (hazard ratio: 0.86; 95% confidence interval [CI]: 0.65–1.13; p=0.27). This answered the second research question of whether plasma exchange reduced the risk of ESRD or death.

In regard to the first research question, the non-inferiority hypothesis was met, with the primary outcome occurring in 28% of patients in the reduced glucocorticoid cohort versus 26% in the standard regimen cohort (absolute risk difference: 2.3%; 90% CI: -3.4–8.0%). Furthermore, there was a significant difference in the incidence rate of serious infections during the first year; the reduced glucocorticoid cohort presented with fewer serious infections (incidence rate ratio: 0.70; 95% CI: 0.52–0.94;

p=0.02). Therefore, these results demonstrated that a reduced dose of oral glucocorticoids resulted in fewer serious infections than the standard dose and did not substantially increase the risk of ESRD or death.

Improved Glomerulonephritis Patient Prognosis in Denmark

PATIENTS in Denmark diagnosed with glomerulonephritis (GN) today have a better 5-year mortality rate prognosis than those diagnosed 30 years ago, despite an increasing number of GN cases being diagnosed. Study results analysing GN incidence data from centres across Denmark from 1985–2014 were presented at ERA–EDTA 2018 and detailed in a ERA–EDTA press release dated 25th May 2018.

...analysis showed the 5-year mortality rate for GN patients fell from 26% to 16%...

After diabetic and hypertensive nephropathy, GN is the third most common cause of end-stage renal disease (ESRD) in Europe and the most common cause of dialysis treatment in young adults. GN, unlike inflammation caused by bacteria, has immunologic or genetic causes and predominantly affects the glomeruli; despite this knowledge a full understanding of GM pathomechanisms is still elusive.

A total of 5,594 patients >14 years old were identified as having biopsy-proven GN from various centres across Denmark, including Rigshospitalet Hospital, København; Herlev Hospital, Herlev; Copenhagen University Hospital, Copenhagen; and Zeeland University Hospital, Roskilde. Comorbidity and other patient data were obtained from the Danish National Patients Registry and the Danish Nephology Registry. During the study period, incidences of GN increased from 37 to 52 cases per year per million population and the average age at diagnosis rose from 46 to 52 years. The most pronounced incidence increase was in those ≥60 years old.

Despite these worrying statistics, analysis showed the 5-year mortality rate for GN patients fell from 26% to 16% and fewer cases progressed to ESRD. The 5-year ESRD risk with dependence on dialysis fell to 16% by the end of the study period from 22% in 1985. Further investigations are needed to elucidate whether these results relate to improvements in specific or nonspecific patient treatment or other factors.

A New Treatment for Lupus Nephritis

SYSTEMIC lupus erythematosus affects 25–91 individuals per 100,000 people in Western Europe and kidney involvement is the most common severe manifestation. In a ERA–EDTA press release dated 25th May 2018, the results of an exciting Phase III clinical trial that investigated the effects of abatacept on the treatment of lupus nephritis.

Current therapy for the chronic inflammatory disease lupus nephritis is well established, but the therapeutic regimen is toxic, poorly tolerated by patients, and, most importantly, not consistently effective. The large, international, randomised, placebo-controlled, Phase III ALLURE trial enrolled >400 patients who were either administer with the selective T cell costimulation modulator abatacept, or a placebo in addition to standard therapeutics.

One year after the study commenced there was no difference in the total number of patients that entered complete remission between the two study groups; however, patients receiving abatacept presented with a number of beneficial effects. Abatacept patients entered remission faster than their placebo counterparts and also exhibited a faster reduction in proteinuria, an important lupus nephritis biomarker. Additionally, patients treated with abatacept had improved recovery or renal function, improved glomerular filtration rate, and large differences in the levels of immune biomarkers, such as anti-double stranded DNA antibodies. Finally, while there was no difference in the number of deaths while receiving both treatments, fewer abatacept patients dropped out of the trial as a result of adverse events compared to placebo.

"Despite failing to achieve its primary endpoints, the ALLURE trial has set a new standard in the design of lupus nephritis trials through its size and duration."

While the abatacept did not impact the 1-year lupus nephritis remission rate, the T cell modulator did show several beneficial effects on the pathogenesis of lupus nephritis, including a reduction in major disease biomarkers, and expressed an acceptable safety and tolerability level. Study lead Prof David Jayne, University of Cambridge, Cambridge, UK, concluded: "Despite failing to achieve its primary endpoints, the ALLURE trial has set a new standard in the design of lupus nephritis trials through its size and duration."

Familial Cystic Kidney Disease: Lanreotide Proves Ineffective

LANREOTIDE, a somatostatin analogue, was the subject of a prospective study of patients with autosomal dominant polycystic kidney disease (ADPKD); however, the results, published in a ERA–EDTA press release dated 25th May 2018, did not show the expected benefits. Familial cystic kidney disease accounts for approximately 10% of European patients on dialysis or living with a kidney transplant; it is the most common inherited kidney disease and affects approximately 4–6 million people globally. With such a large number of people affected by the disease, an effective treatment is of great importance. However, currently, the therapeutic armamentarium available for clinicians to treat this disease is limited; thus, research is being conducted along these avenues.

"A more targeted selection of patients may be necessary for treatment with somatostatin analogues."

Somatostatin is a naturally occurring hormone that has been suggested to slow cyst growth. As the development of cysts in the kidneys, and often in the liver, is one of the key stages in the manifestation of ADPKD, preventing or slowing cyst growth is one of the therapeutic targets for the disease. The somatostatin analogue, lanreotide, was thought to be an ideal candidate in the treatment of ADPKD.

With lanreotide having shown promise in preclinical studies and initial clinical data, a prospective study was conducted. This study evaluated the efficacy of lanreotide in 305 patients with advanced ADPKD aged between 18 and 60 years. The patients were randomised into two groups: the control group received standard care, while the lanreotide group received an additional subcutaneously administered dose of 120 mg of lanreotide once every 4 weeks. Treatment was conducted over 2.5 years.

The results from the study showed that there was a significant slowing in the growth in kidney volume (1.33% less than in the control group; p=0.02). However, the annual loss of kidney function was similar in both groups, with the difference being not statistically significant (annual estimated glomerular filtration rate loss: lanreotide: -3.53; control: -3.46 mL/min/1.73m^2). Furthermore, patients in the lanreotide group presented with a greater number of undesirable side effects, predominantly including liver cyst infections, responses at the injection location, and gastrointestinal side effects.

Lead investigator, Prof Ron Gansevoort, University of Groningen, Groningen, Netherlands, discussed the future implications of this result, stating: "A more targeted selection of patients may be necessary for treatment with somatostatin analogues." He noted that results with octreotide, another analogue of somatostatin, have shown efficacy in ADPKD patients, offering hope to this patient group.

Ferric Citrate Improves Mineral Metabolism

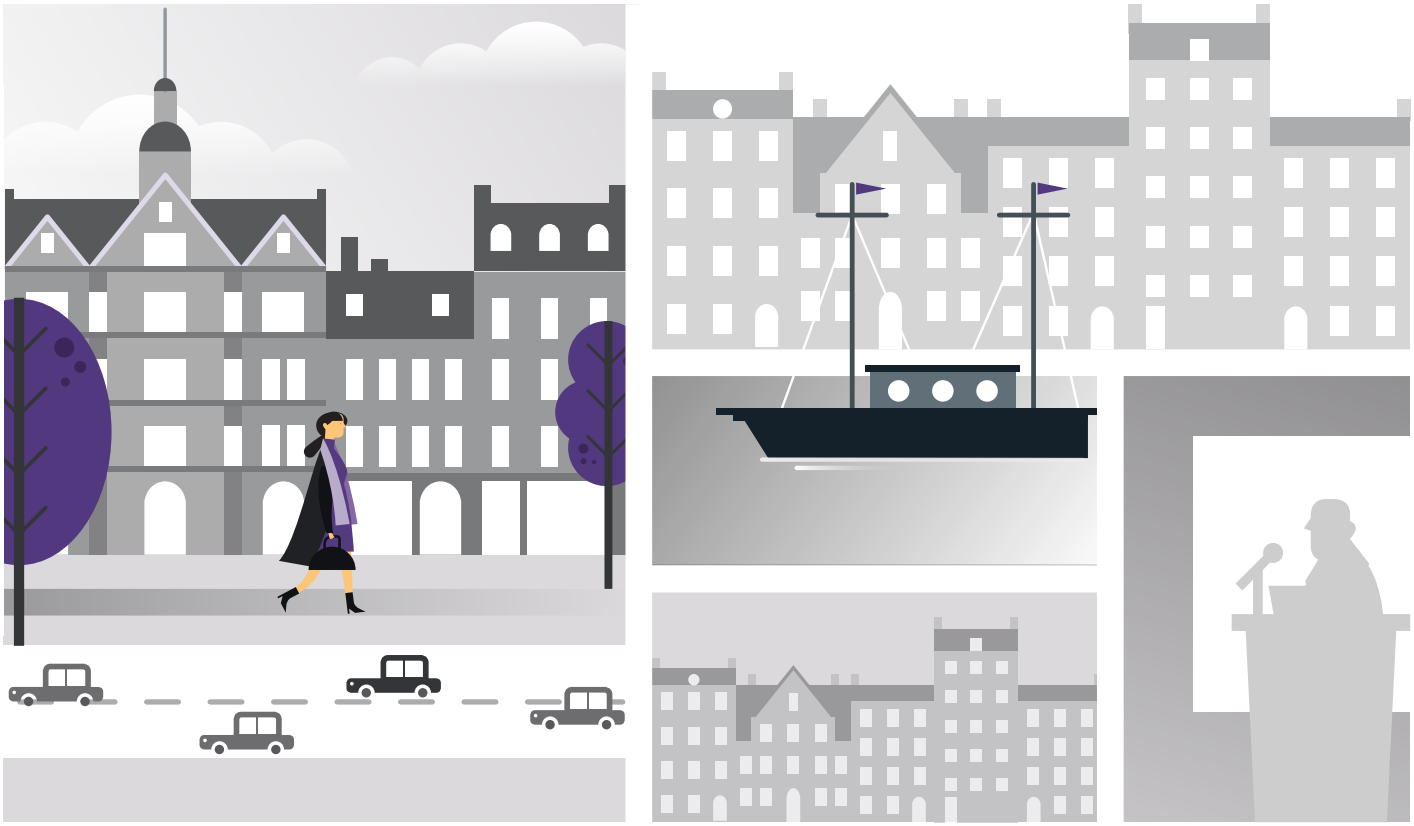
FERRIC CITRATE (FC), a phosphate binder, improves abnormal mineral metabolism and raises haemoglobin in patients with advanced chronic kidney disease (CKD) who do not have abnormal levels of blood phosphate or anaemia. According to a late-breaking clinical study presented at ERA–EDTA 2018 and discussed in a ERA–EDTA press release dated 25th May 2018, the time to renal replacement therapy (RRT) or death was significantly longer for patients treated with a fixed dose of FC.

"In our study we saw that time to RRT or death was significantly longer in the treatment group."

Patients with CKD progressing to its advanced stages are more likely to develop abnormalities in mineral metabolism, including hyperphosphataemia and iron-deficiency anaemia. Previous studies have shown that FC improves levels of transferrin saturation (TSAT), serum ferritin, and haemoglobin in predialysis patients with anaemia. Building on these results, Prof Geoffrey Block, Denver Nephrology, Denver, Colorado, USA, and colleagues set out to assess the effects of FC on TSAT, ferritin, and haemoglobin in CKD patients with an estimated glomerular filtration rate ≤20 mL/min who were not set to start RRT within 8 weeks.

A total of 203 patients were randomised 2:1 to receive a fixed dose of 210 mg FC or standard of care (SOC) treatment. Results from the 199 patients who attended at least one follow-up showed that, compared with SOC treatment, therapy with FC significantly increased mean TAST, ferritin, and haemoglobin, with a significant reduction in mean serum phosphate. Intravenous iron or erythropoietin-stimulating agents were also less likely to need to be administered to the FC group compared with the SOC arm. The overall time to RRT or death was significantly longer for patients in the FC group compared to SOC patients.

Prof Block commented on the study: "We thought that there was a strong rationale for reducing serum phosphate, reducing FGF23, improving iron stores, and increasing haemoglobin before patients needed dialysis. In our study we saw that time to RRT or death was significantly longer in the treatment group." These thought-provoking results could impact the treatment of CKD patients designated for RRT; however, larger, randomised, placebo-controlled trials are needed to validate the study results.



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Interviews

Learn from the experts as we interview members of *EMJ Nephrology*'s esteemed Editorial Board

Featuring: Dr Ziyad Al-Aly, Prof Sebastjan Bevc, and Dr Angela Yee-Moon Wang

Dr Ziyad Al-Aly @zalaly

Washington University in Saint Louis, USA

To begin, what, or who, first inspired you to pursue a career in nephrology?

I was drawn to nephrology in medical school; my interest in nephrology started to blossom in my second year. I remember being fascinated by the kidney, how this one organ regulates electrolytes in the body, and also the broad spectrum of kidney diseases. It was sort of love at first sight; I decided right there and then that I would become a nephrologist.

You published a paper earlier this year in which you reported on the relationship between air pollution and chronic kidney disease (CKD), and its progression to end-stage renal disease (ESRD), using exposure data from National Aeronautics and Space Administration (NASA) satellites. Could you summarise your findings and explain how this relationship was identified?

We wanted to examine the effect of air pollution on kidney function and the risk of developing kidney disease. We first used data obtained from the U.S. Environmental Protection Agency and found that air pollution is associated with an increased risk of kidney disease development and its progression to ESRD.

To test the robustness of the results, we then evaluated this relationship using measures of air pollution obtained from NASA satellite sensors. We downloaded the data and repeated the analyses. Our big "aha!" (reveal) moment was when the NASA results reproduced those obtained from the EPA. This told us that our findings were robust and that air pollution is indeed associated with risk of kidney disease development and its progression to ESRD.

"I remember being fascinated by the kidney, how this one organ regulates electrolytes..."

With some areas of the world experiencing substantial amounts of air pollution, what will be the long-term health consequences of poor air quality, particularly on kidney health, and what can be done to prevent this?

The toll of air pollution on human health should not be underestimated. Air pollution is responsible for 4.2 million deaths per year. Measures must be taken to reduce air pollution. This also makes economic and business sense; the economic health cost of air pollution is exorbitant. It costs much less to reduce air pollution than to deal with its adverse effects on human health.

On a global level, there is substantial geographic variation in the burden of kidney disease, and some endemic areas for CKD also happen to have significant air pollution. We think that air pollution may be an important driver of kidney disease in some areas of the world, and we certainly think that this warrants further investigation. Our hope is that our line of research and thinking will stimulate further examination, both by our group and others, to help develop a greater understanding of the effect that environmental exposure has on kidney health and disease.

You have also investigated the effects of proton pump inhibitors (PPI) on the development of acute kidney injury and CKD. Can you briefly explain the link between PPI treatment and chronic renal outcomes?

When we started looking at this, there was some literature suggesting that PPI use is associated with a risk of interstitial nephritis. We therefore pondered the question of whether PPI use is associated with the risk of developing CKD and ESRD. Our findings confirmed that this is indeed the case.

We then wanted to evaluate if this association (of PPI and CKD or ESRD) is direct, or if it is mediated by the occurrence of intervening acute interstitial nephritis or acute kidney injury; i.e., does PPI use lead to acute interstitial nephritis, which in turn leads to CKD, or does PPI use lead to CKD directly? Our findings suggest that the effect is mediated by the occurrence of intervening acute kidney injury or acute interstitial nephritis in only 50% of cases. There was also a clear and direct pathway of PPI leading to CKD without any intervening kidney event.

With a large number of patients being treated with PPI therapies, how important do you think educating healthcare providers is regarding the potential side effects of PPI on the kidneys? How can clinician education and management of these patients be improved?

People should not be taking PPI for a long duration of time without a prescription from a physician. PPI use should be limited to the minimum effective dose and shortest duration of treatment possible. Prolonged, unnecessary use of PPI may be associated with more harm than good. Promoting awareness of PPI side effects is very important, especially now that these are available for purchase over the counter without a prescription.

You are an advocate of big data and using statistics in epidemiological methods to better understand the risk factors for kidney disease and its progression. Can you explain why such large data sets are advantageous when investigating this disease?

The term big data is used very frequently these days. Our thinking is that real-world health information is very valuable to help us gain a better understanding of health and disease at the personal, population, and planetary levels. The availability of large, rich datasets, coupled with advances in methodologies to analyse these data, represents an opportunity to help us fill important knowledge gaps.

"The toll of air pollution on human health should not be underestimated. Air pollution is responsible for 4.2 million deaths per year. Measures must be taken to reduce air pollution."

What are the main lessons nephrologists have learnt as a result of analysing big data in nephrology research?

Our work on air pollution and kidney disease required us to build a cohort of nearly 2.5 million people and follow them for a decade. We then merged this big dataset with data from EPA monitoring stations and NASA satellite data, both of which provided us with data on pollution levels. This is one example of how large datasets can help us answer questions that are not possible to address with much smaller datasets.

If you could give one piece of advice to aspiring medical students, what would it be? Is there anything you wish you had known before you embarked upon a career in nephrology?

Follow your passion, align your goals with your values, persevere, learn from failure, learn how to fail gracefully, celebrate your wins humbly, and finally, do what you do with a soul.

Prof Sebastjan Bevc

University of Maribor, Slovenia

Firstly, what was the most influential factor that drove you to specialise in nephrology and, particularly, your current research themes?

My focus is on the involvement of the kidneys in many different physiological processes in the human body and the impact of the level of kidney function on the outcome of the individual. At the moment, I am working as part of a number of different research teams occupied with various research themes, including asymptomatic atherosclerosis and epigenetics, therapy for hyperuricaemia in patients with chronic kidney disease, the measurement of breath ammonia for the detection of patients with chronic kidney disease, evaluation of water in the nutritional status of chronically ill individuals, implementation of a standard assay for estimated glomerular filtration rate with iohexol, percutaneous interventions and treatment of arteriovenous fistula stenosis and thrombosis, cell line growth and development for studying nephrotoxicity in an *in vitro* model of the nephron, and more.

What are the current goals of nephrology research in Slovenia? Are there any differences between the treatment of Slovenian nephrology patients and patients from the rest of Europe?

"In the future, more studies should be focussed on determining the best method of detecting dehydration, since all the currently used methods have important limitations."

At the moment there is no accepted strategy for nephrology research in Slovenia. However, nephrologists are generally successful as researchers in small, local groups and as coworkers in international projects. The treatment of Slovenian nephrology patients is based on and validated by accepted international guidelines.

Across the globe there is a shortage of organ donors, and in the UK an opt-out donation system is being introduced to combat this. With many nephrology patients waiting for kidney donations, what do you think can be done to increase the number of kidney donors?

Slovenia is part of the Eurotransplant programme. At the moment, a patient's median wait time for a cadaveric kidney is 290 days and we have a relatively short patient waiting list (around 100 patients). We started with

living donor donations and have a programme for cadaveric kidney donations for people >65 years old.

The 2018 European Renal Association–European Dialysis and Transplant Association (ERA–EDTA) Congress covered a myriad of hot topics within the field of nephrology, from fluids and electrolytes to kidney transplantation and hypertension. In your opinion, what disease deserves more attention from nephrologists at congresses like ERA–EDTA?

Drug-induced nephropathy and drug interactions should receive more attention at big international congresses.

It has been shown that men are far less likely to visit a doctor than women. Is this true for nephrology patients, and how do you propose the medical community, and society in general, can improve the number of men consulting their doctors?

So far, no such problem has been detected in Slovenia.

In November 2017 you published a paper titled 'Dehydration of Older Patients in Institutional Care and the Home Environment'. Could you summarise your findings from this article and explain how the results will impact the care of older patients?

Dehydration in the elderly is an important clinical problem associated with additional comorbidities, longer hospital stays, and higher mortality rates. However, in daily clinical practice there is no single gold-standard marker of the hydration status of elderly patients. We tried to define the fluid balance status in elderly patients in institutional care and in those who reside in their home by using and comparing different methods (including analysing serum osmolality) of identifying dehydration in the studied populations. The results of our study confirmed that dehydration is a very common clinical problem in the elderly population, especially in the elderly in institutional care. In the future, more studies should be focussed on determining the best method of detecting dehydration, since all the currently used methods have important limitations. A promising method for detecting early dehydration seems to be saliva osmolality and should be tested further. At the moment, we cannot talk about the important impact of the results on the care of older patients; however, the awareness of the hydration status in this fragile population has increased as a result of our study.

Biosimilars are growing in popularity in a range of medical fields due to their cost-effectiveness; what are your opinions on the use of biosimilars in nephrology?

Despite warnings about the inequality of biosimilars in nephrology, analysis of the outcomes after biosimilar treatment showed safety of use and no harm to the patients. The question is 'what can we do after we face resistance for both the originators and biosimilars?'

What do you think the biggest challenge for the field of nephrology will be over the next decade?

Managing kidney disease in the geriatric, very fragile, and polymorbid population; home-choice haemodialysis and peritoneal dialysis; and the optimisation of immunosuppression therapy will all be challenging topics for the discipline in the next 10 years.

Are you planning to attend any congresses this year? If so, what do you enjoy most about attending national and international nephrology meetings?

As in the past, I will actively attend different congresses this year. The most important benefits are forming personal contacts with colleagues working on the same areas of research, interacting with novel poster sessions, learning new approaches to old problems, and receiving the latest guidelines statements for daily clinical practice.

"...a patient's median wait time for a cadaveric kidney is 290 days..."

Finally, if you could go back in time and provide your younger self with one piece of advice, what would it be?

Respect the work you have done and respect the work of your colleagues, even if later you cannot agree with some of their results and opinions.

"Drug-induced nephropathy and drug interactions should receive more attention at big international congresses."

Dr Angela Yee-Moon Wang

University of Hong Kong, Hong Kong

Your interests within nephrology also expand into the cardiovascular and nutritional fields. How did you become interested in these additional areas of research?

Kidney disease is regarded as a multisystem disease. The impact of kidney disease crosses multiple specialities and multiple disciplines, and there are important crosstalks between the kidneys and various other organs and systems, including the heart, brain, lungs, gut, liver, endocrine system, haematological system, and even the skin. These connections led to me studying the association between kidney disease, heart disease, and protein-energy wasting syndrome many years ago. We examined how loss of residual kidney function (RKF) in peritoneal dialysis patients may be linked to various metabolic and nutrition derangements, salt and volume overload, inflammation, and cardiovascular comorbidities. Further to the initial studies we performed in peritoneal dialysis patients, we also characterised the nature of cardiovascular complications and cardiac dysfunction in dialysis patients.

The medical world's understanding of renocardiac pathophysiology has increased greatly in the last 5 years. What do you consider the biggest advance for this field in recent years?

The development of sodium-glucose cotransporter-2 inhibitors may be considered one of the biggest advances in the field in recent years. Sodium-glucose cotransporter-2 inhibitors have been shown to have significant cardiovascular and kidney protective benefits beyond the blockade of the renin-angiotensin system in diabetic kidney disease. Interestingly, this class of drug works in an insulin-independent mechanism by promoting glucose excretion, natriuresis, uricosuric effect, and lowering blood pressure and body weight, while avoiding hypoglycaemia. Furthermore, concomitant inhibition of sodium absorption in the proximal tubule causes initial natriuresis, which leads to osmotic diuresis with an attendant reduction in plasma volume. Sodium sensing in the macula densa activates tubuloglomerular feedback and adenosine-mediated dilation of the afferent renal arterioles. The reduction in hyperfiltration and decreased glomerular pressure is associated with a decline in glomerular filtration and albuminuria.

This year, you have been recognised for your enormous contributions to the field of renal nutrition, receiving the National Kidney Foundation Joel D. Kopple Award 2018. What do you consider to be your greatest contribution to this interesting field?

I would like to thank the National Kidney Foundation for giving me this award and recognition. There are three specific areas that I have studied in the field of renal nutrition over the years. Firstly, our previous work demonstrated the importance of RKF in maintaining the nutritional status of peritoneal dialysis patients. Of note, loss of RKF was not only associated

with reduced dietary energy intake but also increased resting energy expenditure. Our data suggested that RKF may play a role in maintaining energy homeostasis in dialysis patients. Secondly, we performed a series of experiments that showed important bidirectional relationships between heart failure and protein-energy wasting syndrome in patients with chronic kidney disease. Lastly, we showed that fibre as a specific dietary component may influence cardiovascular risk in dialysis patients. All these findings reinforce a tight connection between nutrition, kidney disease, and cardiovascular complications.

Based on your experiences, how important is a multidisciplinary approach when treating nephrological conditions?

Given that kidney disease is a multisystem disease, a multidisciplinary approach is essential in managing patients with kidney disease. In particular, dietary and nutrition management may be useful in retarding chronic kidney disease progression and preventing cardiovascular disease in patients with kidney disease. Nutrition management is also required in dialysis patients to prevent or reduce the severity of protein-energy wasting.

This year, you will become President of the International Society of Renal Nutrition and Metabolism (ISRNM). Can you briefly describe what this role will entail and what you hope to achieve during your tenure?

It is an honour to be the President of the ISRNM and with this, I would like to thank the executive committee and the Council of the ISRNM for their important support. During my presidency, I hope to work with the Executive Committee and the Council on various initiatives, with the aim of raising awareness of the importance of diet and nutrition therapy in managing patients with kidney disease and cardiovascular complications around the world, and ultimately promoting interest in renal nutrition and metabolism research. We hope to set up more international collaborative networking in renal nutrition research. Furthermore, we will be working in partnership with the International Society of Nephrology (ISN) Global Kidney Health Atlas Team on a Global Renal Nutrition Care Atlas that aims to evaluate the current renal nutrition care and resource availability around the world. The results will form an important basis for both societies to see how we may jointly improve renal nutrition care in countries with limited resources. Nutritional care is an important strategy in retarding chronic kidney disease progression and may be useful in reducing the need for dialysis in emerging countries with low resources and limited dialysis facilities. We will also be collaborating with ISN for a conjoint symposium at the 19th Congress of ISRNM in Genoa, Italy.

Besides the ISRNM, you have held a variety of leadership positions throughout your career, including your role as an executive committee member for the Standardised Outcomes in Nephrology (SONG) Initiative and subcommittee Chair of the International Society for Peritoneal Dialysis (ISPD) Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS). What qualities do you believe are integral to success as a leader in the medical world?

I believe several qualities are key and integral to success as a leader in the medical world. These include vision, innovation, and collaboration.

You practice medicine at the Queen Mary Hospital in Hong Kong. Are there any nephrological conditions that are particularly prevalent in Hong Kong compared to the rest of eastern Asia? Does the variety of conditions you see when working in Hong Kong differ greatly from the rest of the world?

Like other parts of the world, Hong Kong is facing a huge burden of diabetes and an increasing prevalence of diabetes as the cause of end-stage kidney disease. Hong Kong differs from the rest of the world in that 75% of the end-stage kidney disease patients in Hong Kong are receiving home-based peritoneal dialysis treatment and only 25% are receiving haemodialysis. This difference compared with the rest of the world relates to the local government advocacy and reimbursement policy.

"I believe several qualities are key and integral to success as a leader in the medical world. These include vision, innovation, and collaboration."

What area of nephrology would you like to see more thoroughly researched over the next 5 years?

There are many areas in nephrology that need more research in the next 5 years. In the area of renal nutrition, we need randomised trials to examine the effects of different forms of dietary manipulation or nutrition therapy on kidney and cardiovascular outcomes in patients with chronic kidney disease. The importance of diet on kidney and heart health has been under-recognised. The potential role of dietary manipulation and nutrition therapy in improving kidney and heart health in patients with kidney disease is underexplored. Furthermore, with the evolving concept of precision medicine, research will be needed to understand how variations in dietary prescription, diversity in genetic make-up, intraindividual variations in responses to treatment, changes of gut microbiota in responses to dietary prescription, and psychosocial factors may contribute to the differences in responses. A better understanding of these different factors may help in better implementing an individualised renal nutrition care plan for patients with kidney disease. Furthermore, there is growing interest in understanding the importance of patient-centred outcomes and SONG, and I believe this will also be an important aspect to address in renal nutrition research.

What one piece of nutritional advice would you give to people looking to improve the health of their kidneys?

I would advise people to adopt a healthy dietary pattern (e.g., the Mediterranean diet) to maintain and improve kidney health; that is, adopt a low protein and a low salt diet, but increase natural fibre in the diet by increasing intake of whole wheat, fruits and vegetables, and also drink plenty of water. Dietary component of animal protein should be reduced, especially red meat. I would also encourage patients to have more natural foods in their diet and avoid processed or artificial foods. There is quite convincing data in the general population that the Mediterranean diet is a heart healthy diet. Whether it is in improving the health of the kidneys requires further investigation.

"The importance of diet on kidney and heart health has been under-recognised. The potential role of dietary manipulation and nutrition therapy in improving kidney and heart health in patients with kidney disease is underexplored."

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Prescribing Frequent Haemodialysis in Complex Patients: Highlights from the 55th ERA–EDTA Congress

This symposium took place on 26th May 2018, as part of the 55th European Renal Association–European Dialysis and Transplant Association (ERA–EDTA) Congress in Copenhagen, Denmark

Chairperson: Mari Vilpakka[1]

Speakers: Allan Collins,[2,3] Natalie Borman,[4] Maxence Ficheux,[5] Sunita Nair[6]

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4. Queen Alexandra Hospital, Wessex Kidney Centre, Portsmouth, England
5. CHR Clémenceau, Service Néphrologie-Hémodialyse-Transplantation, Caen, France
6. Shrewsbury and Telford Hospital NHS Trust, Shrewsbury, England

Disclosure: Dr Vilpakka, Dr Borman, Dr Ficheux, and Dr Nair are members of the NxStage European Medical Board and have received speaker honoraria. Prof Collins is employed by NxStage Medical as Chief Medical Officer.

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Meeting Summary

At the 55th European Renal Association–European Dialysis and Transplant Association (ERA–EDTA) Congress in Copenhagen, Denmark, physicians from the USA, UK, and France presented an educational symposium entitled 'Complex Patients May Be Better Treated with Frequent Hemodialysis: A Review and Comparison of Published Evidence and Recent European Experience'. During this symposium, leading physicians discussed the concepts underlying the prescription of frequent haemodialysis (>3 sessions per week), the role of frequent haemodialysis in managing haemodynamic instability, treating patients who require larger volume clearance due to pregnancy or obesity, and utilising frequent home haemodialysis in the palliative care setting. This report briefly summarises the symposium.

Prescribing Frequent Haemodialysis

Professor Allan Collins

Haemodialysis, as it is widely prescribed today, has created a new and unique chronic disease state in patients with end-stage renal disease who previously would not have survived. This disease state is characterised by chronic fluid overload,[1,2] intense ultrafiltration during dialysis,[3] and persistent hyperphosphataemia,[4,5] all of which impact the heart and vessels and eventually induce cardiovascular disease.[1-5]

To address chronic disease, a dialysis prescription must extend beyond clearance of small solutes (e.g., urea) to target the health of organ systems. This shift in focus to monitoring a patient's tolerance of therapy and slowing the decline of cardiovascular health represents a new paradigm in dialysis delivery; this is particularly important when dealing with complex patients, including those with uncontrolled hypertension, left ventricular hypertrophy, heart failure, hyperphosphataemia (despite prescription of phosphate binders), recurrent intradialytic hypotension, and excessive post-treatment fatigue, as well as pregnant or obese patients, and frail patients in need of supportive care.

The haemodialysis prescription can be conceptualised as a two-step approach that focusses primarily on managing fluid, thereby addressing blood pressure and cardiac geometry, and secondarily on managing solute removal.[6] This model begins with setting the weekly fluid removal requirement and then the ultrafiltration rate (UFR), by way of both treatment frequency and session duration, to a rate that minimises cardiac stunning, improves stability during treatment, and minimises post-treatment fatigue. Though a conventional UFR threshold is 10 mL/hour/kg, studies have suggested that limiting UFR as much as possible may reduce all-cause and cardiovascular mortality.[3,6-9] With frequent diurnal therapy for 2–3 hours per session, UFR can be lowered to 6 mL/hour/kg, and with nocturnal therapy, UFR can be lowered to 2–3 mL/hour/kg. Only after managing fluid should the haemodialysis prescription address solute removal with standardised Kt/V as a guiding metric.

Prescriptions that prioritise fluid removal can be derived in the following manner. First, an upper limit of UFR (e.g., 10 mL/hour/kg) is selected and multiplied by body weight. Second, weekly fluid intake (minus cumulative urine volume) is divided by the weight-scaled UFR limit to identify the minimum number of ultrafiltration hours per week. Third, the minimum number of ultrafiltration hours per week is divided by the number of treatments (e.g., 4, 5, or 6) that are desired during the week to target symptom-free haemodialysis and control blood pressure, ideally with minimal use of antihypertensive medication. With a UFR limit of 10 mL/hour/kg in a 70 kg male patient, for example, the maximum rate of fluid removal is 700 mL/hour. With a weekly fluid intake of 10.5 L, ≥15 hours per week of ultrafiltration are required; these could be divided among five sessions of 3 hours each or six sessions of 2 hours each. Since the uremic milieu is different during the first 90 minutes of treatment, a conventional schedule comprising three sessions of 5 hours each does not provide the same amount of clearance, despite equal hours of ultrafiltration.

After addressing fluid volume, the haemodialysis prescription must also maintain adequate solute clearance, a task largely determined by dialysate saturation. High dialysate saturation maximises the removal of small, middle, and large molecular weight solutes, even in a system that utilises low-volume dialysate (e.g., NxStage® System One™, NxStage Medical, Lawrence, Massachusetts, USA). Moreover, a system that utilises low-volume dialysate that is highly saturated during treatment will improve clearance of phosphorus, a molecule that is otherwise difficult to remove. Conventional systems with a flow rate of 500 mL/min, for example, achieve 55% urea saturation and 35% phosphorus saturation (*in vivo*).[10] In contrast, low-volume dialysate systems with a flow rate of 200 mL/min achieve >90% urea saturation and roughly 70% phosphorus saturation (Figure 1). On nocturnal treatment with a flow rate of merely 100 mL/min, nearly 99% urea saturation and 95% phosphorus saturation can be achieved.[10] Dialysate saturation is coupled with the amount of weekly total body water clearance, which varies on different modalities (Figure 2), to provide adequate clearance of solutes, including middle molecules between urea and phosphorus.

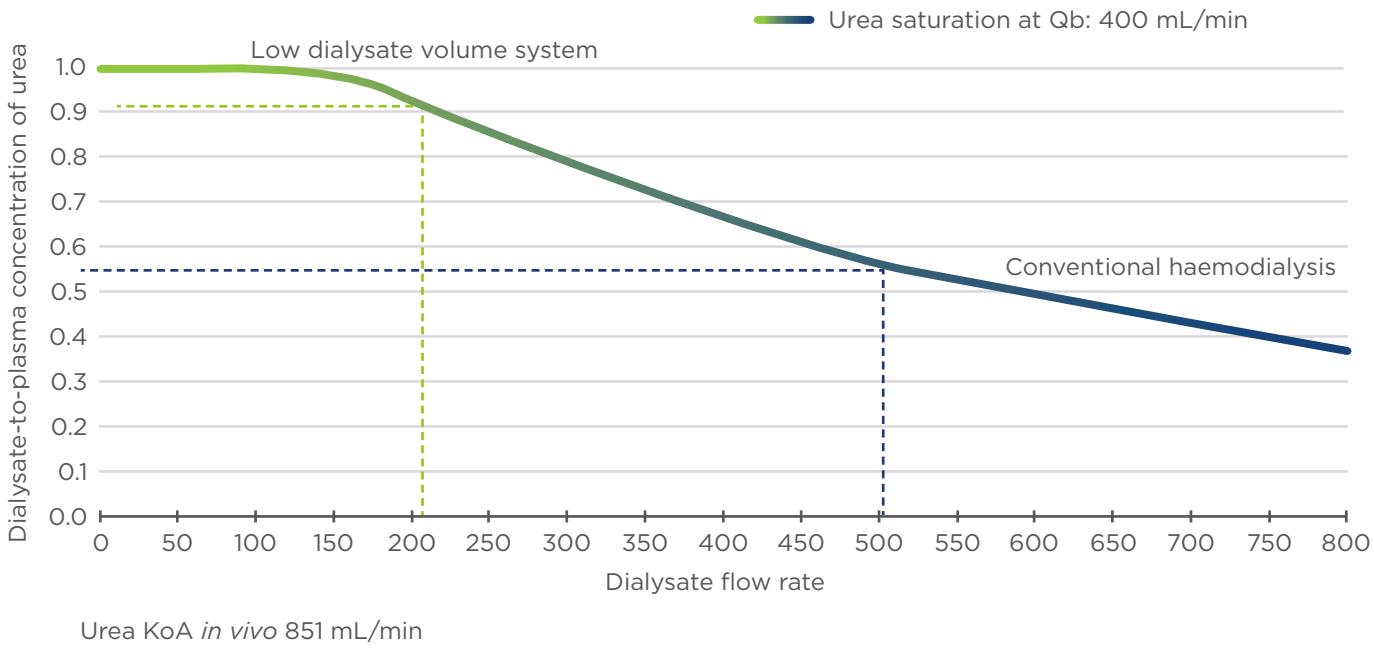

Figure 1: Dialysate-to-plasma concentration of urea as a function of dialysate flow rate.

KoA: dialyser mass transfer-area coefficient; Qb: blood flow rate.

Adapted from Leypoldt K et al.[10]

Nocturnal haemodialysis maximises solute removal and minimises UFR, likely leading to improved cardiovascular outcomes.

A haemodialysis prescription reflecting the paradigm shift to maintaining cardiovascular health will focus first on fluid volume management, thereby minimising UFR and lowering blood pressure. Solute removal is considered next; the adequacy of removal is determined by dialysate saturation. These aims may be best achieved by a frequent treatment regimen with low-volume dialysate, which limits UFR and maximises solute clearance, thus maintaining dialysis patient health.

Managing Haemodynamic Instability with Frequent Haemodialysis

Doctor Natalie Borman

Cardiovascular disease remains the leading cause of death in dialysis patients.[1,11] Through multiple physiological pathways, fluid overload is a key contributing factor to the development of heart failure on dialysis (Figure 3).[1,2] Firstly, within the constraints of thrice-weekly in-centre haemodialysis, a higher UFR is needed to remove excess fluid in an overloaded patient; higher UFR can lead to cardiac and other organ system stunning during dialysis, as well as to intradialytic hypotension.[12] Notably, between 5% and 15% of patients on conventional haemodialysis experience symptomatic hypotension, which is characterised by cramps, dizziness, and nausea.[13,14] Organ system stunning and symptomatic hypotension both contribute to longer post-treatment recovery time, reducing quality of life and potentially leading patients to sign-off early or skip sessions entirely.[15] Incomplete sessions lead to more fluid overload, thus creating a cycle of poor patient outcomes and adverse events. Secondly, chronic fluid overload contributes to uncontrolled hypertension, left ventricular hypertrophy, and heart failure, ultimately leading to increased risk of hospitalisation and death.[16]

The thrice-weekly haemodialysis prescription became the dominant regimen because of feasibility, logistics, and cost, rather than the achievement of optimal health outcomes.

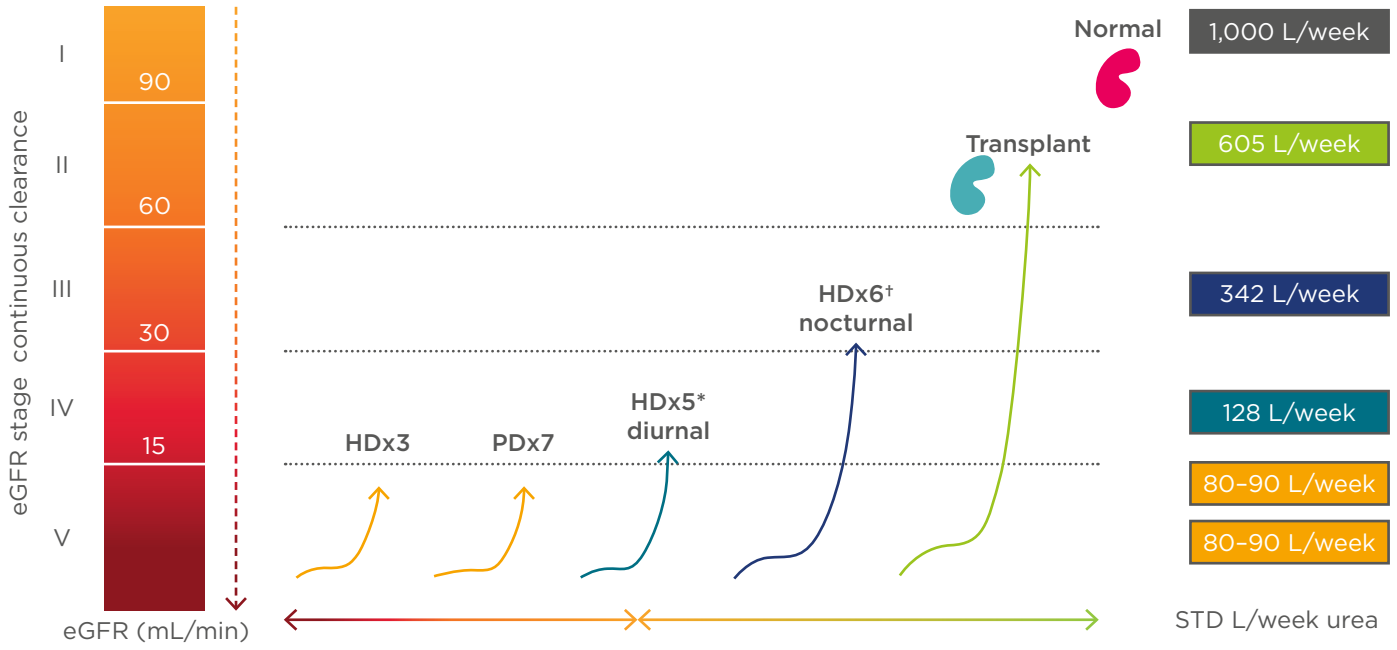

Figure 2: Volumes cleared per week among renal replacement therapies.

*30 L/session of dialysate. †60 L/session of dialysate.

eGFR: estimated glomerular filtration rate; HD: home dialysis; PD: peritoneal dialysis; STD: standard.

Adapted from Leypoldt K et al.[10]

The 2-day gap that is inherent in this schedule is strongly associated with increased risks of death, hospitalisation, and cardiovascular events.[17-19] High UFR, which has been linked to an increased risk of all-cause and cardiovascular mortality, is prevalent in patients on conventional haemodialysis.[3,7-9] Moreover, the prevalence of persistent hypertension on dialysis has not changed during the past 10 years, despite considerable improvements in small solute removal and extensive application of antihypertensive medications.[2]

More frequent therapy has the potential to ameliorate these symptoms and improve patients' outcomes. Data from the Frequent Hemodialysis Network (FHN) Daily Trial show that patients prescribed more frequent haemodialysis for 1.50–2.75 hours per session have favourable outcomes for left ventricular mass, systolic blood pressure, physical health, and even death.[21] Eliminating the 2-day gap not only lowers the associated risks of adverse events but also substantially reduces the likelihood of patients accumulating excess fluid between consecutive dialysis sessions.[21] Furthermore, tailoring the frequency of therapy also allows for increased dialysis duration, permitting the therapy to meet weekly ultrafiltration requirements with low UFR, even in the case of fluid overload.

The KIHDNEy[22] study collected data from 182 home haemodialysis patients using the NxStage System One at nine centres throughout Europe. This retrospective study followed patients for 12 months after initiating frequent home haemodialysis. Patients in the KIHDNEy cohort had a mean UFR of 6.8 mL/hour/kg at 6 and 12 months follow-up after initiating frequent therapy, with 82% of patients having UFR <10 mL/hour/kg.[22] The cohort also exhibited a statistically significant decline in antihypertensive use, averaging 1.51 agents per day at baseline and 0.91 agents per day after 12 months of frequent therapy ($p<0.001$).[22] The number of participants requiring no antihypertensive medication increased from 27% to 42% ($p<0.001$), and the number requiring at least two antihypertensive agents concurrently decreased from 43% to 25% ($p<0.001$).[22]

In a subset of 86 patients dialysing at home for ≥5 sessions per week, under the care of the Wessex Kidney Centre, Portsmouth, UK, 75% reported immediate recovery after dialysis.

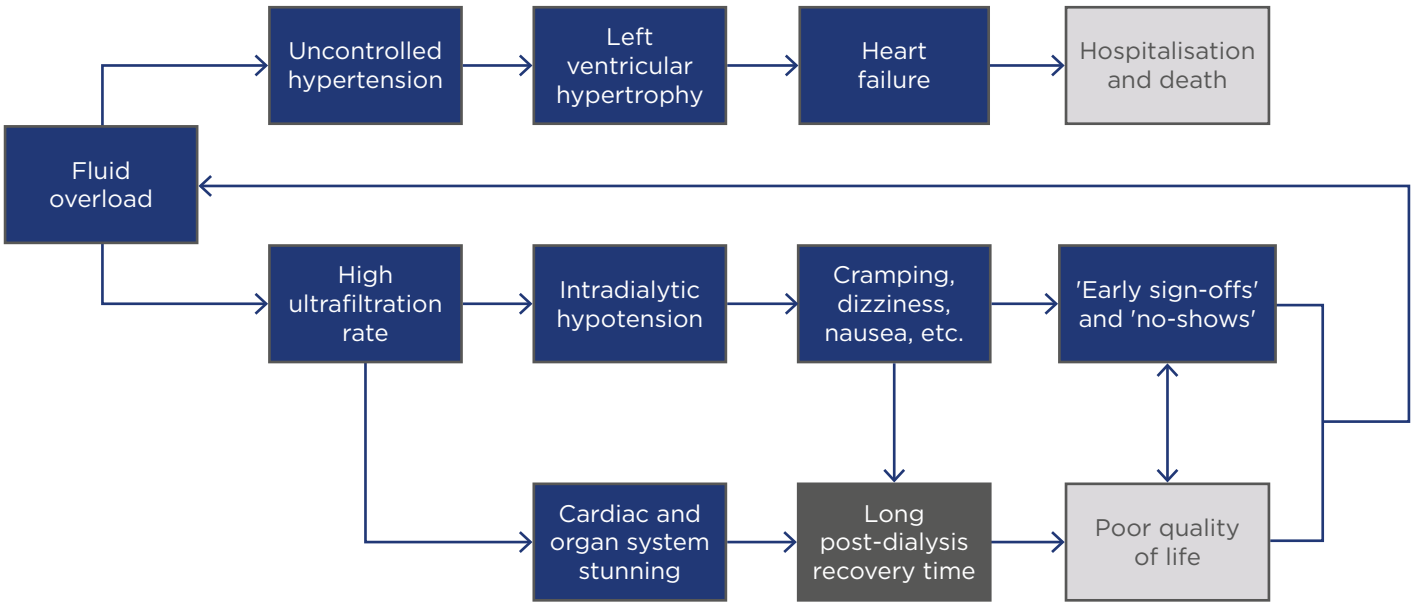

Figure 3: Causal diagram of the clinical pathophysiology of chronic fluid overload.

Across these 7,600 consecutive sessions on frequent therapy, a greater change in intradialytic systolic blood pressure was associated with increased number of symptoms reported ($p<0.0001$) and longer post-treatment recovery time ($p<0.0001$). Maintaining stable blood pressure reduces the likelihood of symptoms on dialysis, leading to fewer early sign-offs and less perpetuation of chronic fluid overload.[15]

An ageing multicomorbid dialysis population has resulted in a patient cohort that is, on average, more susceptible to fluid overload and haemodynamic instability than it was in the past.[23,24] These patients are extremely sensitive to fluid shifts and are at a high risk of hospitalisation due to recurrent episodes of fluid overload, particularly after a 2-day gap in therapy.[2] Furthermore, their haemodynamic instability compounds the difficulty in removing fluid.[25] Providing patients with shorter, more frequent haemodialysis sessions and minimising UFR has been shown, in many cases, to engender fewer symptoms on dialysis, stabilise blood pressure, improve fluid balance, and reduce the risk of hospitalisation.[21,22] The above data suggest that by directly addressing chronic fluid overload, frequent haemodialysis can meaningfully improve both cardiovascular outcomes and quality of life.

Frequent Home Haemodialysis in Complex Patients

Doctor Maxence Ficheux

Managing patients who are either pregnant or obese is uniquely challenging. Each of these patient types requires more volume clearance than the typical haemodialysis patient and presents unique physiological challenges and potentially poor health outcomes.[26,27] More frequent haemodialysis in the home setting may improve outcomes in both pregnant patients and obese patients, as well as provide individualised and convenient therapy for these complex cases.

Women on haemodialysis are likely to experience decreased fertility due to both sexual dysfunction and reproductive hormonal dysfunction, including amenorrhea.[28,29] Specifically, lack of oestradiol-stimulated cyclic luteinising hormone secretion leads to ovarian failure (i.e., anovulation), and an elevated prolactin concentration contributes to abnormal uterine bleeding.[30] These physiological obstacles have historically contributed to a low likelihood of successful pregnancy. Survey data from multiple continents have shown few pregnancies on dialysis and a <50% probability of live birth among pregnant patients.[31-33]

Intensive haemodialysis may help improve poor pregnancy outcomes. One meta-analysis that assessed dialysis schedules and pregnancy outcomes reported a negative correlation between weekly haemodialysis duration and the percentage of pregnancies ending in preterm (i.e., <37 weeks) delivery (R^2=0.22; p=0.044).[34] The same meta-analysis also reported negative correlations between the percentage of small for gestational age infants and both weekly haemodialysis duration (R^2=0.54; p=0.017) and weekly haemodialysis frequency (R^2=0.84; p=0.003).[34] Recent survey results have suggested that although prenatal complications and preterm delivery are still frequent, neonatal survival has improved in the last 30 years, which may be linked to the rise of more frequent and longer haemodialysis sessions.[35]

Obesity, which is prevalent in approximately 1 in 4 dialysis patients in both the USA and France, is a common challenge.[36,37] Patients with a BMI >30 kg/m^2 require more volume clearance than patients with a normal BMI.[27] Frequent haemodialysis in the home setting may address this challenge. Thirty-three (18%) patients in the KIHDNEy cohort had a BMI ≥30 kg/m^2.[22] One year after initiating haemodialysis for ≥5 sessions per week, these patients maintained a mean standardised Kt/V of 2.53 (standard deviation: 0.31) and mean UFR of 4.49 mL/hour/kg. Concurrently, mean serum phosphorus among these patients decreased by 4%, despite a 24% reduction in mean phosphate binder pill count. Furthermore, the use of antihypertensive agents declined by 41%.[22]

These data, along with multiple case studies, provide compelling evidence that frequent home haemodialysis with low-volume dialysate not only maintains adequate small solute clearance, but also leads to improved outcomes and provides patients with a convenient and individualised therapy. In a pregnant patient, increased frequency and duration of haemodialysis may increase the likelihood of live birth and permit the mother and neonate to return home more rapidly. In obese patients, increased frequency and duration of haemodialysis may lessen the need for oral medications and lower the incidence of dialysis-related side effects. Frequent home haemodialysis represents a practical and efficient method of therapy for complex patients and gives new hope to end-stage renal disease patients who wish to conceive but are unable to wait for a transplant.

Frequent Home Haemodialysis as Palliative Care

Doctor Sunita Nair

Since the first successful dialysis treatment in 1945, the goal of dialysis therapy has shifted from saving lives to sustaining lives, and subsequently to rehabilitation, with more frequent haemodialysis prescribed to improve health-related quality of life. However, patients still experience a high burden of symptoms, including pain, itching, lethargy, and restless legs. Dialysis patients also have substantial functional limitations, which place a heavy burden on family members and care partners.

The current dialysis delivery system focusses on achieving fluid volume and biochemical targets, aiming to reduce cardiovascular risk. When these targets can no longer be achieved, the common practice is to withdraw dialysis and assist patients embarking on end-of-life journeys. However, some dialysis patients with significant symptom burden and coexisting terminal illness may wish to continue dialysis. These patients' goals do not align well with the current interpretation of palliative care, which is offered only to patients with a predictably short life expectancy and a desire to forgo life-prolonging treatment. In the UK, for instance, patients are expected to withdraw from dialysis before entering hospice care. A new palliative dialysis care model may address these currently unmet needs.

Merging renal care and palliative care is a dynamic process aimed at offering specialised care for people with chronic or serious illnesses. This care model may be appropriate at any age and at any stage in a serious illness and can be provided alongside curative and life-prolonging treatment. Comprehensive palliative care in patients with end-stage renal disease focusses on providing patients with symptom relief, supporting decision-making, and aligning treatment plans with patients' goals. By adopting a multidisciplinary approach between the renal and palliative care teams, the model provides

truly holistic care by integrating psychosocial and spiritual needs with medical needs, and co-ordinating both medical and social services, thereby providing an extra layer of support for patients and their families.

Frequent haemodialysis in the home setting is arguably the most straightforward method of implementing this new paradigm of palliative dialysis care. Frequent therapy has been shown to reduce symptom burden, reduce morbidity, and improve quality of life, particularly in patients with multiple comorbidities.[38] Home haemodialysis also allows patients to dialyse in their preferred setting, which is especially important during a vulnerable time in life. The NxStage System One enables dialysis delivery in both home and hospice settings without a requirement of costly remodelling of the site. Furthermore, this modality requires less training time, is financially viable, and allows ongoing palliative input through its monitoring system.[39]

This paradigm shift in providing palliative dialysis to patients with coexisting terminal illness resets the treatment goals of dialysis, focussing almost entirely on controlling symptoms and individualising treatment targets. Palliative care should be part of the continuum of holistic, quality care for renal patients. In this way, we will continue to extend the dialysis paradigm from one that rehabilitates patients when life expectancy is long to one that comforts patients when life expectancy is short.

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Abstract Reviews

A snapshot of the wide range of new research presented at the ERA–EDTA 2018 Congress.

Higher Phthalate Exposure May Increase Urothelial Cancer Risk in Patients with Chronic Kidney Disease

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Keywords: Chronic kidney disease (CKD), risk assessment, urinary phthalates metabolites, urothelial cancer (UC).

Citation: EMJ Nephrol. 2018;6[1]:42-44. Abstract Review No. AR1.

Phthalates can disturb the endocrine system and are reported to have associations with breast cancer.[1] Patients with chronic kidney disease (CKD) are known to have a greater risk of urothelial cancer (UC) than the general population.[2] Whether it is related to higher phthalate exposure is not known at present and this study was conducted with the aim of answering this question.

This prospective, multicentre, case-control study of UC was initiated by the Taiwan Urothelial Cancer Consortium with the aim of investigating the risk factors of UC with multiple risk domains. Ten hospitals distributed through different regions of Taiwan joined the consortium. These hospitals had diverse healthcare levels, from tertiary settings to local hospitals. Subjects were Taiwanese patients with CKD but without UC (controls) and patients with ongoing UC. The CKD controls were best matched with UC patients from the same living area. For non-UC patients, blood and urine specimens were collected at the time of the structured interview.

For UC patients, urine and blood were collected before operations.

The collected urine specimens were stored at -80°C before analysis. With liquid chromatography-electrospray ionisation-tandem mass spectrometry (LC-ESI-MS/MS), we measured seven phthalate metabolites (MBzP, MCHP, MiNP, MMP, MCPP, MiBP, and MEHHP) as biomarkers for exposure to phthalates. MiBP is a urinary metabolite of dibutyl phthalate and MEHHP is a urinary metabolite of di-(2-ethylhexyl) phthalate. A multiple logistic regression analysis was performed to evaluate the association between UC risk and clinical parameters, including log-transformed creatinine-corrected urinary phthalate metabolite concentrations. Odds ratios (OR) and 95% confidence intervals of OR were calculated.

From 2013 to 2017, we recruited 224 UC patients and 272 CKD controls who had adequate urine specimen collections and complete datasets. Five of the metabolites, MBzP, MCHP, MiNP, MMP, and MCPP, were detected in <40% of samples, and were not further analysed for statistical significance. Among UC patients, the median concentration of urinary MEHHP was significantly higher in the UC cohort than in the control group (42.41 µg/g versus 22.03 µg/g, respectively); however, the median concentration of MiBP did not show any difference between groups (9.71 µg/g versus 10.74 µg/g, respectively). The adjusted OR of MEHHP was 1.42 (95% confidence interval: 1.21–1.68; p<0.001) in multivariate logistic regression after adjusting for age, renal function, non-steroidal anti-inflammatory drug use, exposure to environmental toxins, and the use of traditional Chinese medicine. Analysis within MEHHP concentrations showed a dose-response relationship of OR for urothelial cancer UC risk (Figure 1).

Previous studies have shown that phthalates promote and induce tumourigenesis in a variety of cell types through aryl hydrocarbon receptor-mediated genomic and non-genomic pathways.[3] We speculate the activation of these pathways by phthalates may be related to our observations.

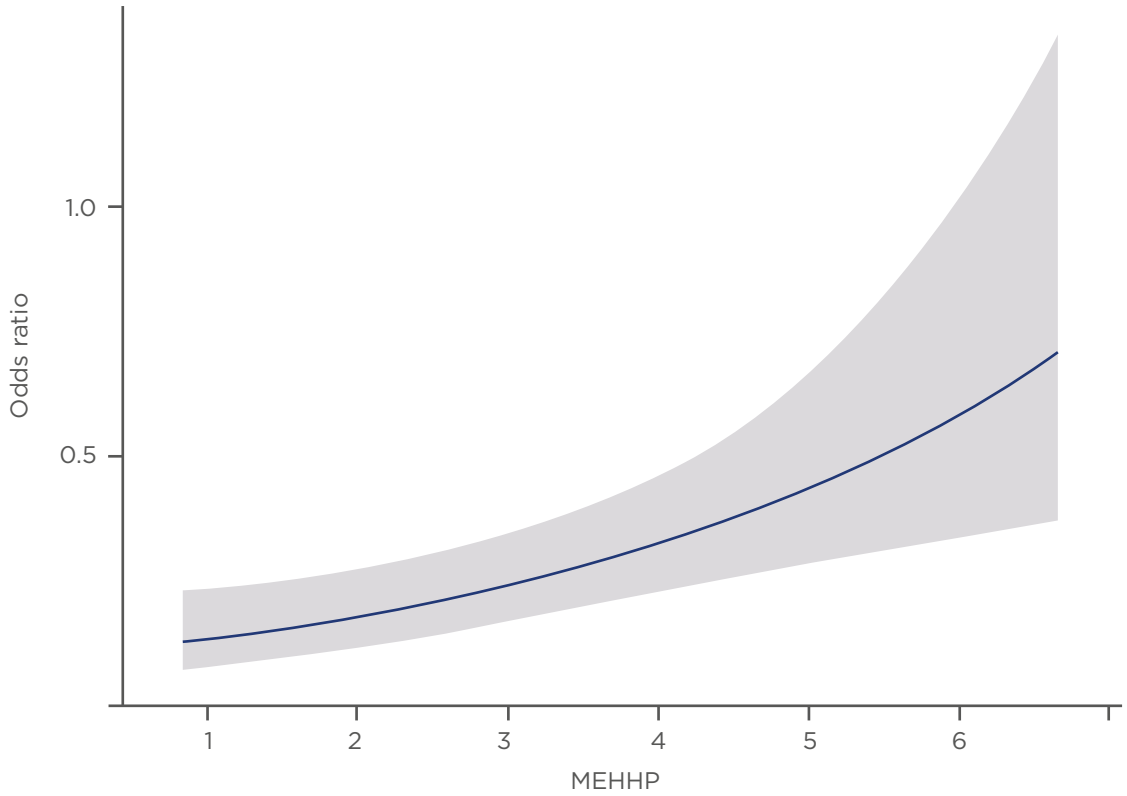

Figure 1: Analysis within urinary MEHHP concentrations (log-transformed) showed a dose-response relationship of odds ratios for urothelial cancer risk.

In conclusion, higher urinary concentration of MEHHP is correlated with the increased risk of UC. These findings suggest high environmental exposure to phthalates may contribute to the development of UC in CKD patients. Further studies are needed from other populations with a different range of phthalate exposure to confirm our findings.

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Aiming to Increase Adherence to Treatment in Patients with Chronic Kidney Disease: The Use of Technology

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Keywords: Adherence to treatment, chronic kidney disease (CKD), patient education, technology.

Citation: EMJ Nephrol. 2018;6[1]:44-45. Abstract Review No. AR2.

Chronic kidney disease (CKD) is a public health problem worldwide, and, in Brazil, an increasing number of patients requiring dialysis and transplantation has been observed. Knowledge about CKD and other diseases is poor among the general population in many parts of the world.[2-4] Adherence to treatment is a problem that impacts patient outcomes, and technology can be a good ally for increasing patient health education and adherence to treatment.[5,6] At the ERA–EDTA Congress 2018, we presented the 'Renal Health Project', which used a multidisciplinary approach to build technological tools to increase patient education and self-monitoring of treatment through an application for smartphones and educational videos. The project was started in 2015 by a group of nephrology professors and students from the University of Fortaleza (UNIFOR), Fortaleza, Brazil, in partnership with the Technology Innovation Laboratory (UNIFOR) and with support from the International Society of Nephrology (ISN) Clinical Research Program, Brazilian Society of Nephrology (SBN), and Edson Queiroz Foundation/UNIFOR. The project was planned in three phases.

Phase 1: Development of an application for smartphones to help patients with CKD to better control their treatment. The application was intended for transplant patients and those undergoing dialysis. The application also provides information for the general population and provides a tool to estimate glomerular filtration rate and indicate if someone is at risk of CKD. This application was called 'Renal Health', and the first version was in Portuguese, the official language of Brazil. A team of professionals and students from the fields of health and computer sciences worked together to build the first version of the application, and then a usability test was performed with a group of nephrology professionals (physicians, nurses, dietitians, and psychologists) and patients (patients on haemodialysis and transplant patients).

Phase 2: Elaboration of the digital educational material to be connected to the application and available on the internet.

Phase 3: Clinical study on the impact of these tools on patient outcomes. The clinical study, which is designed to investigate if the use of the application has a beneficial effect on patient outcomes (both on dialysis and transplantation), is planned to start in Brazil by the second half of 2018. We also intend to test the application in other countries, so an English version is already being developed. We welcome partnerships with researchers interested in testing the application and developing educational materials for patients and testing technological tools to increase adherence to treatment.

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Correlation Between Pleural Comets and Spectroscopy Bioimpedance in Haemodialysis Patients

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Citation: EMJ Nephrol. 2018;6[1]:45-47. Abstract Review No. AR3.

INTRODUCTION

Overhydration (OH) is highly prevalent in haemodialysis (HD) patients[1] and is a strong risk factor for mortality.[2,3] It has been shown that pleural B lines, also known as pulmonary or pleural comets, appear alongside the presence of extravascular pulmonary fluid. Absent in normal lungs, the resolution of B lines in HD patients seems to occur in real time as the ultrafiltrate (UF) progresses.[4] However, it has not been investigated whether this technique has a relationship with the results obtained by bioelectrical impedance analysis (BIA)[5,6] in the estimation of OH and if it can be used to estimate the UF to be removed through HD. The study's main objective was to evaluate the presence of B lines in patients with OH data according to their BIA assessment.

Table 1: Demographic, clinical, and laboratory characteristics of the study participants (N=17).

Characteristic	Value
Female sex, n (%)	8 (47.0)
Age (years), mean (SD)	44.1 (20.8)
Systemic hypertension, n (%)	13 (76.5)
Diabetes, n (%)	7 (41.2)
Antihypertensive treatment, n (%)	9 (52.9)
Oedema, n (%)	4 (23.5)
Jugular engorgement, n (%)	6 (35.3)
BMI: malnutrition, n (%)	4 (23.5)
BMI: normal, n (%)	7 (41.2)
BMI: overweight, n (%)	6 (35.3)
Adherence to nutritional recommendations, n (%)	4 (23.5)
Residual uresis ≥100 mL/24 hours, n (%)	12 (70.6)
Haemodialysis minutes per week, mean	592.9
Haemodialysis sessions per week, mean	2.8
Dialysate sodium (mS/cm), mean	13.6
Left ventricular ejection fraction (%), mean	59.6
Albumin (g/dL), mean	3.7
Haemoglobin (g/dL), mean	10.7
Ultrafiltration (kg), mean	1.9

STUDY DESIGN

This study was based on a unicentric transversal observational cohort.

METHODS AND PARTICIPANTS

Hydration status was assessed using BIA and pulmonary ultrasound in 17 patients who received HD for at least 6 months. The inclusion criteria were no amputations, metal prostheses, or pacemakers; an ejection fraction of the left ventricle >50%; and no New York Heart Association (NYHA) Class IV heart failure or any history of cardiovascular or pulmonary decompensation in the last 3 months.

RESULTS

The demographic, clinical, and laboratory data of the participants are described in Table 1. The mean age of the patients was 44.1 years, 76.5% were hypertensive, 41.2% were diabetic, 23.5% presented with oedema of the lower extremities, and 35.3% had jugular engorgement. A normal BMI was measured in 41.2% of the patients and only 4 patients (23.5%) followed the nutritional recommendations.

The patients received an average of 2.82 sessions of HD per week, with equal sodium conductivity in all cases (13.6 mS/cm) and an average UF of 1.94 kg. The average serum sodium level was 134.4 mEq/L (standard deviation: 2.5) and average serum albumin was 3.66 g/dL (standard deviation: 0.4). A positive correlation was found between OH and the number of B lines ($r=0.62$; $r^2=0.38$; $p=0.008$). No correlation was found between the dry weight and the number of B lines. The distribution of B-type natriuretic peptide in the sample ranged between 12 and 5,000 pg/mL, with a mean of 1,038.9 pg/mL (standard deviation: 1,448.27), showing a positive correlation with the number of B lines ($r=0.70$; $r^2=0.52$; $p=0.001$). Systolic blood pressure also positively correlated with the number of B lines ($r=0.71$; $r^2=0.21$; $p=0.001$).

CONCLUSION

Analysis of the data showed that there was a positive correlation between OH measured by BIA, B-type natriuretic peptide, and systolic blood pressure with the number of B lines shown on pulmonary ultrasound. These findings show these methods can be used to estimate OH

in HD patients, with the advantages of being affordable and accessible methods that can be performed at the patient's bedside.

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Twitter-Based Case Conferences: An Online Learning Tool for Nephrologists

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Nephrology, social media, Tweetchat, Twitter, #ECNeph, #SoMe.

Citation: EMJ Nephrol. 2018;6[1]:47-48. Abstract Review No. AR4.

INTRODUCTION

The use of social media as a means for dispersing knowledge has been gathering pace in recent times.[1] This is especially true for Twitter, which has emerged as one of the foremost tools among social media platforms. The medical community has taken to Twitter in great numbers to connect with peers, debate, and spread knowledge and information on breaking news and trials in the medical field. It is interesting to note that, within this community, nephrologists have taken to Twitter like fish to water and have become a force to be reckoned with. Various learning tools have been developed on Twitter, including journal clubs, quiz sessions, blogs and essays, and slide and video presentations.[2]

MATERIAL AND METHODS

We developed a case discussion session on Twitter in the form of a tweet chat session entitled: 'Everyday Cases in Nephrology' and associated it with the hashtag #ECNeph. This form of discussion is unique and, to our knowledge, has not been attempted before on Twitter. This discussion was conducted for an hour every Thursday at a specified time and was attended online by nephrologists, nephropathologists, and radiologists from all over the world.

RESULTS

Twenty-two Twitter case conferences were conducted in the 8-month period from May–December 2017. A total of 3,957 tweets

were composed during these case conferences. Specialists from 18 countries (including India, Canada, Mexico, China, UK, Myanmar, Malaysia, Spain, Turkey, Serbia, USA, Australia, and the Gulf countries) took part.

On average, 22 doctors joined the #ECNeph case discussion session with a total of 96 physicians interacting with the sessions during the 8-month period. The number of tweets per learning session varied from 110–316, with a mean of 180 tweets per session (Figure 1). The total percentage of tweets that included additional media in the form of slides of laboratory findings, radiological investigations, or renal biopsies was 10.45% (423 tweets). Following a mid-course change in the timings of the #ECNeph Twitter session from 8 pm Indian Standard Time to 10 pm, the number of participants increased from 16 to 22 on average.

In a bid to increase our reach, another course change consisted of live streaming of case discussions and the inclusion of guest nephrologists and pathologists in the sessions. Twitter links were provided and enabled 1,242 doctors to view case discussions live through periscope videos of five case discussions on two different days.

CONCLUSION

Twitter-based case conferences are a unique mode of Twitter chat that is gaining popularity. Including other nephrologists and pathologists as discussants has helped to increase our reach. We have described a unique effort on the part of the nephrology Twitter community to help each other and impart knowledge at the same time.

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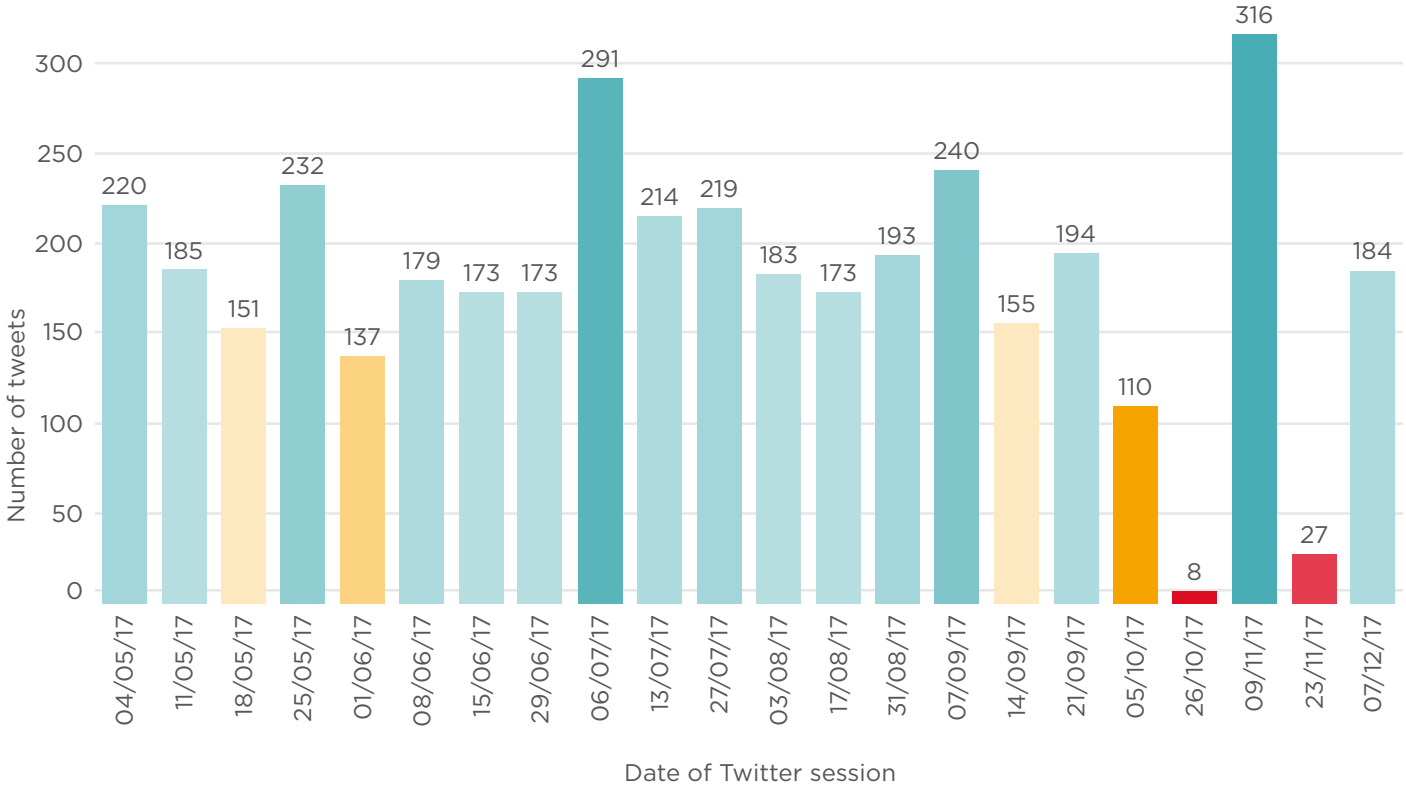

Figure 1: The number of tweets during each session of #ECNeph.

Mean: 180 tweets.

Characterisation and Quantification of Proteasuria in Nephrotic Syndrome

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Nephrotic syndrome, protease activity, proteasuria, proteinuria, serine proteases.

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Proteases are involved in various physiological processes, such as enzyme activation, signalling pathways, post-translational modifications, and protein degradation and digestion. In the blood plasma, proteases mostly circulate as inactive zymogens. Nephrotic syndrome is characterised by increased glomerular permeability for plasma proteins, which is expected to lead to urinary excretion of proteases. At the same time, in the distal tubule of nephrons, some proteases may overactivate the epithelial sodium channel by proteolytic release of an inhibitory peptide in the γ-subunit. This leads to increased sodium retention and, ultimately, to the typical symptoms associated with sodium retention and oedema formation.[1] There is a lack of data on the quantity, activity, and class specificity of aberrantly filtered proteases in nephrotic syndrome.

A biochemical assay was established to quantify protease activity in urinary samples based on a substrate library containing 195 different pentapeptides covering all combinations of protease cleavage sites (P-CHECK®, Panatecs, Germany).[2] Each peptide was enframed by a fluorescence resonance energy transfer (FRET) pair with 7-methoxycoumarin-4-acetic acid (Mca) as the fluorophore and 2,4-dinitrophenyl (Dnp) as the quencher. Mca was released upon proteolysis and emitted fluorescence at 405 nm. To measure urinary protease activity, samples from healthy and nephrotic syndrome humans and mice were incubated with the substrate library at 37°C for a 48-hour period. The proportions of the respective protease classes were determined after the addition of optimised high amounts of specific inhibitors against serine (AEBSF), cysteine (E-64), aspartate (pepstatin A), and metalloproteases (EDTA). Protease activity was expressed in relative units (1 RU=1,000 relative fluorescence units/mg creatinine).

We analysed urine samples from 18 patients with acute nephrotic syndrome of varying aetiology (average proteinuria: 5,805±3,713 mg/g creatinine) and compared the results with those obtained from the urine samples of 10 healthy individuals without proteinuria. The nephrotic patients were found to have a total protease activity of 524±422 RU, which was increased by a factor of 2.36 compared to that of a healthy person (222±141 RU; p=0.016). A high proportion of the urinary protease activity of nephrotic syndrome and healthy persons was sensitive to inhibition by AEBSF (82±15% and 75±31%, respectively). The remaining protease activity was distributed among the other protease classes; metalloproteases also had a high proportion (33±20% and 40±29%, respectively), while cysteine and aspartate proteases were less abundant (<25%). The data also suggested an overlap of effects between the inhibitors. Mice with doxorubicin-induced experimental nephrotic syndrome exhibited increased urinary protease activity from 3,287±1,315 RU at baseline to 52,135±28,166 RU (p=0.0002), corresponding to an increase by a factor of 16.50±5.31. Similarly, in humans, serine proteases accounted for the highest proportion of urinary total protease activity, followed by metalloproteases.

In conclusion, nephrotic syndrome leads to increased urinary excretion of active plasma proteases, which can be termed proteasuria. Serine proteases account for the vast majority of urinary protease activity in healthy people and nephrotic syndrome patients. The identification of the specific proteases involved in the increased protease activity can be accomplished

by a proteomic approach, and the physiological role of the potential candidates can be further validated using knockout mice.

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Candesartan Decreases Kynurenic Acid Production in Rat Kidneys *In Vitro*: A Novel Mechanism of Nephroprotection?

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Keywords: Candesartan, kidney, kynurenic acid (KYNA), nephroprotection, renin-angiotensin system.

Citation: EMJ Nephrol. 2018;6[1]:50-51. Abstract Review No. AR6.

Arterial hypertension and diabetes are major causes of kidney failure. Despite there being many potent antihypertensive agents currently available, kidney damage is still an important clinical problem and delaying kidney function decline remains crucial to prolonging patient survival.

Increased activation of the renin-angiotensin system, especially the angiotensin II Type 1 receptors (AT_1), leads to blood pressure elevation as well as tissue remodelling. It is widely known that treatment with AT_1 receptor antagonists (ARB) inhibits kidney function impairment. Beyond hypotensive properties, a decrease in proteinuria and oxidative stress is responsible for the nephroprotective effects of ARB.

Kynurenic acid (KYNA), a tryptophan degradation product, has natriuretic and hypotensive properties. Kynurenine aminotransferases (KAT) are responsible for KYNA synthesis from the precursor kynurenine (KYN). KYNA is an endogenous broad-spectrum ionotropic glutamatergic receptor antagonist. In this regard, KYNA should be considered to be involved with kidney physiology and pathology. According to some researchers, KYNA can be classified as a uremic toxin.[1] High-serum KYNA levels were found in animals and humans with kidney failure.

The aim of this study was to analyse the effect of candesartan, one of the most frequently used ARB, on KYNA production and the activity of KAT isoenzymes (i.e., KAT I and KAT II) in rat kidneys *in vitro*. Moreover, molecular docking of candesartan to KAT II crystal structure was conducted, along with a search of publicly available microarray data repositories for data on candesartan's effects on the expression of KAT-coding genes in rat kidneys. The effect of candesartan on KYNA synthesis, as well as KAT I and KAT II activity, was examined in rat kidney homogenates *in vitro* after a 2-hour incubation in the presence of KYN. KYNA was subjected to

high-performance liquid chromatography and quantified fluorometrically.

Candesartan at 0.5 mM and 1 mM concentrations decreased KYNA production in kidney homogenates *in vitro* to 58% ($p<0.001$) and 44% ($p<0.001$) of control values, respectively. At 0.1 mM, 0.5 mM, and 1.0 mM concentrations, candesartan decreased KAT I activity in kidney homogenates *in vitro* to 66% ($p<0.05$), 56% ($p<0.01$), and 49% ($p<0.01$) of control values, respectively. Candesartan at 0.1 mM, 0.5 mM, and 1.0 mM concentrations decreased KAT II activity in kidney homogenates *in vitro* to 51% ($p<0.01$), 10% ($p<0.001$), and 3% ($p<0.001$) of control values, respectively. Molecular docking results suggested that candesartan binds to residues within the active site of KAT II, mirroring the interactions of the natural substrate KYN, which suggests a competitive mechanism of inhibition. The available data do not confirm the effect of candesartan on KAT-coding genes.

In conclusion, candesartan inhibits KYNA production because it decreases KAT I and KAT II activity in rat kidneys *in vitro*. Our findings present a novel mechanism of candesartan's action in rat kidneys that may be correlated with its nephroprotective properties.

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Tuberous Sclerosis: Clinical Characteristics and Renal Management Strategies. A Single-Centre Experience

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Keywords: Angiomyolipoma (AML), mammalian target of rapamycin (mTOR) inhibitors, tuberous sclerosis (TS).

Citation: EMJ Nephrol. 2018;6[1]:51-52. Abstract Review No. AR7.

Tuberous sclerosis (TS) is a rare genetic disorder affecting multiple organ systems, including the kidneys, where TS presents as angiomyolipoma (AML) and cysts.[1] With the advent of mammalian target of rapamycin (mTOR) inhibitors, a new dimension has been achieved for the management of this condition.[2] Our institution is a tertiary renal and neurological centre that has a growing cohort of TS patients monitored in the multispeciality and multidisciplinary (MD) TS clinic. In this cross-sectional observational study, we shared our experiences of TS patient characteristics and renal management strategies and explored the correlation between the number of AML and both patient age and estimated glomerular filtration rate (eGFR).

A total of 25 TS patients are currently monitored in our MD clinic. The mean age of the cohort was 40 years, with 14 males and 11 females. Prior to the study, 24 of the 25 patients had some form of imaging scan (magnetic resonance imaging [MRI] or computed tomography [CT]) of their abdomen and/or kidneys. Of these 24 patients, 15 (63%) had an AML >3 cm in size and qualified for mTOR inhibitor therapy based on current international guidelines. Five patients had an AML <3 cm in size and 4 had no renal involvement. The mean eGFR of the sample was 74.6 mL/min/1.73m^2, with a mean haemoglobin concentration of 130 mg/dL. A clear correlation

was not observed between eGFR and the number of AML; however, an increasing linear trend was noted for the size of AML with age (Figure 1), an association that has been previously reported.[3] The mean decrease in eGFR over a follow-up period of 4.6 years was 1.59 mL/min/1.73m^2/year. Of the 15 patients eligible for mTOR inhibitor treatment, 8 were administered sirolimus, 1 received everolimus, and the rest were under assessment. Following review of the neurological manifestations, 85% (17 of the available 20 patients) had radiological evidence of cortical tubers in the brain, 21 had subependymal nodules, and 7 had subependymal giant cell astrocytoma. Phenotypically, 14 patients out of the total 25 had an intellectual disability, with 23 having active epilepsy; of these, 18 had generalised onset and 17 had coexistent focal onset epilepsy. The seizure type was unclassified in 5 patients. All 25 patients were taking at least two antiepileptic drugs.

In conclusion, this study has given further insights into TS patient characteristics and management strategies. Long-term follow-up will better characterise the factors that can determine renal function decline, and with expanding indications of the use of mTOR inhibitors, a MD approach would be an appropriate management strategy in the future. At the European Renal Association–European Dialysis and Transplant Association (ERA–EDTA) 2018 Congress, discussions were focussed around a MD clinic and response to treatment with mTOR inhibitors, which our follow-up data would be able to address.

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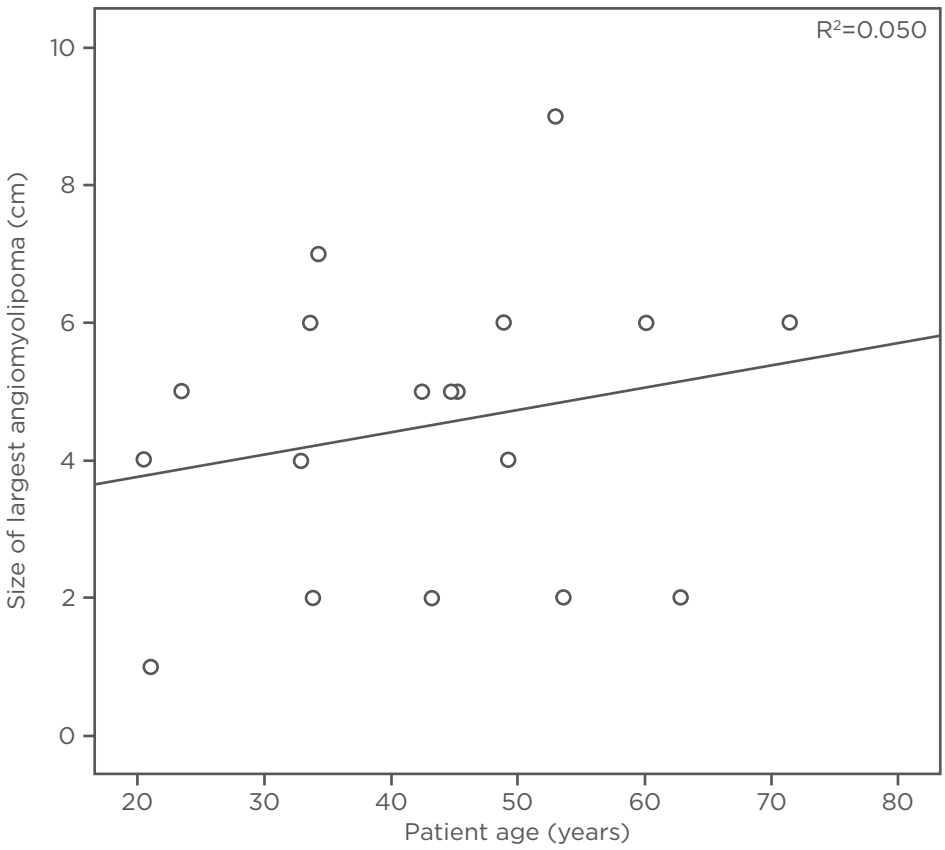

Figure 1: The association between size of largest angiomyolipoma and age of patient.

Parents Diagnosed with Hereditary Nephropathy by the Paediatric Nephrologist

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Chronic kidney disease, hereditary nephropathy, paediatric nephrology.

Citation: EMJ Nephrol. 2018;6[1]:53-54. Abstract Review No. AR8.

INTRODUCTION

Hereditary nephropathies should be suspected in adults with a family history of chronic renal alterations,[1] and children should be screened, particularly in autosomal-dominant diseases.[2] However, there are cases of hereditary nephropathies that manifest in childhood (linked to the X chromosome and atypical cases), and from the correct aetiology these cases could be identified in some adults with an erroneous or unknown diagnosis of chronic kidney disease. It could even be possible to discover patients who should be followed up with nephrology consultations.[3]

OBJECTIVES

The objectives of this study were to analyse patients referred to the nephrology department with hereditary nephropathies diagnosed based on their children in the paediatric nephrology department, and to determine the correct diagnosis of patients with chronic kidney disease not previously identified.

MATERIALS AND METHODS

Paediatric patients in a paediatric nephrology clinic were diagnosed by neonatal screening for cystinuria[4] or by a positive genetic study of another aetiology. Adult patients with hereditary nephropathy were then identified following the screening of their children.[5] Variables in the study included the age and sex of children and adults with chronic kidney disease, aetiology of the hereditary nephropathy, genetic study, and clinical profile (blood, urine, and renal ultrasound).

RESULTS

The study included 68 children (65% males) aged 0–7 years at diagnosis; 14 were diagnosed following a positive genetic study. After the screening of the paediatric patients, 76 adults (58% males) were identified, with 8 shown to have previously been in follow-up due to undiagnosed chronic kidney disease.

Two different groups were identified: those diagnosed by neonatal screening (62 cystinurias) and those diagnosed via genetic study of their children (1 case of Alport syndrome,[6] 3 cases of hepatocyte nuclear factor 1β-associated kidney disease,[7] 1 case of Barakat syndrome, 1 case of autosomal dominant polycystic kidney disease,[8] 6 cases of Dent disease,[9] 1 case of *PAX2*-related disorder, and 1 case of hypophosphataemic rickets linked to the X chromosome [Figure 1]).

CONCLUSION

The consultation of paediatric nephrology provides a step towards the improvement of the diagnosis of hereditary nephropathy, especially in cases of undiagnosed chronic kidney disease. As nephrologists, we should suspect these diseases upon the first examination of adult patients.[10]

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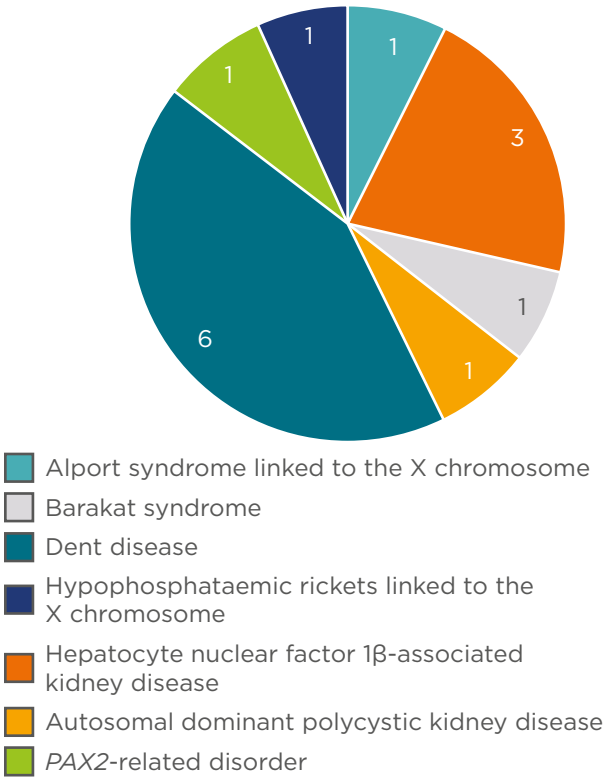

Figure 1: Number of adult patients diagnosed with hereditary nephropathy (not cystinuria) via genetic study.

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Peritonitis in Peritoneal Dialysis Patients: The Case for Rapid Diagnosis, Targeted Treatment, and Monitoring to Improve Outcomes

EDITOR'S PICK

Chakera and colleagues have provided an excellent review on the latest developments in microbiological diagnostic techniques for peritonitis in peritoneal dialysis. Despite being a cost-effective, home-based treatment option for patients with end-stage renal disease, peritoneal dialysis use is declining in many countries due to the concerns clinicians and patients have regarding peritonitis infection. To restore confidence, better diagnostics are required to enable appropriate treatment to be started earlier, alongside improved understanding of the biology of peritonitis. I hope this paper will spark discussion and debate among clinicians.

Samantha Warne

Editor

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Abstract

Peritoneal dialysis (PD) is a cost-effective, home-based treatment option for patients with end-stage renal disease; however, PD is declining in many countries. A major reason for this is peritonitis, which commonly leads to technique failure and has led to negative perceptions of PD by clinicians and patients. To restore confidence in PD, better diagnostics are required to enable appropriate treatment to be started earlier; this needs to be coupled with improved understanding of the biology of peritonitis. Advances in culture-independent microbiological methods, in particular the use of bacterial flow cytometry and immune fingerprinting techniques, can enable organism

detection and antimicrobial susceptibility testing to be performed in as little as 3 hours after samples are received. At the same time, improved understanding of peritoneal mesothelial cell responses to infection is providing insights into pathways that may be targeted to dampen deleterious elementsof the host immune response, promote healing, and preserve membrane function.

INTRODUCTION

Worldwide, >2.5 million people have end-stage renal disease and are receiving renal replacement therapy.[1] Over 250,000 patients with end-stage renal disease are treated with peritoneal dialysis (PD) worldwide,[2] which equates to ~10% of all dialysis patients, but this figure can be as high as 60–70% in some countries where a PD first strategy is employed.[3,4] PD is cost-effective, offers a better quality of life compared to haemodialysis, and, in some settings, may be the only available treatment option. The annual global growth rate of PD is estimated to be ~8%, which is higher than for haemodialysis (~6–7%).[2] However, the proportion of dialysis patients treated with PD is declining in developed countries, despite PD being associated with superior survival in the first few years, better quality of life, and lower treatment costs; this is, therefore, of great concern.[5-8]

PD uses a catheter placed into the abdomen, with instillation of dialysis solutions of varying composition to enable fluid and toxin removal; as a result, a major complication of PD is the development of a peritonitis infection. Peritonitis is the single largest cause of patients failing on PD; approximately half of all PD technique failures are due to peritonitis, with peritoneal infection also strongly associated with mortality.[9] Fear of peritonitis is a major reason for patients and clinicians not choosing PD.[10] Gram-positive cocci, such as *Staphylococcus epidermidis* and other staphylococcal species, are the most frequent cause of PD-associated peritonitis worldwide, with Gram-negative organisms accounting for 20–25% of cases and fungal infections ~4%.[11,12] Despite the use of broad spectrum antibiotics when patients present with peritonitis, many develop relapsing or recurrent life-threatening infections. Even when treatment is successful, deleterious changes may occur in peritoneal membrane function, which ultimately lead to inadequate solute or fluid removal and technique failure.

The treatment of, and outcomes from, peritonitis are highly variable between countries and even within medical centres in the same country. This is despite the publication of treatment guidelines.[13] This suggests that despite decades of research and clinical experience, there remains concerns regarding guideline content and that there is a lack of consensus about the management of peritonitis.[14-16] A major barrier to improving the treatment of patients with peritonitis is the use of traditional, culture-based diagnostic microbiology to confirm the presence of infection. These techniques are slow, with cultures usually taking 1–3 days to become positive, which can cause delays in diagnosis. In addition, many organisms are either difficult or impossible to culture,[17] with reported culture-negative rates of up to 20% in some centres.[11] As a result, clinicians commence empirical antimicrobial therapy based on historical profiles and published guidelines rather than patient-specific laboratory evidence. Even when cultures are positive, definitive antimicrobial susceptibility results that enable the tailoring of antibiotic treatment to the most effective regimen often require a further 1–3 days. This delay likely contributes to the increased mortality and morbidity of patients on PD and the emergence of drug-resistant microbes.[18,19] Reducing the time taken for clinicians to receive results that guide effective therapeutic decision-making is therefore critical to achieving better outcomes for patients.

A better understanding of the molecular pathways that control infection (susceptibility, initiation, severity, recovery, and/or relapse) should enable their manipulation to improve outcomes and reduce peritoneal membrane damage. New advances in culture-independent diagnostic methods and knowledge of mesothelial cells and peritoneal responses to infection provide hope that much-needed improvements in peritonitis outcomes are in sight.

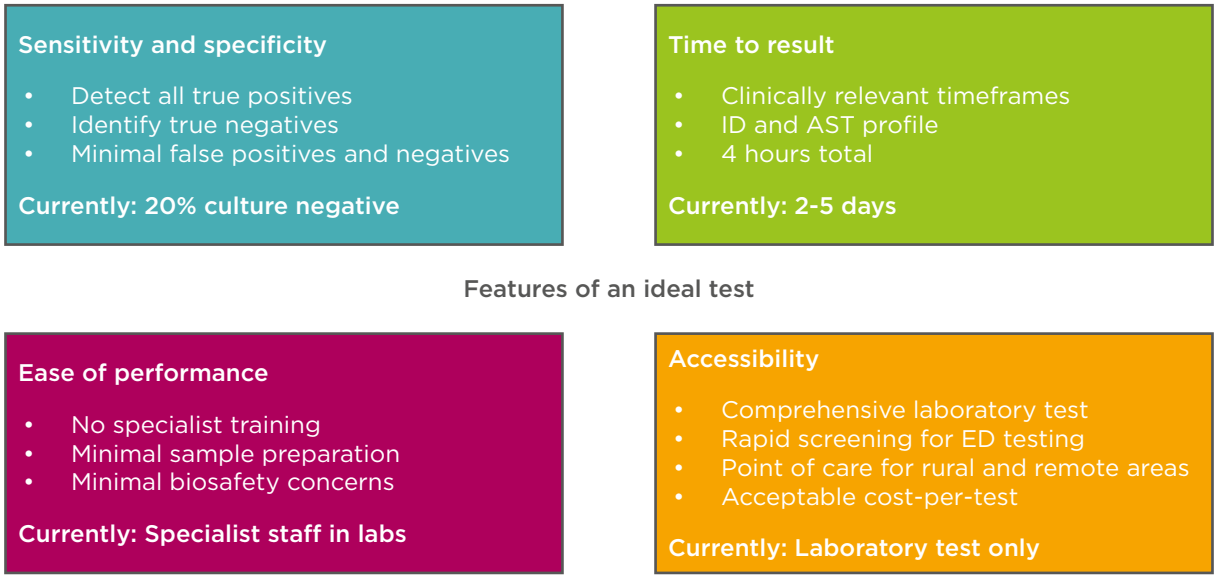

Figure 1: Features of an ideal diagnostic test for kidney disease.

AST: antimicrobial susceptibility testing; ED: emergency department; ID: identification of infecting organism.

ADVANCING CULTURE-INDEPENDENT MICROBIOLOGY

A number of culture-independent laboratory methods are now available that promise faster, more sensitive, and more specific aetiological diagnoses across a broad spectrum of pathogen and specimen types.[20] Examples include nucleic acid-based approaches to detect bacteria-specific DNA or RNA, and protein-based assays, such as matrix assisted laser desorption/ionisation time-of-flight (MALDI-TOF) mass spectrometry (MS), which identifies organism-unique protein signatures.[21,22] These techniques are relatively rapid, leading to faster reporting times and the detection of organisms that may be difficult to culture.[23] Each approach, however, has significant limitations. They do not distinguish viable from nonviable organisms, the number of defined genetic targets for nucleic acid-based detection are currently limited, and the interpretation of results can be complicated in polymicrobial infections contaminating species and/or the presence of commensal bacteria.[23,24] In addition, even if specific resistance genes are detected by polymerase chain reaction (PCR), expression of these genes may vary and multiple genes may be required to yield functional resistance *in vivo*.[25,26]

To date, neither bacterial nucleic acid nor protein-based detection techniques are routinely used for analysis of samples from patients with suspected PD peritonitis.[27] Major limitations of these techniques for the analysis of PD samples are the high bacterial concentrations required for adequate sensitivity during protein detection[28,29] and the poor accuracy of nucleic acid detection, which has unacceptably high false negative rates, thought to be due to the presence of inhibitors in dialysate (Figure 1).[30] Bacterially derived DNA fragments in PD effluent show some value as a prognostic marker for relapsing peritonitis episodes, but as the presence of bacterial DNA does not directly correlate with live organisms capable of causing infection, the clinical applicability is limited.[31] 23S ribosomal (r)RNA PCR and sequencing has been applied to the problem; however, the authors concluded that this method was best reserved as an adjunctive tool to traditional culture techniques given the lack of specificity when applied as a diagnostic test.[32] While not an exhaustive set of examples, this illustrates the complexity faced when attempting to use nucleic acid-based technology in a sample as complicated as PD effluent.

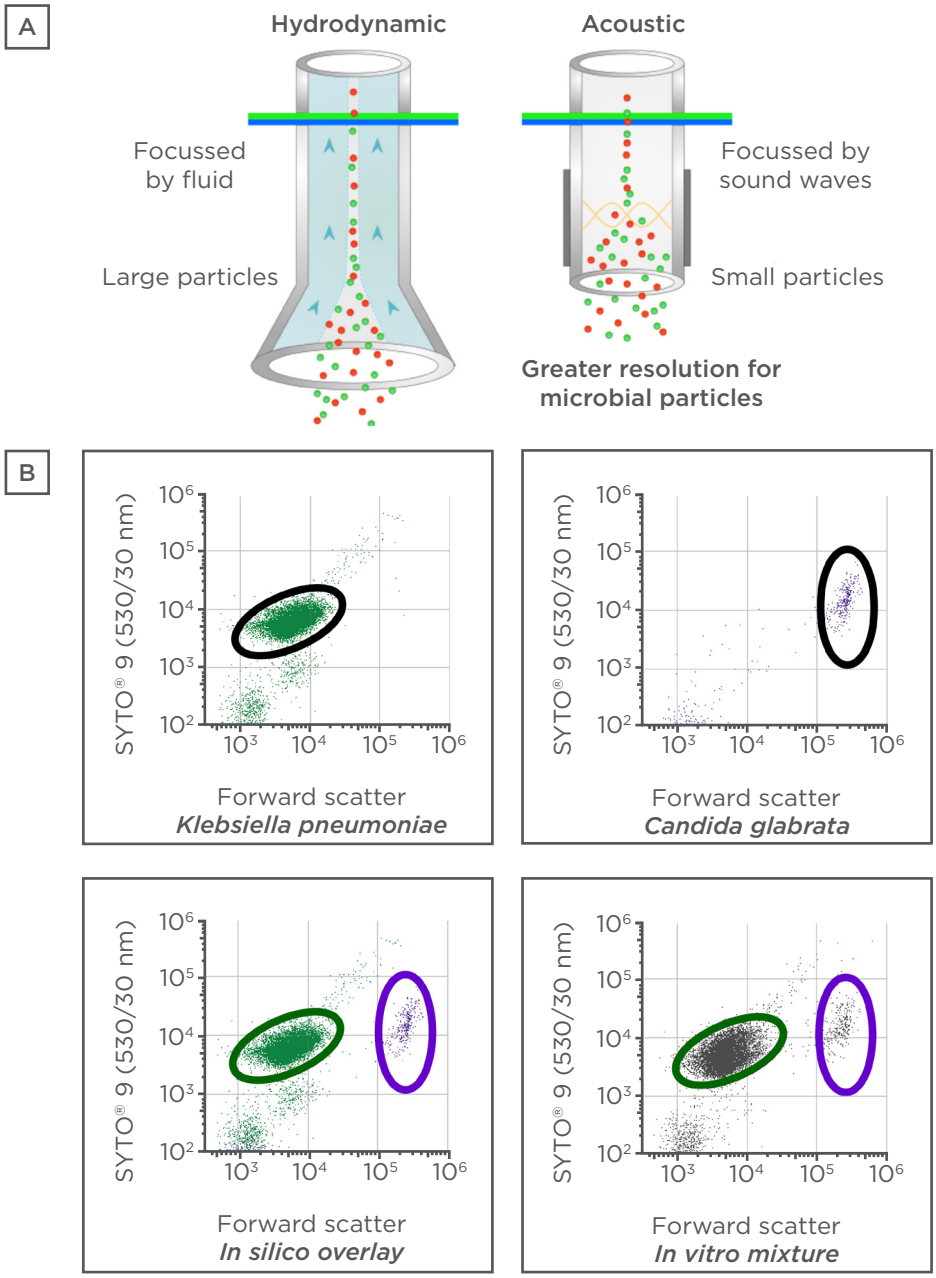

Figure 2: A) Acoustic versus standard hydrodynamic focussing for flow cytometry. B) Clear separation between bacterial and fungal pathogens in peritoneal dialysis dialysate as assessed by acoustic flow cytometry.

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ADVANCES IN FLOW CYTOMETRY ENABLE DIRECT VISUALISATION OF BACTERIA AND FUNGI

While flow cytometry (FC) has been extensively used to detect eukaryotic cells, the smaller size of bacteria coupled with variability in cell wall structures has limited its use for bacterial detection.[33] However, recent advances in hardware design, including the use of acoustic-focussing technology (Figure 2A), have greatly improved the effective resolution capable for small particles. Reliable detection of biological particles as small as 250 nm is now considered routine.[34] Coupling this technology with DNA-intercalating and protein-binding fluorescent dyes improves resolution further and makes accurate identification of bacteria or fungi directly from clinical samples possible (Figure 2B). The quantitative nature of particle characterisation by FC also permits direct

enumeration of bacterial counts in dialysate providing information on inoculum dose, which may be an important feature in influencing clinical outcomes.

One unique aspect of this approach is the separation of bacterial detection from identification of their species (or Gram type), which may prove challenging for clinicians and microbiologists who have traditionally decided upon treatment options based on this knowledge. While this has implications for epidemiological data collection (if a traditional culture is not also conducted),[35] this approach can provide answers where traditional culture techniques have failed, for example in cases of culture-negative peritonitis, or where recent exposure to antimicrobial agents might impact culture. Furthermore, sample preparation for this technique can require as little as 25 minutes of manual handling, followed by 10 minutes for data acquisition and processing, representing a potential gain of >18 hours compared to traditional culture-based methods.[36]

CULTURE-INDEPENDENT ANTIMICROBIAL SUSCEPTIBILITY TESTING

Most antimicrobial agents used in the treatment of PD peritonitis have bacterial (or fungal) cell lysis as their final mechanism of action. As FC detection of this mechanism works by identifying cell shape, size, and wall integrity, the effects of antibiotics on cells can be analysed and antimicrobial susceptibility profiles determined *ex vivo* in samples. This method, termed flow-assisted antimicrobial sensitivity testing (FAST), has demonstrated a strong positive correlation (r^2: 0.81; $p<0.0001$) with current international standard culture-dependent methods, and has been demonstrated to be useful for common PD pathogens across a range of relevant antimicrobials (Figure 3).[36] Extensive development work is ongoing to assess the application of this technology to detect bacteria directly from PD effluent and determine the cost-effectiveness of this approach and its performance compared to standard culture-based assays. As a guide, currently a 96-well plate for antimicrobial susceptibility profiling with 12 minimum inhibitory concentrations being assessed costs <$100, including consumables and technician time.

While improved diagnostic tools are clearly essential and have demonstrated promise in controlled situations with small cohorts, the majority of patients who develop peritonitis receive effective antimicrobial therapy. In these cases, peritonitis resolves within 7–10 days and most patients are managed in an outpatient setting.

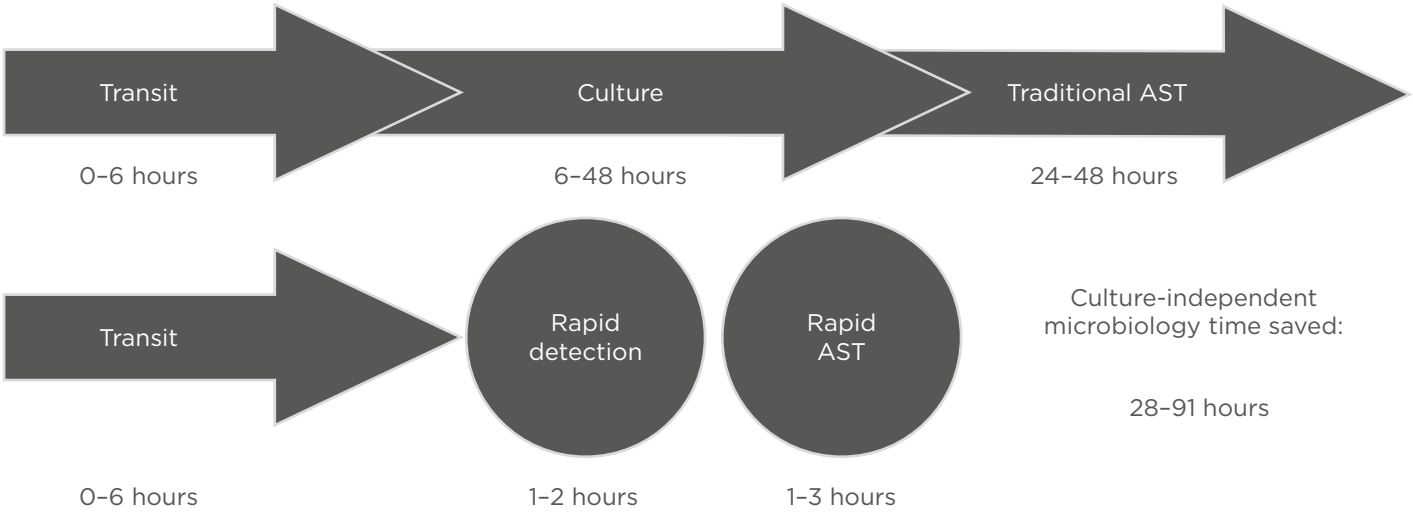

Figure 3: Comparison of timeframes for culture-dependent and culture-independent diagnostic methods to provide results in.

AST: antimicrobial susceptibility testing.

However, epidemiological data demonstrate clear differences in outcomes depending on the class of organism causing peritonitis, with Gram-negative and fungal species generally associated with higher morbidity and mortality.[37] Even in successful respondents, the impact of peritonitis on the long-term durability of PD is significant, with a high incidence of membrane dysfunction, leading to inadequate fluid and solute removal and technique failure.[38,39] To alter these outcomes, detection must be improved to provide more rapid and targeted treatment, and, even more importantly, understanding of the host responses to different types of infection needs to be improved. Only by elucidating all the factors can the clinical course of PD peritonitis be better understood (resolution versus relapse, benign versus severe). This will allow the ability to develop new or modify existing treatments to reduce morbidity and mortality, and to preserve and protect the peritoneal membrane so that patients can continue on PD for longer.

IMMUNE FINGERPRINTING

As opposed to detecting the infecting micro-organisms directly, an alternative approach has been to study pathogen-specific host responses instead, which has particular advantages in settings where organism numbers are below the detection limit of current tests. One novel approach to faster identification of bacterial peritonitis is to analyse the nature of the host response elicited by infection. This technique, known as 'immune fingerprinting', utilises the fact that humans have evolved specific mechanisms to detect and respond to invading micro-organisms that the species have encountered throughout millions of years of evolution.[24,40] These pattern recognition receptors and their signalling pathways define the initial host response to microbial infection, and systematic analysis of samples from patients with PD peritonitis has demonstrated that a unique signature can be identified that accurately distinguishes Gram-negative, Gram-positive, and culture-negative peritonitis at presentation, which are important distinctions when deciding upon the most appropriate treatment.[24,41] These fingerprints can be rapidly determined through measurement of secreted proteins (present in PD fluid) and may be suitable for the development of point-of-care testing. Although this technique does not provide information about antimicrobial susceptibility profiles, which still rely on standard cultures being performed, it is highly complementary to organism-based approaches as it integrates the host responses into a comprehensive view of local infection and may offer additional insights into virulence and immunopathology. Studies assessing the accuracy and efficacy of immune fingerprinting and culture-independent approaches in comparison to standard traditional culture techniques are ongoing, and these studies will also provide important information on the real-world cost of these assays.

UNDERSTANDING PERITONEAL IMMUNITY AND ITS PROGNOSTIC SIGNIFICANCE

The central players in the initial host response to infection are the local immune and non-immune cells that survey the peritoneal cavity in the steady state and respond rapidly to injury and infection. While the role of peritoneal macrophages in the local inflammatory response has been established,[42,43] the contribution of mesothelial cells, a single cell monolayer that lines the visceral and parietal surfaces of organs within the abdominal and chest cavities,[44] to peritoneal immunity remains less well understood. These cells are highly metabolically active, have phagocytic properties, and produce numerous cytokines,[45,46] which recruit other immune cells and initiate repair processes following resolution of infection.[47,48]

Few studies have directly assessed how different bacteria affect mesothelial cells, despite clear evidence that this influences clinical outcomes.[49,50] Recent work has shown that mesothelial cells vary widely in their responses to *S. epidermidis* isolates cultured from patients with PD peritonitis,[51] indicating that unique characteristics of the specific bacterial isolates are responsible for the different patterns of gene expression observed. The variation in individual peritoneal inflammatory responses seen in peritonitis episodes caused by the same species clearly indicates that the quality and magnitude of the activation process varies significantly. This may be related to many factors, including

the individual's immune competence, genetic variants that influence responses,[52] the growth environment, the time between the start of the infection and presentation to hospital and commencement of treatment, and the virulence of the infecting organism. To date, this has not been examined in detail but may be of great significance in understanding the relationship between patient inflammatory responses and long-term outcomes. For example, recent analysis of γδ T cell numbers and their activation by bacteria has been linked to technique failure and mortality in PD patients.[24,41]

Significant genetic variation between isolates of the same bacteria is known to occur, with many bacterial species capable of exchanging segments of DNA, which can contain genes that confer virulence or fitness advantages to the isolate under specific environmental conditions (e.g., iron acquisition systems, antibiotic resistance genes, protein secretions systems, invasins, adhesins, and toxins).[53-55] These genomic islands have been identified in all of the major bacterial species responsible for PD peritonitis,[11] including *S. epidermidis*,[56,57] *Staphylococcus aureus*,[58] *Streptococcus* spp.,[59] *Enterococcus* spp.,[60] *Klebsiella* spp.,[61] and *Pseudomonas* spp.[62]

Studies to assess the impact of individual bacteria and virulence factors on mesothelial cell activation, and the role that different dialysate solutions may play in modulating their expression and the host response, will help identify why particular types of infections promote long-term membrane damage and has the potential to discover pathways that may be therapeutic targets. These studies will require systematic analysis of mesothelial cell responses to pure isolates of bacteria cultured in spent dialysate from patients and correlation of these results to hard clinical endpoints. Given the complexity of the biological processes involved in PD peritonitis, such analyses will benefit greatly from the emerging power of systems biology-based approaches and the integration of mathematical modelling in experimental and observational studies.[41]

CONCLUSION

Currently, the assessment of infection has not advanced substantially since the times of Anton van Leeuwenhoek, Robert Koch, and Louis Pasteur, with reliance on microscopy and culture of patient specimens to confirm the diagnosis and guide appropriate treatment. This outdated approach has left the medical community with high incidences of culture-negative peritonitis in some units and relatively slow turnaround times. As a consequence, clinicians continue to rely on broad-spectrum empirical therapies, exposing patients to potentially unnecessary treatments with potential side effects, including the development and spread of antimicrobial resistance and high rates of long-term technique failure. Advances in laboratory technology over the past decade, particularly with culture-independent microbiology, are showing promise. However, despite repeated calls in international guidelines and research initiatives for translation of these new techniques to the clinical setting, progress has been slow. Even with the promise of improved and more rapid diagnostics, our understanding of host–microbe interactions in the peritoneal cavity remains poor. This needs to be a focus of ongoing research if we are to understand how infection-driven inflammation contributes to poor outcomes and to use this for diagnostic and prognostic gain. This knowledge will guide more rapid and effective interventions and lead to an increase in patient and clinician confidence in PD as a therapy through achieving better membrane preservation and long-term outcomes.

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Update on the Treatment of Glomerulonephritis in Adults in Low-to-Middle-Income Countries

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Abstract

Glomerular diseases are a common cause of chronic kidney disease in several low-to-middle-income countries (LMIC). Additionally, they represent up to 52% of patients with end-stage renal disease (ESRD) in Africa. Current guideline recommendations for the treatment of glomerular diseases may not always be applicable in LMIC due to various challenges related to disease diagnosis and the availability of medicines. A treatment approach that starts with disease diagnosis and proper use of adjuvant therapies mainly targeted at blood pressure and proteinuria reduction is an effective therapeutic option and is recommended for patients in LMIC with glomerular pathologies. The use of immunosuppressive therapies in adults with glomerular diseases should, as far as is possible, be guided by the histological diagnosis obtained through renal biopsy. Prednisone and cyclophosphamide still form the bulk of treatment for glomerular diseases in most countries. Due to the adverse effects associated with immunosuppression, prednisone and cyclophosphamide use must be carefully weighed against the risk of potential side effects, and there is a need for frequent monitoring to assess treatment efficacy, patient response, and adverse effects. It is not advisable to use immunosuppressive drugs (e.g., cyclosporine) that require monitoring of plasma levels in centres where such facilities are not available, given the possible associated nephrotoxicity. The purpose of this narrative review is to provide an update on the treatment of common glomerular diseases and to highlight simple approaches to treatment in LMIC. Knowledge of guideline recommendations on the treatment of various glomerular diseases will provide important understanding on useful therapeutic approaches.

BACKGROUND

Glomerular diseases are a significant cause of chronic kidney disease (CKD) in many low-to-middle-income countries (LMIC), and CKD has been associated with a significant socioeconomic burden in many areas, particularly LMIC.[1] The impact of CKD in these countries has particularly increased given the limited, or total lack of, access to renal replacement therapies.[2,3] Due to the increasing prevalence of Type 2 diabetes mellitus globally, diabetic nephropathy has become a major player in the epidemiology of CKD and end-stage renal disease (ESRD).[4]

Table 1: The frequencies of primary and secondary glomerular pathologies in selected locations.

Region	Male (%)	Mean age in years (range)	Sample size	MCD (%)	Mes PGN (%)	MCGN (%)	FSGS (%)	MGN (%)	IgAN (%)	Cres GN (%)	LN (%)	Hep B (%)	Amyloid (%)	HIVAN (%)
Africa;* Okpechi et al.,[14] 2016	45.2–68.8	Data not available (1–79)	12,093	16.5	9.2	11.8	15.9	6.6	2.8	2.0	7.7	8.3	2.9	1.0
Latin America;† O'Shaughnessy et al.,[15] 2017	36.4	30.0 (17–71)	2,561	6.8	2.4	2.8	15.8	11.1	6.1	4.7	38.1	NR	1.4	NR
China;‡ Xu et al.,[16] 2016	46.5	35.2 (10–76)	4,931	1.8	14.4	1.2	3.6	13.3	43.5	0.7	47.4	10.6	2.7	NR
India; Beniwal et al.,[17] 2016	66.1	30.3 (12–70)	622	21.1	6.4	9.6	10.5	15.0	7.4	1.9	7.6	NR	5.9	NR
Iran; Ossareh et al.,[18] 2010	54.2	36.5 (12–84)	1,407	8.3	0.9	5.5	10.0	26.8	11.0	5.8	11.0	NR	3.3	NR

*Represents data from 13 countries: Cameroon, Democratic Republic of Congo, Egypt, Ghana, Kenya, Morocco, Namibia, Nigeria, Senegal, South Africa, Sudan, Tunisia, Zimbabwe. †Represents data from three countries: Brazil, Colombia, and Mexico. ‡Data presented separately for primary and secondary GN.

CresGN: Crescentic GN; FSGS: focal segmental glomerulosclerosis; GN: glomerulonephritis; Hep B: hepatitis B; HIVAN: human immunodeficiency virus associated nephropathy; IgAN: IgA nephropathy; LN: lupus nephritis; MCD: minimal change disease; MCGN: mesangiocapillary GN; MGN: membranous GN; MesPGN: mesangial proliferative GN; NR: not reported.

However, in most developing countries, including those in Asia, Africa, and Latin America, glomerular diseases remain a major cause of CKD and of incident dialysis patients.[5-7] In various instances, the cause of CKD remains unknown and thus the condition is labelled as CKD of unknown aetiology.

Data from 12 African countries showed that glomerular diseases were responsible for 10.2–52.0% of patients diagnosed with ESRD in adults and children (Morocco: 10.2%; South Africa: 52.0%).[8] Furthermore, data from a large Chinese study[9] that reviewed 65,074 dialysis patients from 27 provinces showed the main causes of ESRD were glomerulonephritis (GN) (45%), diabetes (19%), hypertension (13%), polycystic kidney disease (2%), and others or unknown (20%). An assessment of children with CKD in Guatemala showed that diagnosis with glomerular disease was associated with a significant risk of progression to ESRD in comparison with other diagnoses (hazard ratio: 4.84; 95% confidence interval: 1.31–17.91; p=0.02), underlining the importance of GN as a cause of CKD in this population.[10] Even within developed countries, glomerular diseases tend to play a major role in the epidemiology of kidney diseases among the poorer or minority groups.[11]

The recent Global Kidney Health Atlas (GKHA)[12] publication by the International Society of Nephrology (ISN) showed that use of guidelines in treating kidney diseases is particularly reduced in low-income countries. This suggests that use of guidelines, such as those of the Kidney Diseases Improving Global Outcomes (KDIGO),[13] for treating glomerular diseases in LMIC may also be low. The purpose of this review is to provide an update on the treatment of common glomerular diseases and to highlight simple approaches to treatment in LMIC.

EPIDEMIOLOGY OF GLOMERULONEPHRITIS IN LOW-TO-MIDDLE-INCOME COUNTRIES

Table 1 provides a summary of the frequency of common patterns of glomerular diseases seen in selected LMIC.[14-18] Due mainly to a

low workforce and inadequate infrastructure, renal biopsies are often unavailable in many developing countries;[19,20] as a result, published reports only represent a fraction of true disease prevalence. Glomerular diseases in LMIC often present as nephrotic syndrome. Although published reports show that GN in these countries tends to be of the proliferative type, the indication that promotes the use of renal biopsies is the occurrence of nephrotic syndrome or nephrotic range proteinuria.[21,22] Immunoglobulin (Ig)A nephropathy is rarely reported in African countries, but is very common in Asia.[16,23] Although several LMIC have a high burden of glomerular diseases related to chronic infections, such as HIV and hepatitis B, these diseases appear to occur more commonly in countries in sub-Saharan Africa. As seen in developed countries, lupus nephritis (LN) is also the most common secondary glomerular disease seen in most LMIC.[24]

TREATMENT OPTIONS FOR GLOMERULONEPHRITIS IN LOW-TO-MIDDLE-INCOME COUNTRIES

In LMIC, glomerular diseases should be suspected early when patients present with typical clinical and urinary features, such as body swelling, rash, proteinuria, and haematuria. Knowledge of local or regional disease patterns should be used for initiating treatment, especially as renal biopsy may not be readily available. Early diagnosis and initiation of treatment could slow or halt disease progression. Figure 1 provides a summary of possible treatment options, indications for use, commonly associated complications, and the relative cost of treatment for each group of commonly occurring glomerular diseases.

General Treatment Measures

Adjuvant therapies form an important part of treatment of glomerular diseases. The KDIGO GN guidelines recommend measures that are directed towards control of hypertension, proteinuria, dyslipidaemia, oedema, hypercoagulable state, and increased risk of infection.[13] The use of renin angiotensin aldosterone system blockade (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) is associated with a reduction in proteinuria and better control of blood pressure. Renin angiotensin aldosterone system blockade should be prescribed to all patients with nephrotic syndrome. Several studies have shown that hypertension is a predictor of poor renal outcome in patients with glomerular diseases and blood pressure control is protective against the cardiovascular risks of hypertension and delays progressive loss of glomerular filtration rate.[25-27] A study[28] from Brazil that evaluated the combined effects of ethnicity and hypertension in the evolution of creatinine levels between Caucasians and people of African descent showed that black patients experienced worse prognosis of renal function, probably because of hypertension and not ethnicity (p=0.027). Other general therapeutic measures employed depend on the type of disease, extent of other features of nephrotic syndrome (e.g., dyslipidaemia, presence of thrombosis), and whether immunosuppression will be used for treatment of disease. For instance, chloroquine has been shown to be useful in patients with LN and should be given to all patients who can tolerate it. One study[29] from Cape Town, South Africa, showed that patients with Class V LN who were treated with chloroquine had a significantly better renal outcome than those who were never treated with chloroquine. LUMINA data also highlighted that patients treated with hydroxychloroquine showed a reduced frequency of disease activity, a lower frequency of proliferative LN, and received lower glucocorticoid doses than patients who were not treated with hydroxychloroquine.[30] Bone protection with calcium and vitamin D supplements is recommended for those who will receive long-term treatment with corticosteroids to prevent osteoporosis and fractures. Infection prophylaxis against tuberculosis with isoniazid is not universally used but can be useful in areas with a high risk of such infections. Prophylaxis against other antimicrobials may be dependent on local prevalence and the pattern of disease. Other general measures include use of diuretics for oedema, vaccination to prevent infections, and anticoagulation for those at a high risk of venous thrombosis. Treatment of the specific cause of glomerular disease is important to reduce further damage to the kidneys (e.g., the use of antiviral agents for hepatitis B and C and HIV infection).

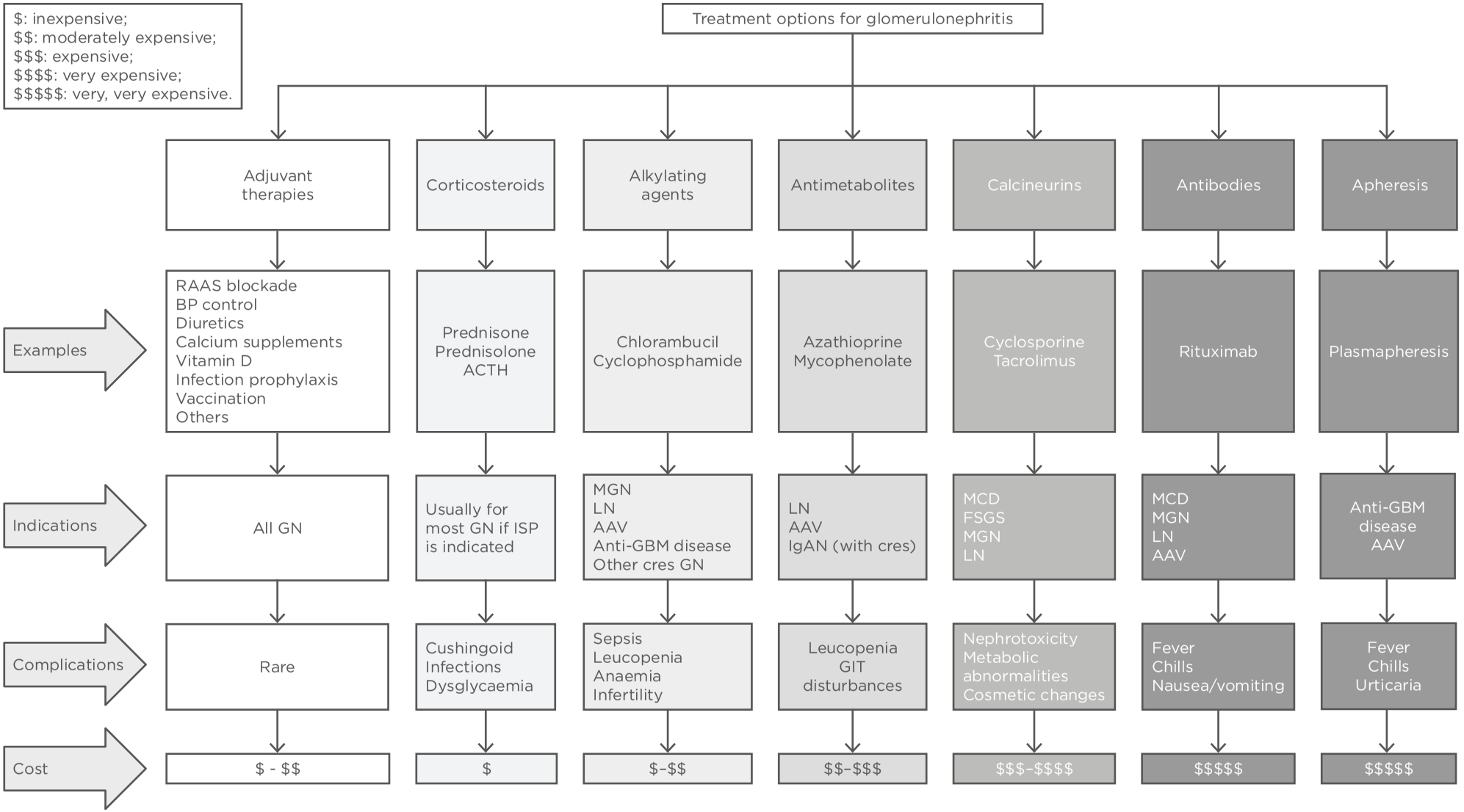

Figure 1: Treatment options for glomerulonephritis.

AAV: antineutrophil cytoplasmic autoantibody-associated vasculitis; ACTH: adrenocorticotrophic hormone; BP: blood pressure; cres: crescentic; FSGS: focal segmental glomerulosclerosis; GBM: glomerular basement membrane; GIT: gastrointestinal tract; GN: glomerulonephritis; IgAN: immunoglobulin A nephropathy; ISP: immunosuppression; LN: lupus nephritis; MCD: minimal change disease; MGN: membranous glomerulonephritis; RAAS: renin angiotensin aldosterone system.

Corticosteroids

Corticosteroids, such as prednisone, form the backbone of treatment of glomerular diseases where indicated.[13] Corticosteroids may be used alone in conditions such as minimal change disease (MCD) and mesangial proliferative GN (non-IgA subtype), and in patients with idiopathic focal segmental glomerulosclerosis (FSGS) if there is a good early response and achievement of early complete remission. Corticosteroids are recommended for use in combination with other immunotherapies (e.g., alkylating agents or calcineurin inhibitors) if early complete remission is not achieved in patients with MCD, FSGS, membranous GN, and in other proliferative forms of glomerular diseases. Although trialling steroid therapy without biopsy is not recommended in adult nephrotic syndrome, steroids may be given to patients who present with this condition in centres with no option for renal biopsy.

Important adverse effects of steroid therapy are often related to cumulative dose used (e.g., cushingoid appearance, osteoporosis, infections, weight gain, diabetes, or psychosis), and clinicians should be aware of these effects and frequently monitor their patients who are treated with steroids. Although steroids should be tapered during treatment, there is no consensus regarding how tapering should be carried out. KDIGO recommends to "taper slowly over a period of 6 months" for most of the conditions requiring steroid use.[13] In the authors' experience, some clinicians will taper by 5 mg every 2 weeks and others by 10 mg every month. The optimal timing of steroid discontinuation is not clear in patients with glomerular diseases; however, steroids should be discontinued early in those with resistant nephrotic syndrome to minimise adverse effects. Thus, there is a continuous need for biochemical monitoring of a patient's response to treatment with regular assessments of protein-to-creatinine ratio in the urine. Also, for patients with steroid-dependent nephrotic syndrome, alternative treatment options should be considered early to avoid the risk of adverse effects of steroids. In centres where renal biopsy is not readily available, a trial of corticosteroids may be useful in those presenting with nephrotic syndrome, especially in children. One study[31] of Indian children with frequently relapsing nephrotic syndrome reported that long-term therapy with a small daily dose of prednisolone can significantly reduce the number of relapses in patients, and that the beneficial effect may continue even after its stoppage. It is important for patients on long-term treatment to have regular assessments of their blood pressure, blood glucose, and bone scans to monitor side effects of treatment. A low threshold should be maintained for infection monitoring (blood count; X-rays; and sputum, blood, and urine cultures), and antibiotic treatment should not be delayed and should be guided by sensitivity results for those with infections.

Alkylating Agents

Due to their relatively low cost, alkylating agents, such as chlorambucil and cyclophosphamide, are readily available for the treatment of some glomerular diseases in LMIC. A recent systematic review on standard of care of patients with LN in Africa found the combination of prednisone and cyclophosphamide to be the most common therapy.[32] However, given the high prevalence of infectious diseases in many LMIC (e.g., HIV, hepatitis B and C, and tuberculosis), the benefits of using an alkylating agent in any patient must always be weighed against the potential risks for infection-related adverse events. Studies from South Africa have often reported the high prevalence of infection-related complications in those treated with cyclophosphamide, with one study reporting up to 37.5% of deaths to be related to sepsis in all patients treated with cyclophosphamide.[25,29] Side effects, including bone marrow suppression, infections, cystitis, and malignancies, are often related to administered dose or cumulative dose received. Trials of alkylating agents are not recommended when histological diagnosis is not available as the patient may have advanced disease. When appropriately indicated, the use of intravenous (IV) pulse dosing is a strategy that reduces the total cumulative dose of cyclophosphamide given to the patient; however, there is need to follow appropriate treatment protocols. For instance, one study[33] from South Africa that looked at the outcomes of patients with idiopathic membranous GN reported poor outcomes to treatment, even though patients were not treated strictly following the Ponticelli regimen but received pulse IV cyclophosphamide. Following the study, they revised their treatment

protocol for idiopathic GN to use the Ponticelli regimen, which uses daily oral cyclophosphamide. IV pulse cyclophosphamide is recommended for induction therapy in a number of diffuse proliferative GN, such as Class III and IV LN, and other forms of rapidly progressive glomerulonephritides, such as antineutrophil cytoplasmic autoantibody (ANCA)-associated GN. Although IV cyclophosphamide may be used in cases of crescentic IgA nephropathy or post-infectious GN, it is not generally recommended in non-crescentic forms of these conditions.

Daily oral cyclophosphamide is mainly recommended in adults with MCD who are intolerant of steroids or those with frequent relapsing or steroid-dependent MCD, or for those with idiopathic membranous GN or idiopathic mesangiocapillary GN (MCGN). Alkylating agents must be stopped in patients who become pregnant during therapy as they are associated with fetal malformations. Routine monitoring for side effects should include regular assessments of full blood counts and clinical assessments or surveillance for infections.

Antimetabolites

Antimetabolites (azathioprine or mycophenolate mofetil [MMF]) are often used to maintain remission in proliferative GN after induction therapy with an alkylating agent, especially in patients with LN and ANCA-associated vasculitis. However, MMF is increasingly used for induction therapy in patients with LN, although issues of cost may be a problem in some regions.[32] In patients with generalised vasculitis, the withdrawal of cyclophosphamide and substitution with azathioprine after remission did not increase the rate of relapse.[34] In the ALMS study,[35] although MMF failed to show superiority over cyclophosphamide for induction treatment of LN (56.2% response to MMF versus 53.0% response for IV cyclophosphamide; p=0.58), MMF showed benefit in a subanalysis mainly made up of black Africans and individuals with parents of mixed ancestry (60.4% for MMF versus 38.5% for IV cyclophosphamide; p=0.033). However, MMF was superior to azathioprine for maintaining renal response and preventing relapse in patients who had a response to induction therapy.[36] MMF is also recommended in adults with MCD who cannot tolerate corticosteroids, cyclophosphamide, and calcineurin inhibitors; however, antimetabolites have not been found to be effective in patients with FSGS.[13,37] MMF is not recommended in patients with IgA nephropathy unless they have crescentic disease; MMF has also not shown efficacy in patients with idiopathic membranous GN and is not recommended as initial therapy or monotherapy in such patients.[13,38] Although azathioprine is relatively inexpensive, the use of MMF is often limited by its cost and availability. Bone marrow suppression with increased risk of infections is a major side effect of antimetabolites. Azathioprine can also cause hepatic and pancreatic dysfunction, while MMF has been associated with significant gastrointestinal effects (e.g., bloating, nausea, and diarrhoea). In female LN patients receiving MMF, it is recommended to stop MMF and change to azathioprine if they become pregnant.

Calcineurin Inhibitors

Calcineurin inhibitors, including cyclosporine and tacrolimus, are often used as a second-line agent for treating GN in instances where patients have not responded to initial therapy or when patients are intolerant of first-line treatment. Thus, they are useful for frequently relapsing or steroid-dependent MCD, and in idiopathic FSGS and membranous GN when there are contraindications to steroid use. In patients with LN, calcineurin inhibitors are indicated in patients with Class II and in other classes for maintenance treatment in patients who cannot tolerate MMF or azathioprine, or in those with resistant disease. Multitarget therapies combining a calcineurin inhibitor (tacrolimus) and MMF have been compared with cyclophosphamide for induction therapy in a number of LN studies.[39,40] One multicentre study[39] from China reported more patients in the multitarget group (45.9%) than in the IV cyclophosphamide group (25.6%) reaching complete remission after 24 weeks (p<0.001); the incidence of adverse events did not significantly differ between the multitarget and IV cyclophosphamide groups (50.3% versus 52.5%). The choice of calcineurin inhibitor may be guided by cost and availability of medications. One randomised controlled study[41] in children with steroid-resistant nephrotic syndrome in India showed no difference in efficacy between cyclosporine and tacrolimus when combined

with low dose corticosteroids; however, the authors suggested tacrolimus as an alternative to cyclosporine in view of the lower risk of relapses and absence of cosmetic side effects.[41] The cost of treatment with calcineurin inhibitors, availability of medications, and a lack of capacity for monitoring drug levels could be major issues with their usage in LMIC. Coadministration of a calcineurin inhibitor with ketoconazole could be used as a strategy for reducing the administered dose and cost. In one study,[42] concomitant use of ketoconazole with a calcineurin inhibitor led to a 38% cost saving. The lack of capacity for monitoring drug levels in many countries may render this approach impractical given the nephrotoxicity associated with calcineurin inhibitors.

Monoclonal Antibodies

Due to a lack of data from randomised controlled trials, rituximab and other novel agents are usually reserved as rescue therapies in patients with disease resistant to other immunosuppressive therapies. Rituximab is recommended in patients who have failed more than one of the recommended initial regimens.[13] Available data on rituximab have been largely obtained from small studies, mainly on LN and membranous GN.[43-46] In many instances, the results of these studies have not been compelling enough to make strong recommendations about the use of rituximab. For instance, in the LUNAR trial,[46] 144 patients with Class III or IV LN were randomised to receive rituximab or placebo. The overall (complete and partial) renal response rates were not significantly different between patients receiving placebo and those treated with rituximab (45.8% versus 56.9%; p=0.18, respectively). In patients with ANCA-associated vasculitis, the RITUXVAS trial[47] reported similar remission induction rates and safety between rituximab and cyclophosphamide. Similarly, in a longer-term outcomes study[48] after treatment with rituximab for ANCA-associated renal vasculitis, rates of the composite outcome of death, ESRD, and relapse did not differ between the group treated with rituximab and the group with cyclophosphamide alone. The dose and treatment schedule have also varied between studies; while some studies have used 375 mg/m^2 in 1–4 doses,[43,47,49] others used 1,000 mg in 2–4 doses.[46,50] In reality, there are only a few centres in LMIC that can afford to provide this treatment to patients because of the high cost associated with therapy and need for monitoring lymphocyte subsets (CD19+ B cells).

Plasma Exchange

Glomerular diseases requiring apheresis have not been commonly reported in LMIC (Table 1). The low reported prevalence of such conditions could be related to low incidence or lack of resources for diagnosis and subsequent treatment.[51,52] Arogundade et al.[52] suggested that there is a significant limitation in accessibility, availability, and use of therapeutic plasma exchange in Nigeria, and that knowledge of this treatment and its applications is minimal among nephrology professionals. Many centres are not equipped with serological assays for making a diagnosis or are unable to perform diagnostic renal biopsies. Reports from studies in LMIC often highlight poor outcomes associated with such conditions, as many patients often present late when the disease has already advanced.[53-55] One trial, which assessed whether the addition of plasma exchange was more effective than IV methylprednisolone in the achievement of renal recovery in patients with ANCA-positive vasculitis and serum creatinine >500 µmol/L, reported increased renal recovery in the plasma exchange group when compared with IV methylprednisolone.[56] KDIGO recommends the use of plasma exchange or plasmapheresis in patients with hepatitis C with glomerular disease and severe kidney involvement, in patients with LN with thrombotic microangiopathy, in those with ANCA-positive vasculitis with diffuse alveolar haemorrhage or renal failure, and in patients with anti-glomerular basement membrane disease.[13]

BARRIERS TO EFFECTIVE TREATMENT OF GLOMERULAR DISEASES IN LOW-TO-MIDDLE-INCOME COUNTRIES

Several barriers hinder the adequate treatment of glomerular diseases in LMIC. In sub-Saharan Africa, for instance, renal pathology services are scarcely available in several centres.[3,20] This means patients with glomerular diseases are more likely to be treated empirically (i.e., without knowledge of the underlying pathology) with oral prednisone alone and sometimes in combination with other immunosuppressive therapies. The recently published report of

the GKHA survey[20] of the ISN revealed that, in several LMIC, availability of essential laboratory services, such as measurement of urine protein-to-creatinine ratio for quantifying proteinuria and measurement of serum creatinine with estimated glomerular filtration rate are often absent. Other factors, such as the cost of treatment (given that patients are often required to pay out of pocket for treatment) and availability of an adequately trained workforce, as well as availability of specific therapies, also constitute barriers to effective care for patients with glomerular diseases in LMIC.[12,19]

CONCLUSION

Although LMIC have the same options as developed countries for treating glomerular diseases, the frequent lack of opportunity for renal biopsy diagnosis and the high cost and unavailability of other diagnostic services, as well as the costs of some forms of therapy, constitute significant barriers towards reducing the burden of CKD associated with glomerular diseases in these regions. Efforts to improve diagnostic services for early identification of glomerular diseases, as well as early initiation of therapies, are recommended.

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Pregnancy and Peritoneal Dialysis: An Updated Review

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Abstract

Women who conceive while receiving peritoneal dialysis (PD) are at a high risk of encountering maternal and fetal complications. Although the occurrence of successful pregnancies in women with end-stage renal disease undergoing PD is becoming more common with advancing dialysis technology, women in this population must be monitored by a team of dedicated renal physicians and obstetric teams to ensure the best maternal and fetal outcomes are achieved. Given the haemodynamic advantages of PD over haemodialysis in pregnancy, PD therapy is the favoured renal replacement option in pregnant women with end-stage renal disease. This is particularly true when PD is initiated after conception or if pregnancy occurs within 1 year of starting PD. The management of anaemia, hypertension, dry weight adjustment, and dialysis regimen in a pregnant PD patient will undergo continuous adjustment to maintain haemodynamic and physiologic stability to meet the demands of the pregnancy-associated changes. In this article, the incidence and management of fetal and maternal complications and pregnancy outcomes in women receiving PD are reviewed based on the latest literature available.

INTRODUCTION

While transplantation provides the best pregnancy outcomes for pregnant patients with kidney disease, dialysis during pregnancy is now a viable option for those who anticipate difficulty receiving a renal transplantation. The first successful full-term pregnancy in an end-stage renal disease (ESRD) patient on haemodialysis was first reported in 1971 by Confortini et al.[1] Some 12 years later, the first sustained pregnancy where the mother received peritoneal dialysis (PD) was reported in a patient who had been receiving the treatment for 2.5 years. The pregnancy was sustained until 30 weeks, but a stillborn infant was delivered, albeit after a spontaneous labour.[2] Despite the many challenges faced by pregnant ESRD women, the rate of successful pregnancy and live birth has increased from 50% in the 1990s[3] to near 80% in recent years,[4] once the patient has successfully conceived. From the 54 reported cases of pregnant women receiving PD available in the literature since 1983, 47 cases (87%) have resulted in a successful pregnancy, but only 6 cases were full-term deliveries (Table 1).[2,5-36] The improved pregnancy outcomes are interlinked with adequate residual urine,

conception during peri-initiation of the PD period, medication adjustment, tailoring PD prescription, blood pressure control, and correction of metabolic and nutrition profiles.

EPIDEMIOLOGY

Pregnancy in women with ESRD has always been challenging, not only for the mother but also for the newborn and the attending specialists. Therefore, the achievement of pregnancy may come as a surprise for women on PD because most have irregular menstruation, or even amenorrhea due to anovulation, making a period of amenorrhea a condition they are accustomed to. Moreover, early symptoms of pregnancy, such as early morning nausea and vomiting, are examples of, and similar to, the symptoms of uraemia or abdominal distension from PD dialysate. Achievement of pregnancy is further compounded by a failure in the surge of both luteinising hormone and follicle-stimulating hormone and low progesterone during the menstruation phase. In addition, hyperprolactinaemia is common and seen in >70% of women on dialysis. Coupled with reduced libido, it is not surprising that the conception rate in ESRD women on regular dialysis is low, reported to be in the region of 0.3–4.1%.[4,37,38]

Over time, improved outcomes of pregnancies in ESRD women have been increasing. The successful pregnancy rate varied from 23%, as reported by the European Dialysis and Transplant Association (EDTA),[39] to as high as 70% as reported in previous case series.[16,40] An evidence-based analysis of pregnant ESRD women on haemodialysis carried out from 2000–2008 showed that the overall possibility of a pregnancy resulting in living offspring is encouraging, in the range of 50–100%.[41] Based on data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA), conception on haemodialysis is approximately twice as likely as on PD.[42] In another large survey of pregnancy and ESRD from the USA, 1.1% of reproductive-aged women receiving PD conceived versus 2.4% on haemodialysis.[43]

This lower conception rate in PD women has been postulated to be related to the presence of fluid in the abdominal cavity or inadequate dialysis intensity.[42] Another hypothesis is that hypertonic dextrose solutions and the fluid-filled peritoneum interfere with ovum transit to the uterus.[3] However, once conception was successful, infant survival was not significantly different between the haemodialysis and PD patients. It is also clear from the literature that the outcome of pregnancy was better in women who conceived before starting dialysis than in women who conceived after starting dialysis.[5,7,13,16,26,27,30,43] Fourteen patients conceived before starting PD and all but three had successful pregnancies.[2,16] There were also reported cases of using PD as a bridging therapy for optimising the renal profile of chronic kidney disease (CKD) patients during pregnancy; PD treatment was discontinued post-delivery, with patients remaining dialysis free for 2–4 years.[27] A recent case report has also shown a successful, near full-term delivery in a geriatric multigravida (aged 42 years) who was receiving continuous ambulatory PD.[36] In total, there have been 47 successful pregnancies from 54 pregnant women on PD during 1983–2017. These cases are summarised in Table 1.

RENAL EFFECTS OF PREGNANCY

During pregnancy, the kidneys undergo pronounced haemodynamic, structural, and endocrine changes as part of the physiological adaptation to ensure a successful pregnancy outcome. These adaptations occur as early as 6 weeks after conception and include the dilatation of the urinary collecting system, a decrease in systemic vascular resistance, and an increased glomerular filtration rate, as well as a corresponding drop in serum creatinine. During a healthy pregnancy, the kidneys will also increase the production of erythropoietin, active vitamin D, and renin. Various hormones controlling vessel tone, such as nitric oxide, endothelin, and mediators of the renin-angiotensin-aldosterone system, will also undergo adjustment. However, ESRD women are less able to make these unique renal adaptations, and this inability often leads to various clinical features characterised by normochromic normocytic anaemia, reduced expansion of plasma volume, and vitamin D deficiency. Furthermore, up to one-third of patients may experience a progressive deterioration in renal function.[3,44] The risk of an irreversible loss of renal function is further magnified when the mother has uncontrolled hypertension and proteinuria.[44]

Table 1: Reported case series of pregnant women on peritoneal dialysis.

Study	Number of reported pregnancies	Infant survival (%)	Gestational age (months)	Delivery type	Birthweight (g)	Peritoneal dialysis complications	Maternal complications	Fetal complications
Cattran and Benzie,[2] 1983	1	0	32	Vaginal	960	None	Anaemia (5.4 g/dL), transfusion	Hydramnios, stillborn
Kioko et al.,[5] 1983	1	100	34	Caesarean	1,700	Peritonitis	None	Premature
Melendez et al.,[6] 1998	2	100	34 36	Caesarean	1,332 2,778	None	None	Premature
Lavoie et al.,[7] 1988	2	100	34.5 34.0	Caesarean	2,160 1,200	Catheter-related pain	None Anaemia, transfusion	Polyhydramnios, premature
Redrow et al.,[8] 1988	8	62.5	32–36	Caesarean	1,100–2,780	Haemoperito-neum	N/A	Premature
Bennet-Jones et al.,[9] 1989	1	100	35	Caesarean	1,900	None	None	Polyhydramnios, premature
Dunbeck et al.,[10] 1992	1	100	35	Vaginal	1,446	Exit site infection, peritonitis	None	Premature
Lew and Watson,[11] 1992	1	100	35	Vaginal	1,899	None	None	Premature
Gadallah et al.,[12] 1992	3	66	29 28 24	Vaginal	1,895 2,230 N/A	None None Peritonitis	Anaemia None Premature rupture of membrane	Premature Premature Stillborn
Jakobi et al.,[13] 1992	1	100	34	Vaginal	2,400	Peritonitis	Premature rupture of membrane	Premature
Hou et al.,[14] 1996	1	100	36	Vaginal	2,388	Catheter migration	Right facial nerve palsy	Premature
Tison et al.,[15] 1996	1	100	32	Caesarean	1,545	*Escherichia coli* peritonitis 5 days postpartum and peritoneal dialysis catheter removed	*Escherichia coli* chorioamnionitis	Premature
Romão et al.,[16] 1998	3	66	32	NR	1,400 1,410 N/A	Eosinophilic peritonitis (n=1)	NR	Polyhydramnios, gestational diabetes, fetal distress, premature (n=2) Death on third day postpartum (n=1) Death at 19 weeks (n=1)
Tuncer et al.,[17] 2000	1	100	38	Vaginal	1,900	Peritonitis	None	None
Chang et al.,[18] 2002	1	100	33	Vaginal	994	Drainage pain, reflux, diphtheroid exit site infection	None	Premature
Smith et al.,[19] 2005	1	100	33	Vaginal	1,730	Haemoperito-neum	None	Premature, gestational diabetes

Table 1 continued.

Study	Number of reported pregnancies	Infant survival (%)	Gestational age (months)	Delivery type	Birthweight (g)	Peritoneal dialysis complications	Maternal complications	Fetal complications
Chou et al.,[20] 2006	1	0	19	Caesarean	NR	Haemoperito-neum	Uterine serosal tear, catheter or post amniocentesis-related emergency laporatomy	Abortion
Tan et al.,[21] 2006	1	100	33	Vaginal	1,325	Postpartum peritonitis	Polyhydramnios pre-elampsia, postpartum haemorrhage	Premature
Lew,[22] 2006	1	100	21	Vaginal	NR	Haemoperito-neum	None	Abortion
Schneider et al.,[23] 2006	1	100	34	Caesarean	1,100	None	None	Premature
Asgari et al.,[24] 2007	1	100	36	Caesarean	NR	None	None	Premature
Altay et al.,[25] 2007	1	100	39	Vaginal	2,480	Haemoperito-neum	Hypertension, facial palsy	None
Gómez Vázquez et al.,[26] 2007	2	100	36 38	Vaginal	1,925 2,700	None	None	Premature None
Jefferys et al.,[27] 2008	5	100	35 24 31 38 38	Vaginal (n=2) Caesarean (n=3)	2,095 478 1,060 2,735 2,008	Gram-negative peritonitis (n=1) Staphylococcus exit sites infection (n=3) Catheter migration (n=1)	Hypertension (n=2) Pre-eclampsia (n=1) None (n=2)	Ventricular septal defect, premature (n=3) None (n=2)
Chou et al.,[28] 2008	3	33	35 34 22	NR	2,388 1,004 440	None None None	None None None	Premature (n=2) Stillborn Polyhydramnios
Oguzhan et al.,[29] 2009	1	100	35	Caesarean	1,900	None	Hypertension	Intrauterine growth restriction, premature
Inal et al.,[30] 2012	1	100	34	Caesarean	2,370	None	None	Premature
Sivasuthan et al.,[31] 2013	2	100	31	Caesarean	900	None	Pre-eclampsia Microangiopathic haemolytic anaemia (systemic lupus erythematosus)	Premature
Abu-Zaid et al.,[32] 2013	1	100	29	Caesarean	780	None	Hypertension, pre-eclampsia	Small gestational age
Alhwiesh,[33] 2014	1	100	37	Vaginal	1,500	None	None	Ventricular septal defect, acute kidney injury
Batarse et al.,[34] 2014	1	100	32	Vaginal	1,435	Exit site cuff protrusion	None	Premature
Ross et al.,[35] 2016	1	100	37	Caesarean	3,005	None	None	None
Lim et al.,[36] 2017	1	100	36	Caesarean	2,500	None	None	Premature

N/A: not available; NR: not recorded.

Table 2: Peritoneal dialysis vintage, prescription, and residual urine.

Study	PD prescription	Residual urine	PD vintage before conception
Cattran and Benzie,[2] 1983	CAPD: 4 daily 2 L exchanges CAPD: 6 daily 1 L exchanges	Yes	3 years*
Kioko et al.,[5] 1983	CAPD: 3 daily 2 L exchanges	Yes	Started at Week 12
Melendez et al.,[6] 1988	CAPD: 6 daily 1.5 L exchanges	NR	N/A
Lavoie et al.,[7] 1988	CAPD: 6 daily 1.5 L CAPD: 4–6 daily 2 L Cycler at night combined with three per week HD subclavian catheter	Yes Yes	Started Week 12 Started Week 8
Redrow et al.,[8] 1988	CAPD: 5 daily 1.5 L and 1 L overnight CAPD: 4–5 daily 1.5 L exchanges CAPD: 5–6 daily 2 L exchanges	N/A	N/A
Bennet-Jones et al.,[9] 1989	CAPD: 4 daily 1.5 L exchanges CAPD: 3 daily 2 L exchanges	Yes	4 months post PD
Dunbeck et al.,[10] 1992	CAPD: 4 daily 1.5 L exchanges	N/A	N/A
Lew and Watson,[11] 1992	APD: 8–16 L daily, 0.8 L per dwell, and 2 manual exchanges	N/A	12 months post PD
Gadallah et al.,[12] 1992	CAPD: 3 daily 2 L exchanges CAPD: 5 daily 2 L exchanges CAPD: Regime NR	Yes N/A N/A	1 month post PD 2 months post PD 3 years post PD*
Jakobi et al.,[13] 1992	CAPD: 4 daily 1.5 L exchanges	N/A	Started at Week 24
Hou et al.,[14] 1996	APD: 13.0–14.5 L per day and 2 L per exchange; 6 night-time and 3 daytime exchanges	Yes	2 years
Tison et al.,[15] 1996	APD: 17–22 L daily and 1 L per exchange	N/A	6 months post PD
Romão et al.,[16] 1998	CAPD: 5/6 daily 2 L exchanges	Yes Yes Yes	1.5 years post PD* Started at Week 13* Started at Week 22
Tuncer et al.,[17] 2000	CAPD: 4 daily 2 L exchanges CAPD: 5 daily 1.5 L exchanges	N/A	8 months post PD
Chang et al.,[18] 2002	APD: 3 cycles of 3 L exchanges plus 2 daytime 2.5 L exchanges; 5 cycles of 2.8 L/2.38 L plus 3 daytime 2.5 L exchanges	Yes	10 months post PD
Smith et al.,[19] 2005	CAPD: 4 daily 2 L exchanges 4 daily 2.5 L exchanges APD: 4 cycles of 2 L exchange plus 1–2 daytime exchanges of 2 L; subsequently APD 1.6–1.8 L dwells, total therapy volume: 12.8–14.4 L per day; Kt/V 2.6	N/A	4.5 months PD
Chou et al.,[20] 2006	CAPD: 6 exchanges of 1.5 L	N/A	1 year post PD*
Tan et al.,[21] 2006	N/A	N/A	N/A
Lew,[22] 2006	N/A	N/A	2 years post PD*
Schneider et al.,[23] 2006	CAPD: 4 daily 1.5 L exchanges, gradually decreased to 0.6 L Kt/V approximately 5	Yes	6 months post PD
Asgari et al.,[24] 2007	CAPD then APD: regimen N/A	Yes	2 months post PD
Altay et al.,[25] 2007	CAPD: 4–5 daily exchanges of 2 L then 6 daily 1.5 L exchanges Kt/V 6	Yes	2 years post PD
Gómez Vázquez et al.,[26] 2007	CAPD: 6 exchanges of 1.5 L Kt/V 1.9	Yes Yes	Started at Week 16 Started at Week 27
Jefferys et al.,[27] 2008	CAPD: 5 daily 1.5–2.0 L exchanges 3 daily 1.8 L exchanges 4 daily 1.5 L exchanges APD: 5 daily 2 L and 1 manual day exchanges	Yes Yes Yes Yes Yes	Started at Week 13 (CKD) Started at Week 14 (CKD) Started at Week 16 (CKD) Started at Week 16 Started at last trimester

Table 2 continued.

Study	PD prescription	Residual urine	PD vintage before conception
Chou et al.,[28] 2008	CAPD: 2–6 daily exchanges of 1.5 L 5 daily exchanges of 2 L	Yes Oliguria Yes	3 years 2 years 8 months
Oguzhan et al.,[29] 2009	CAPD: 4 daily exchanges of 2 L	Yes Residual Kt/V 4.38	N/A
Inal et al.,[30] 2012	CAPD: 4 daily exchanges of 1.5 L 6 daily exchanges of 1.2 L	Yes	Started at Week 16
Sivasuthan et al.,[31] 2013	APD: 3 exchanges of 6 L over 8 hours, 6 cycles CAPD: 5 exchanges of 1.5 L	N/A	2 years post PD
Abu-Zaid et al.,[32] 2013	CAPD: 18–22 hours per week	N/A	14 months post PD
Alhwiesh,[33] 2014	APD: 10 L over 9 hours, 2 L exchanges, and 3 L extraneal last fill APD: 10 L physioneal solution over 9 hours	Yes	2 years post PD
Batarse et al.,[34] 2014	APD: 12–20 L of 0.75 L	No	4 years HD converted PD 3 years post PD
Ross et al.,[35] 2016	APD: 4 exchanges of 2 L plus 3/4 daily exchanges of 2L APD supplemented by intermittent HD 3.0–4.5 hours, 5 times per week (start Week 19) Kt/V 2.95-3.3 (PD)	Yes	3 years post PD
Lim et al.,[36] 2017	CAPD: 4 exchanges of 2 L Kt/V 1.93–2.73	Yes	5 months post PD

*Pregnancy failure.

APD: automated peritoneal dialysis; CAPD: continuous ambulatory peritoneal dialysis; CKD: chronic kidney disease; HD: haemodialysis; K: dialyser clearance of urea; N/A: not available; NR: not recorded; PD: peritoneal dialysis; t: dialysis time; V: volume of distribution of urea, approximately equal to patient's total body water.

IMPORTANCE OF RESIDUAL URINE

Over the last decade, the literature has stressed the importance of residual urine output with regard to successful pregnancy outcomes.[45] From the 54 pregnancies documented, 27 patients had good residual urine (defined as >500 mL per day) during pregnancy and all except three patients experienced a successful delivery (Table 1).[2,5-36] The ADEMEX trial[46] showed that residual urine can predict survival in PD populations. More recently, the presence of residual urine has been shown to be more efficient in removing uraemic toxins and protein-bound solutes compared to increasing PD prescription.[47] The progressive reduction in peritoneal space in the presence of the gravid uterus in the last trimester means that the surface for adequate peritoneal exchange is insufficient and the catheter is subjected to mechanical pressure. This concern can be overcome by performing multiple frequent, but smaller, dwells. Thus, PD patients should be encouraged to try to achieve pregnancy early in the course of their treatment because it is hoped that survival benefits can be extrapolated to the products of gestation.

CONFIRMATION OF PREGNANCY

The confirmation of pregnancy in ESRD patients is challenging due to the chronically increased serum levels of beta-human chorionic gonadotropin (hCG) even in the absence of pregnancy. Apart from in placenta tissue, beta-hCG is produced in small amounts by all cells and is dependent on the kidney for a substantial proportion of beta-hCG excretion. As a result, it is not surprising that the average time taken to confirm pregnancy in an ESRD patient is 16.5 weeks.[1] Therefore, among women suspected of being pregnant who have elevated

serum beta-hCG, ultrasonography should be performed to verify the presence of a viable fetus and obtain the approximate gestational age.

PREGNANCY COMPLICATIONS IN MOTHERS RECEIVING PERITONEAL DIALYSIS

Women on dialysis have at least a two-fold increased risk of developing adverse maternal outcomes, including gestational hypertension, pre-eclampsia, eclampsia, and maternal mortality.[45] Sonographic assessment of uterine artery blood flow at 20–24 weeks gestation can refine the risk of later pre-eclampsia and fetal growth restriction and should be used as part of the standard care. If pre-eclampsia develops, maternal renal function often deteriorates further, which can sacrifice the residual urine of the PD patients.

There are also complications that are specific to PD women: eight episodes of peritonitis and five episodes of exit site infection have been reported in pregnant women (Table 1). The postpartum period also presents an increased risk of peritonitis, during which two of the eight episodes occurred. Peritonitis was associated with premature rupture of the membrane, postpartum haemorrhage, and chorioamnionitis. Although one neonatal death has been reported,[12] and another case in which the PD catheter had to be removed,[15] the remainder of the cases were successfully treated. Other complications that are unique to PD therapy include haematoperitoneum,[8,19,20,22] catheter malposition,[14,27] catheter-related pain,[7,18] and flow issues. Uterine trauma from the PD catheter remains a distinctly possible complication.[20]

Although maternal hypertension is associated with at least half of the cases of obstetric haemorrhage and abruptio placentae, such complications are rarely reported. Only 7 of the 53 pregnancies were documented to have maternal hypertension, which constituted a serious under-reporting. Maternal death is uncommon and has been reported to occur in 1.5% (2 out of 135 pregnancies) in a registry study of pregnant dialysis patients in the USA.[43]

Immunological phenomena, such as haemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome; microangiopathic haemolytic anaemia; thrombotic thrombocytopenic purpura; and haemolytic uremic syndrome are more commonly reported in pregnant women with acute kidney injury than those with ESRD.[48] In fact, there is a lack of reported literature regarding their occurrence in pregnant women on PD. There was only one case of microangiopathic haemolytic anaemia that occurred during the postpartum period in a patient with systemic lupus erythromatosis.[31]

COMPLICATIONS OF PERITONEAL DIALYSIS TO THE FETUS

A total of 42 out of 47 successful pregnancies were preterm births (Table 1). Other common fetal complications reported were polyhydramnios (n=6), intrauterine death (n=4), stillborn (n=3), gestational diabetes (n=2), fetal distress (n=2), intrauterine growth retardation (n=1), neonatal mortality (n=1), ventricular septal defects (n=2), and neonatal acute kidney injury (n=1).[2,5-36] A recent meta-analysis by Piccoli et al.[49] noted a significantly higher rate of small-for-gestational-age babies born to mothers on PD compared to babies born to mothers on haemodialysis; however, there was no evidence of an increased risk of congenital abnormality.

PERITONEAL DIALYSIS TREATMENT CHARACTERISTICS

While haemodialysis enables precise fluid control and, to a certain extent, adjustable clearance, it may lead to marked haemodynamic fluctuation that will disturb the placental blood flow. PD, on the other hand, provides a more stable metabolic milieu via its continuous mode of dialysis and can better preserve residual renal function. The stable intrauterine metabolic environment can reduce the risk of developing polyhydramnios, a risk that correlates with elevated urea levels that occur before a haemodialysis session.[50] Polyhydramnios could also be caused by enhanced solute diuresis by fetal kidneys or decreased oncotic pressure as a response to the rapid fluctuation in urea level. Once polyhydramnios develops, the risk of premature labour is increased.[50,51]

DOSE OF PERITONEAL DIALYSIS AND UREA REDUCTION

There is not a clear guideline regarding the target clearance for pregnant PD patients. A target clearance of Kt/V in the range of 2.2–2.4 has been advocated since the early 1990s.[52] More recent literature reported that Kt/V in the range of 2.2–6.0 has been achieved and, more importantly, these clearances are in part supplemented by a respectable renal clearance.[15,18,19,23,25,35,36] To achieve this Kt/V target, a dialysate volume of up to 22 L per day has been suggested.[15] This approach will invariably double the dialysate cost alongside requiring a PD continuous cycler machine that would further inflate the cost of treatment. A combination of haemodialysis and PD was first described by Lavoie et al.[7] in 1988, whereby the patient received a standard 8 L per day of continuous ambulatory PD supplemented by haemodialysis three times a week through a subclavian catheter. This baby was successfully delivered at 34 weeks gestation through a caesarean section. In 2016, Ross et al.[35] described another case of successful pregnancy, where the patient received cycler PD treatment of 8 L per day supplemented by intermittent haemodialysis for 3.0–4.5 hours, five times per week, starting at 9 weeks gestation.[35] Table 2 illustrates the different regimes of PD prescriptions used in pregnant PD patients.[2,5-36]

In continuous ambulatory PD, the PD prescription can be modified by increasing the number of exchanges rather than using larger volumes, since large volumes are not well tolerated in the last trimester. In patients receiving automated PD, the dialysis prescription should be modified with an increase in the total volume and therapy time, increasing the number of cycles and using smaller dwell volumes. In the practical sense, most nephrologists would choose to treat the patient clinically, monitoring blood parameters and adjusting the PD prescription as needed rather than following the Kt/V number; this is supported by an Italian best position paper and guidelines published in 2015.[53] In the guidelines, the authors do not recommend using Kt/V and/or peritoneal creatinine clearance as a measurement of dose of dialysis in pregnancy due to the lack of studies considering these markers with respect to pregnancy outcomes. This contrasts with data derived from a haemodialysis population in which a meta-regression analysis showed an inverse relationship between hours of dialysis per week and haemodialysis, preterm delivery, and small for gestational age fetuses.[53]

ELECTROLYTE IMBALANCE

During the course of pregnancy, potassium levels remain normal despite an increase in serum aldosterone, perhaps due to the potassium-sparing effects of elevated progesterone.[54] For ESRD women with residual urine, there will be a further risk of hypokalaemia due to vomiting during morning sickness, PD dialysate loss, and the effect of aldosterone on renal tissues.[54] The total serum calcium concentration falls during pregnancy due to reduced serum albumin, but ionised calcium levels remain normal.[54]

ANAEMIA

Erythropoietin-stimulating agent (ESA) regulates erythropoiesis by stimulating the differentiation and proliferation of erythroid precursors and the release of reticulocytes into the circulation, as well as synthesis of cellular haemoglobin. The usual dose of ESA for a patient on PD is 50 U/kg twice weekly.[53] It is worthwhile to note that although ESA is recognised by the U.S. Food and Drug Administration (FDA) as a Category C drug in pregnancy, it has been widely prescribed in pregnant CKD women without many adverse events.[53] In fact, the dosage of ESA is frequently adjusted upwards by 50–100% due to increasing body weight. Iron supplementation at a dose of 1–15 mg/day and folic acid 1 mg/day enhance the efficiency of ESA and iron stores should be assessed before ESA is initiated.[53] It is advisable that the patient maintains their haemoglobin levels at 10–11 g/dL, haematocrit at 30–35%, and serum ferritin of 200–300 µg/mL.[53]

DRY WEIGHT ADJUSTMENT

The patient's fluid status should be reviewed by the nephrologist and obstetrician closely. Ideally a weekly or fortnightly ultrasound of the uterus should be carried out from the second trimester onwards to assess the growth and

weight of the fetus. Dry weight must be reviewed continuously because the patient is expected to gain between 0.3 kg and 0.5 kg of weight per week during the second and third trimesters. The dry weight of pregnant women on dialysis can be difficult to ascertain. The patient will have to be assessed using a traditional method of examining overloaded symptoms, such as orthopnoea and shortness of breath, and signs including bibasal crepitations, bipedal oedema, and raised jugular venous pressure. The use of a bioimpedence device to assess dry weight is not recommended due to a lack of safety data in this group of patients.

BLOOD PRESSURE

Poorly controlled hypertension contributes significantly to the risk of pregnancy failure, including the risk of early pregnancy loss, superimposed placental ischaemia, and pre-eclampsia, as well as premature delivery and fetal growth restriction.[55] Extrapolating the data from Control of Hypertension in Pregnancy Study (CHIPS),[56] which randomised women to a diastolic blood pressure of 85 or 100 mmHg, showed that treating hypertension in pregnancy to a tighter target is not associated with adverse neonatal effects or pregnancy outcomes. As such, blood pressure should be tightly controlled with pregnancy-safe medications, such as long-acting nifedipine, labetalol, and methyldopa.[57]

NUTRITION

Supplementation of water-soluble vitamins and minerals, such as folic acid, is essential in early pregnancy. Other vitamins that should be supplemented are vitamin C, thiamine, riboflavin, niacin, and vitamin B6. Since malnutrition is common in pregnancies of ESRD patients, it is mandatory to avoid protein restriction in pregnant women on PD. Malnutrition is often caused by the lack of appetite experienced by pregnant women on PD due to the sugar load in dialysate and the delayed gastric emptying effect of dialysate inside the peritoneal cavity. Malnutrition can also be caused by the hypercatabolic effect of pregnancy in ESRD and the decreased appetite induced by acidosis and urea levels. Since malnutrition is a constant problem experienced by pregnant ESRD patients, attention should be paid to reaching the caloric target of 3,035 kcal/kg/day to reduce protein wasting. Individualisation of specific nutrient needs is paramount and the patient should have a dietary plan tailored by a dietitian or nutritionist. It has been estimated that the minimal daily dietary protein intake in pregnant haemodialysis patients should be 1.8 g per kg body weight/day;[58] however, there has been no recommendation of dietary protein intake for pregnant PD patients. The closest recommendation is extrapolated from those PD patients who are at risk of protein depletion, for whom 1.4–2.1 g per kg body weight/day of protein is advised.[59] The precise control of calcium and phosphorus metabolism may also be disturbed by pregnancy. Routine vitamin D supplementation during gestation may reduce the risk of pre-eclampsia, low birthweight, and preterm birth in the normal population.[60] Vitamin D deficiency (<20 ng/mL) and insufficiency (20–29 ng/mL) are more prevalent among patients undergoing dialysis due to defective 1,25-dihydroxycholecalciferol synthesis.[61] Thus, supplementation of sufficient calcium and vitamin D3 should occur to ensure patients remain in a positive calcium balance.

MEDICATIONS

Low-dose aspirin is recommended for the prevention of pre-eclampsia in pregnant patients with CKD;[62] however, there is no recommendation for routinely prescribing aspirin for pregnant PD patients. Commonly used medications that are harmful to the fetus are angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers. Both medications have significant teratogenic effects if their use is not monitored and is continued beyond the first trimester.[63] If the patients have autoimmune diseases or have undergone renal transplantation, the use of immunosuppressive therapy, such as cyclophosphamide, mycophenolate, methotrexate, and mTOR inhibitors is to be avoided. Phosphate binders, such as sevelamer carbonate, lanthanum carbonate, aluminium hydroxide, cinacalcet, and paricalcitol, have not been tested or established for use during pregnancy or lactation.[64,65] In patients with residual renal function, potential nephrotoxic agents, such as aminoglycosides and nonsteroidal anti-inflammatory drugs, should be avoided.

DELIVERY AND POSTPARTUM CARE

Planned induction of labour at 37 weeks gestation or just beyond is routinely recommended for patients with no maternal or fetal complications. Planned induction allows clinicians to drain the dialysate, ensuring the patient is well dialysed prior to delivery. Vaginal delivery is preferred, and caesarean delivery is recommended only when there is a clear clinical indication. After a successful pregnancy, it usually takes a few months for the physiological changes of pregnancy to resolve completely. During this transition period, readjustment of the dry weight, residual urine monitoring, blood pressure, and a complete review of drug treatment, with special attention to the antihypertensive agent or ESA, are necessary. Breast milk analysis from lactating dialysis patients was similar to samples from low-risk control mothers, and therefore breastfeeding can be considered a viable option for mothers receiving dialysis.[66] Similarly, breastfeeding should be encouraged in women on PD. Contrary to popular belief, ACE inhibitors are barely detectable in breast milk; captopril, enalapril, and quinapril are the preferred ACE inhibitors to use in the postpartum period because they not found in breast milk.[67]

CONCLUSION

Successful management of pregnant women with ESRD on PD must emphasise a comprehensive and co-ordinated approach between the nephrologist, obstetrician, primary care physicians, and the patient. Preservation of residual urine plus frequent monitoring of blood pressure, adjustment of dry weight, fetal growth, and biochemical features will enable timely expert intervention to achieve optimal pregnancy outcomes in pregnant ESRD women on PD. It remains to be seen whether active supplement with vitamin D or hybrid therapy (frequent or prolonged haemodialysis or haemofiltration to mimic renal clearance) will bring any additional positive impact on pregnancy outcome.

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Induction Therapy in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis with Renal Involvement: The Nephrologist's Point of View

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Abstract

Renal involvement with rapidly progressive glomerulonephritis is a common manifestation of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides characterised by end-stage renal disease and high mortality rates in untreated and late referral patients. Long-term renal survival has improved dramatically since the addition of cyclophosphamide and, more recently, rituximab in association with corticosteroids to remission induction therapeutic regimens. However, renal prognosis remains unfavourable for many patients and mortality is still significantly higher than in the general population. In this review, the open challenges to be addressed to optimise remission induction therapy, especially in patients with advanced kidney failure, are analysed. This concerns the first-line therapy (cyclophosphamide or rituximab) based on different parameters (estimated glomerular filtration rate at baseline, new or relapsed disease, ANCA specificity, tissue injury, and safety) and the role of plasma exchange. Furthermore, the paper discusses future perspectives on induction remission therapy by reporting recent advances in new targeted therapies, with particular reference to avacopan, an orally administered selective C5a receptor inhibitor.

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA).[1] These autoimmune disorders can affect any organ system, but the kidneys are often involved. Renal involvement ranges between 71% and 88% in patients with GPA and MPA,[2] whereas in EGPA it occurs in up to 25% of cases.[3] Severe renal involvement is an uncommon finding in cases of EGPA;[4] therefore, this review is focussed exclusively on GPA and MPA as two clinical conditions with major renal involvement.

Prior to the introduction of cyclophosphamide (CYC)-based regimens in the late 1970s, the 2-year survival rate of AAV patients was approximately 20%.[5] Standard immunosuppression with CYC

and gradually tapered corticosteroids (CCS) for remission induction therapy have dramatically improved the prognosis of the disease in patients with generalised or severe GPA or MPA, with overall remission rates usually exceeding 90% and 5-year patient survival rates as high as 80%.[5] However, this treatment is associated with significant toxicity, including an enhanced risk of infection, myelosuppression, infertility, malignancy, and cardiovascular disease.[6]

Consequently, there has been a growing impetus to look for a new, less toxic, and more specific treatment for patients with generalised and severe disease. Two randomised controlled trials (RAVE[7] and RITUXVAS[8]) found that rituximab (RTX), a B cell-depleting agent, is as effective as CYC for induction of remission in patients with newly diagnosed GPA and MPA. The RAVE trial[7] also demonstrated the superiority of RTX versus CYC in patients with relapsing disease. Nevertheless, in both trials the short-term adverse event rate after RTX treatment was not lower than of CYC.

Despite this advancement and the enrichment of therapeutic armamentarium, the management of remission induction in patients with AAV and renal involvement continues to challenge nephrologists because renal prognosis is still unfavourable and a significant proportion of patients (20–25%) develop end-stage renal disease (ESRD) within a few years of diagnosis.[9]

This review will discuss the remaining challenges in the management of remission induction in AAV with renal involvement, answering crucial questions and presenting recent advances in novel targeted therapies and treatment strategies that may further help to modify the disease course, thereby leading to improved renal outcomes and patient survival.

SHOULD ALL PATIENTS WITH RENAL INVOLVEMENT BE TREATED WITH RITUXIMAB, EVEN IF THEY HAVE ADVANCED RENAL FAILURE?

What the Results of Current Studies Tell Us About the Renal Outcomes

RTX was initially used in open-label trials of patients with refractory or relapsing GPA and MPA and demonstrated clinical remission rates in approximately 90% of cases within 6 months.[10-14] However, these preliminary studies did not include patients with severe renal involvement. The RAVE trial[7] enrolled 197 patients, of whom approximately half had significant renal disease defined by the presence of at least one of the following findings at baseline: active, biopsy-proven, pauci-immune glomerulonephritis; red blood cell casts on urine microscopy; and/or increase in serum creatinine >30% or a >25% decrease in creatinine clearance. Although in patients with significant renal disease, the baseline mean estimated glomerular filtration rate (eGFR) was worse in the RTX group (41 versus 50 mL/min per 1.73 m^2; p=0.05), a post hoc analysis of the trial showed that RTX was as effective as oral CYC in this subgroup.[15] The proportion of patients who achieved complete remission at 6 months was not significantly different between the two treatment groups (RTX: 61% versus CYC: 63%) and there was no difference in the proportion of patients with sustained remission at 18 months (RTX: 75% versus CYC: 76%).[15] The latter finding is significant because, in order to achieve remission at 3–6 months, a maintenance regimen with azathioprine (AZA) was administered only to patients in the CYC group, whereas those in the RTX group received no further therapy.[7,15] Mean eGFR also increased similarly in both groups when patients were stratified by baseline eGFR, even among those with an eGFR <30 mL/min per 1.73 m^2.[15] These data represent the strengths of the RAVE trial[7] in supporting the use of RTX in patients with major renal involvement; however, a limitation of the RAVE trial was the exclusion of patients with advanced renal failure (serum creatinine >4 mg/dL), as the clinical evidence was not sufficient to suggest their inclusion in an investigational treatment study at the launch of the trial. Therefore, the authors concluded that additional studies were required to understand the applicability of RTX for patients with advanced kidney failure.[15]

In contrast with the RAVE trial, RITUXVAS[8] enrolled 44 patients newly diagnosed with GPA and MPA with severe renal disease (median eGFR: 20 mL/min per 1.73 m^2), also including patients requiring dialysis at trial entry. The participants were randomised in a 3:1 ratio to receive either RTX plus CCS without further maintenance treatment or intravenous CYC for 3–6 months plus CCS followed by AZA in the

maintenance phase. At 12 and 24 months, there was no difference in the proportion of sustained remission and ESRD between the RTX and CYC groups.[8,16] However, the weakness of the RITUXVAS trial, beyond the small number of participants, was that patients in the RTX group also received two concomitant pulses of intravenous CYC, and, for those with progressive disease within the first 6 months, a third dose of intravenous CYC was allowed, making it very difficult to discern the specific contribution of CYC in the RTX-treated patients. Based on these data, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines[17] recommend the use of RTX plus CCS as an alternative initial treatment only in patients without severe renal disease or in whom CYC is contraindicated (Box 1).

Recently, two retrospective multicentre studies evaluating the efficacy of RTX plus CCS without concomitant CYC in patients with severe renal involvement have achieved high rates of remission and dialysis independence.[19,20] However, these studies have limitations due to their retrospective designs and small sample sizes. Further prospective randomised trials are needed to confirm these findings in this subset of patients.

In 2016, the 2009 European League Against Rheumatism (EULAR) recommendations for the management of ANCA-associated vasculitis were updated by the European Renal Association–European Dialysis and Transplant Association (ERA–EDTA).[18] For remission induction of new-onset or major relapse of organ or life-threatening GPA and MPA, treatment with a combination of CCS and either CYC or RTX is now recommended. The grade of recommendation was A for both CYC and RTX but with a different level of evidence 1A for CYC and 1B for RTX, confirming the need for further evidence in this field (Box 1).

What is the Impact of Renal Tubular Lesions on Therapeutic Choice?

The evaluation of histological parameters along with clinical parameters could also be relevant in determining therapeutic choice. Among patients in the RITUXVAS trial, both B cell and T cell-mediated tubulointerstitial lesions were present in renal biopsies before treatment with RTX. However, only tubular intraepithelial T cells were predictive of impaired renal function during follow-up. The analysis of patients treated with CYC, an immunosuppressive agent directed towards both B cells and T cells, did not show any evidence that T cell tubulitis was related to renal outcome.[21] These data raised the question of whether T cell tubulitis represents a negative predictor for all treatments or whether its predictive significance is limited to RTX due to undertreatment of T cell-mediated lesions by B cell-depleting agents.

Recently, Geetha et al.[22] conducted a similar study using renal biopsies from patients who participated in the RAVE trial. In contrast to the results of the RITUXVAS study, this study showed that interstitial B and T cell infiltrates had no significant impact on long-term prognosis, regardless of the immunosuppression regimen used (RTX or CYC).[22]

Repeat renal biopsies in future trials would help to clarify these contradictory results and identify the extent of B and T cell infiltration, which could potentially be a significant clinical factor in determining the adequate therapy for individual patients to ensure that active lesions are adequately treated.

What is the Impact of Safety and Adverse Events on Therapeutic Choice?

Given that safety is a key concern in the evaluation of immunosuppressive agents, there may be individual clinical situations in which RTX is more appropriate than CYC. These may include patients with a high cumulative dose of CYC due to previous exposure, those with a history of malignancy, and those who are of childbearing age but do not yet have any offspring. However, RAVE[7] and RITUXVAS[8] did not show any benefit of RTX in terms of incidence of adverse events, regardless of severity.[23] Particularly, the incidence of severe infections was considerable in the RAVE and RITUXVAS trials (12% and 18%, respectively) and did not differ between the CYC and RTX-based induction treatments. Initial renal dysfunction determined by eGFR was also associated with a higher risk of subsequent infection for both treatment groups.

Box 1: Current guidelines for remission induction therapy for antineutrophil cytoplasmic antibody-associated vasculitides with severe renal involvement.

KDIGO recommendations[17]
Initial treatment of pauci-immune focal and segmental necrotising GN with or without systemic vasculitis, and with or without circulating ANCA: › It is recommended that CYC and CCS be used as initial treatment. (1A) › It is recommended that RTX and CCS be used as an alternative initial treatment in patients without severe disease or in whom CYC is contraindicated. (1B) › The addition of PLEX is recommended for patients requiring dialysis or with rapidly increasing serum creatinine. (1C)
Treatment of relapse: › It is recommended that patients with severe relapse of ANCA vasculitis (life or organ-threatening) are treated according to the same guidelines as for the initial therapy. (1C)
EULAR/ERA–EDTA recommendations[18]
For remission-induction of new-onset organ or life-threatening AAV, treatment with a combination of CCS and either CYC or RTX is recommended: › CYC: Level of evidence 1A for GPA and MPA; grade of recommendation A; strength of vote 100%. › RTX: Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 82%.
For a major relapse of organ or life-threatening disease in AAV, treatment as per new disease with a combination of CCS and either CYC or RTX is recommended: › CYC: Level of evidence 1A for GPA and MPA; grade of recommendation A; strength of vote 88%. › RTX: Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 94%.
PLEX should be considered for patients with AAV and a serum creatinine level >500 mmol/L (5.7 mg/dL) due to rapidly progressive GN in the setting of new or relapsing disease. Level of evidence 1B; grade of recommendation B; strength of vote 77%.

AAV: antineutrophil cytoplasmic antibody-associated vasculitides; ANCA: antineutrophil cytoplasmic antibody; CCS: corticosteroids; CYC: cyclophosphamide; ERA–EDTA: European Renal Association–European Dialysis and Transplant Association; EULAR: European League Against Rheumatism; GN: glomerulonephritis; GPA: granulomatosis with polyangiitis; KDIGO: Kidney Disease Improving Global Outcomes; MPA: microscopic polyangiitis; PLEX: plasma exchange; RTX: rituximab.

Although using RTX in patients with severe infection has been reported as an efficacious remission induction treatment,[24] this is not recommended because moderate-to-severe hypogammaglobulinaemia occurs in >50% of AAV patients treated with RTX, resulting in an increased risk of infections that could be even higher in those with reduced renal function.[25] Hypogammaglobulinaemia with an early onset is usually transient and benign,[26] whereas hypogammaglobulinaemia with a late onset is commonly severe and associated with infection.[27] Late-onset neutropenia (LON), defined as an absolute neutrophil count <$1.0x10^9$ for >1 month after the last RTX infusion with spontaneous recovery when other causes are ruled out, has also been described in both GPA and MPA, and has been reported to be associated with a high incidence of infections. For example, in a recent single-centre analysis of 59 patients with AAV, LON developed in 12% of patients.[28]

Uncommon but serious adverse events after RTX treatment include hepatitis B reactivation, which is largely preventable with antiviral prophylaxis, and progressive multifocal leukoencephalopathy, caused by reactivation of the human John Cunningham polyomavirus.[29-31] However, progressive multifocal leukoencephalopathy and hepatitis B reactivation have also been reported in patients with GPA treated with CYC.[32,33]

The malignancy incidence in patients treated with RTX or CYC has been recently investigated in a retrospective study of 323 patients with AAV.[34] During a mean follow-up of 5.6 years, patients treated with RTX did not show an increased risk compared with the general population. In contrast, patients treated with CYC had a 4.61-fold higher risk of developing malignancies than those treated with RTX. Longer follow-up studies are now required to validate these data.

THERAPEUTIC APPROACH: PATIENTS WITH NEWLY DIAGNOSED ANTINEUTROPHIL CYTOPLASMIC ANTIBODY-ASSOCIATED VASCULITIDES AND THOSE WITH DISEASE RELAPSE

The therapeutic approach to relapse in patients with GPA or MPA and renal involvement depends on the degree of severity and whether the patient is still undergoing treatment with a maintenance immunosuppressive regimen at the time of relapse.

Treatment of Mild Renal Relapse

Patients with mild, non-organ-threatening relapse (e.g., recurrent red blood cell casts on urine microscopy without concomitant increase in serum creatinine) who are still undergoing maintenance therapy can initially be treated by increasing the dose of CCS and of the respective immunosuppressive agent used for maintenance therapy, if the relapse occurs during a reduction in dose of maintenance therapy.[18,35] Mild, non-organ-threatening relapses that arise after discontinuation of maintenance therapy can be treated with the resumption of the prior maintenance therapy. In the latter case, the maintenance therapy should be continued for a more extended period than planned before the relapse.[18] If the nephrologist is uncertain that the relapse is mild, a kidney biopsy must be performed to clarify whether the repeat-induction therapy is warranted. In patients with multiple mild relapses, B cell depletion with RTX must be considered as an alternative approach.[35] Most recommendations for non-severe relapses come from the 2016 EULAR/ERA–EDTA guidelines for the management of AAV; however, these recommendations do not provide a level of evidence or a grade of recommendation.[18]

Treatment of Severe Renal Relapse

The 2016 EULAR/ERA–EDTA recommendations for the management of AAV suggest that severe relapses should be treated with the resumption of induction therapy using a CYC-based or RTX-based regimen (CYC: level of evidence 1A; Grade of recommendation A versus RTX: level of evidence 1B; Grade of recommendation A).[18] In patients who relapse after successfully achieving remission with a CYC-based regimen, RTX is preferred because the cumulative dose of CYC is associated with significant toxicity.[18,33] RTX is also the therapy of choice for patients who relapse after previously achieving remission with RTX-based therapy.[18,36]

The best data in patients with relapsing GPA and MPA come from the RAVE trial. The rate of remission induction in patients with relapse was higher with RTX at 6 and 12 months, but not at 18 months.[7,23] RTX and CYC followed by AZA achieved similar remission rates at 18 months, although patients in the RTX group who achieved a complete remission by 6 months received no additional immunosuppression for >1 year.[23] However, CYC-based therapy should be considered for patients whose relapse is characterised by advanced renal failure, as it is for patients with newly diagnosed AAV, for the reasons mentioned above (Box 1).

What is the Impact of Antigenic Specificity of Antineutrophil Cytoplasmic Antibodies on Therapeutic Choice?

To date, there is growing evidence that ANCA specificity is superior to clinical diagnosis in defining homogeneous groups of patients, since proteinase 3 (PR3)-ANCA and myeloperoxidase (MPO)-ANCA are associated with different genetic backgrounds and epidemiologic patterns.[37] Data from most cohorts show that patients with MPO-ANCA have poorer renal outcomes than those with PR3-ANCA.[38-40] However, regarding the frequency of relapses, numerous studies have shown that these are much more frequent in patients with PR3-ANCA seropositivity.[2,38,41]

In the RAVE trial,[7] at the 6-month timepoint, significantly more patients became PR3-ANCA negative after RTX therapy than after CYC

with AZA therapy (50% versus 17%), whereas comparable proportions of patients receiving each therapy became MPO-ANCA-negative. Most importantly, a post hoc analysis of the RAVE trial showed a similar ratio of complete remission at 6 months in both treatment groups among the subgroup of patients with MPO-ANCA seropositivity, whereas RTX was significantly more effective than CYC with AZA in the subgroup of patients with PR3-ANCA (65% versus 48%).[42] Moreover, among patients with PR3-ANCA who had relapsing disease at baseline, the risk of disease relapse in RTX-treated patients was inferior not only at 6 months, but also at 12 and 18 months, despite the fact that patients randomised to RTX had not received a maintenance regimen.[42] However, in another post hoc analysis of patients with renal involvement enrolled in the RAVE trial, no variations in remission rates or improvements in eGFR at 18 months were observed when the analysis was stratified by ANCA type, AAV diagnosis (GPA versus MPA), or new diagnosis versus relapsing disease at entry.[15]

In conclusion, the demonstrated superiority of RTX compared to CYC in patients with PR3-ANCA and in those with relapsing disease has not yet been confirmed in long-term follow-up of patients with renal involvement.[15] Further clinical trials are needed to evaluate this question in well-defined homogenous patient populations, according to ANCA specificity.

Table 1: Trials for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitides with renal involvement and corticosteroid-sparing regimens.

Trial (number of patients)	Inclusion criteria	Treatment groups	Primary endpoints	Outcome
LoVAS. Furuta et al.,[50] 2017 (140)	New clinical diagnosis of MPA or GPA, age >20 years, and eGFR >15 mL/min	Low-dose CCS (0.5 mg/kg/day tapered and off within 6 months) plus RTX versus high-dose CCS (1.0 mg/kg/day tapered to 10 mg/day within 6 months) plus RTX	Proportion of the patients achieving remission at 6 months (BVAS: 0 and CCS <10 mg)	Ongoing trial
PEXIVAS. Walsh et al.,[48] 2013 (704)	New or previous clinical diagnosis of MPA or GPA, age >15 years, and eGFR <50 mL/min	Without PLEX: normal versus reduced CCS versus with PLEX: normal versus reduced CCS (reduced dose regimen provides approximately 55% of the standard dose regimen over the first 6 months)	All-cause mortality and ESRD at 2 years	Ongoing trial
CLEAR. Jayne et al.,[51] 2017 (67)	New or previous clinical diagnosis of MPA or GPA, age >18 years, and eGFR >20 mL/min	Placebo plus 60 mg prednisone versus avacopan (30 mg twice per day) plus 20 mg prednisone versus avacopan (30 mg twice per day) without prednisone	Safety of avacopan in subjects with AAV over the 12-week treatment period	Avacopan can replace high-dose CCS efficiently and safely in patients with newly diagnosed or relapsing AAV
ADVOCATE ChemoCentryx[52] (300)		Avacopan in combination with RTX or CYC/AZA versus prednisone in combination with RTX or CYC/AZA	The proportion of patients achieving disease remission at Week 26	Ongoing trial

AAV: antineutrophil cytoplasmic antibody-associated vasculitides; AZA: azathioprine; BVAS: Birmingham Vasculitis Activity Score; CCS: corticosteroids; CYC: cyclophosphamide; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; PLEX: plasma exchange; RTX: rituximab.

Table 2: New agents investigated in preclinical models and clinical trials in humans for antineutrophil cytoplasmic antibody-associated vasculitides with renal involvement.

Agent	Therapeutic target	Preclinical models	Human trials
Avacopan	Complement C5a receptor inhibitor	Mice; Walsh et al.,[48] 2013	CLEAR: A Phase II trial. Status: Completed. Jayne et al.,[51] 2017 CLASSIC: A Phase II trial. Status: Completed. Merkel et al.,[53] 2016 ADVOCATE: A Phase III trial. Status: Recruiting. ChemoCentryx[52]
Bortezomib	Proteasome inhibitor	Mice; Bontscho et al.,[54] 2011	Not available
Fostamatinib	Spleen tyrosine kinase inhibitor	Mice; McAdoo et al.,[55] 2014	Not available
Anakinra	IL-1 receptor antagonist	Mice; Schreiber et al.,[56] 2012	Not available
Gusperimus	NF-κB translocalisation inhibition in leucocytes; IFNγ, IL-6, and IL-10 production reduction	Mice; Birck et al.,[57] 2006	Phase II trials. Status: Completed. Birck et al.,[58] 2003 Schmitt et al.,[59] 2005 Flossmann et al.,[60] 2009
Alemtuzumab	Anti-CD52 humanised antibody inducing T cell and macrophage depletion	Not available	Phase II trial Status: Complete. Walsh et al.,[61] 2008

IFN: interferon; IL: interleukin; NF-kB: nuclear factor kappa B.

SHOULD ALL PATIENTS WITH ADVANCED RENAL INVOLVEMENT BE TREATED WITH ADJUNCTIVE PLASMA EXCHANGE SESSIONS?

The rationale for plasma exchange (PLEX) in AAV is that removal of ANCA and other plasma constituents involved in the pathogenesis of the disease could reduce further tissue damage and promote reversal of the pathologic process.[43] The effect of PLEX in addition to standard immunosuppressive therapy in patients with AAV and renal involvement was evaluated in an initial randomised trial that demonstrated the efficacy of PLEX only in the subgroup of patients with serum creatinine ≥500 mmol/L (5.8 mg/dL) or on dialysis at diagnosis.[44] In 2007, the MEPEX trial,[45] the largest randomised trial in patients with severe renal disease (serum creatinine >500 mmol/L), was published. At 3 months, a significantly higher number of patients were alive and independent of dialysis in the PLEX group. Additionally, PLEX was associated with a 24% reduction in the risk of progression to ESRD at 12 months.[45] A subsequent meta-analysis of 387 patients from nine trials, including the MEPEX trial, showed a 20% relative risk reduction in the composite outcome of death or ESRD requiring dialysis after the addition of PLEX to standard immunosuppressive therapy.[46] However, too few patients were randomly assigned and sensitivity analyses were not sufficiently robust to reliably conclude that PLEX results in at least a moderate decrease in the composite endpoint of ESRD or death.[46]

Moreover, although these short-term PLEX results are encouraging, the long-term benefits remain unclear. In fact, long-term follow-up of the MEPEX trial showed an attenuated benefit of PLEX with no significant reduction of progression to ESRD at 4 years, and equivalent mortality in both groups (51%).[47] Currently, the most recent EULAR/ERA–EDTA recommendations for the management of AAV suggest that PLEX should be considered for patients with AAV and a serum creatinine level

>500 mmol/L in the setting of new or relapsing disease (Box 1).[18] In conclusion, PLEX continues to be a promising therapy, but further trials are required before its widespread use for patients with renal vasculitis can be implemented. The ongoing PEXIVAS trial[48] should help to further clarify the value of PLEX in these patients.

NOVEL TARGETED AGENTS AND FUTURE PERSPECTIVES ON INDUCTION REMISSION THERAPY FOR ANTINEUTROPHIL CYTOPLASMIC ANTIBODY-ASSOCIATED VASCULITIDES WITH RENAL INVOLVEMENT

The greatest challenge in the management of AAV is the development of new agents and innovative strategies, which are urgently needed to improve patient prognosis and reduce the comorbidities associated with current regimens.

As previously mentioned, to date, high-dose CCS remain an integral part of induction remission therapy for AAV, in combination with CYC or RTX. Even though CCS rapidly control inflammation and prevent further renal damage, the increased susceptibility to infections and other potential comorbidities, such as diabetes, cardiovascular events, osteoporosis, cataracts, and gastrointestinal complications,[49] has prompted researchers to reduce or replace their use. The aforementioned multinational PEXIVAS trial[48] and the LoVAS trial[50] could provide valuable information on this crucial question (Table 1).

However, the most promising advancement for remission induction therapy is avacopan (CCX168), an orally administered selective C5a receptor inhibitor (Table 2). The efficacy of avacopan was first tested in an ANCA-associated glomerulonephritis mouse model induced by injection of MPO immunoglobulin G.[62] The recently completed CLEAR study,[51] a Phase II, randomised, double-blind, placebo-controlled trial, met its primary endpoint, indicating that avacopan can replace high-dose CCS efficiently and safely in patients with newly diagnosed or relapsing AAV (Table 1). The 67 enrolled patients were randomised to receive placebo plus prednisone starting at 60 mg daily (control group), avacopan (30 mg twice daily) plus reduced-dose prednisone (20 mg daily), or avacopan (30 mg twice daily) without prednisone. The early efficacy of avacopan was substantiated by a rapid improvement in albuminuria, which was statistically significantly superior to the control group. Moreover, renal inflammation improved rapidly and to a higher degree in the avacopan groups compared with the control group, as demonstrated by the greater reduction of urinary monocyte chemoattractant protein-1 levels, a renal inflammation marker, in the avacopan groups. The most important finding from the CLEAR trial regarding renal outcomes is that eGFR and haematuria improved similarly in all three groups over the 12-week treatment period, indicating that improvement in renal function in patients receiving avacopan did not require high-dose CCS. Another Phase II trial, the CLASSIC trial,[53] investigated the addition of two different doses of avacopan or placebo to standard-dose CCS with CYC or RTX. No safety concerns were described in the avacopan treatment groups, and a trend towards a dose-dependent improvement in clinical responses was shown. ADVOCATE,[52] a Phase III trial, is now enrolling patients and will assess the safety and effectiveness of avacopan as an alternative to prednisone in inducing and maintaining remission in patients with AAV (Table 1).

Ofatumumab, a humanised anti-CD20 monoclonal antibody, which, like RTX, acts by depleting B cells, has been shown to be effective in the treatment of AAV patients, including those with renal involvement, thereby making this agent a possible alternative for use in patients who cannot take or tolerate RTX.[63] Other new potential therapeutic agents in the induction remission therapy of AAV with major renal involvement include (Table 2):

- Bortezomib, a proteasome inhibitor, found to be more efficacious than CYC combined with CCS in decreasing the number of MPO-specific plasma cells and anti-MPO titres, thereby preventing the development of necrotising crescentic glomerulonephritis in a mouse model of MPO-AAV.[54]
- Fostamatinib, a selective spleen tyrosine kinase inhibitor that blocks B cell activation, shown to be an effective treatment for crescentic glomerulonephritis and lung haemorrhage in a rodent model of MPO-AAV.[55]

- Anakinra, a recombinant non-glycosylated human interleukin-1 receptor antagonist used in the treatment of rheumatoid arthritis, reducing the severity of necrotising crescentic glomerulonephritis in a mouse model of MPO-AAV.[56]

Other agents, such as gusperimus[57-60,64] and alemtuzumab,[61] despite having been demonstrated to be effective, should not be used in AAV due to serious adverse events (Table 2).

Belimumab, a human monoclonal antibody that inhibits B cell activating factor, also known as B lymphocyte stimulator, is currently approved for the treatment of active systemic lupus erythematosus excluding renal involvement. In AAV, the effect of belimumab in combination with AZA is currently underway as a remission maintenance strategy in the BREVAS trial,[65] but its role in induction therapy, particularly in patients with renal involvement, is unknown and could be investigated in future trials in combination with standard therapy.

CONCLUSION

In recent years, RTX has enriched our armamentarium for remission induction treatment for severe organ or life-threatening AAV; however, data from randomised controlled trials on the efficacy of RTX in patients with advanced kidney failure without concomitant CYC are lacking. Additionally, despite the reported superiority of RTX in patients with relapsing disease and those with PR3-ANCA seropositivity, no differences in remission rates or increases in eGFR are evident when the analysis is stratified by ANCA type or by new diagnosis versus relapsing disease in patients with major renal involvement.[15] For that reason, new clinical trials in well-defined homogeneous patient populations, selected according to their ANCA specificity and renal function, are needed. Until then, CYC should remain the first-line treatment in the induction of remission for patients with severe renal involvement. Similarly, further data are needed to unambiguously define the use of PLEX in the treatment of AAV with severe renal involvement. The results of the PEXIVAS study[48] are expected to elucidate this question. Other general issues in the induction treatment of AAV vasculitis, including the use of oral or intravenous CYC, the preferred induction protocol for RTX, and the tapering of CCS during induction, remain to be elucidated, but a detailed discussion on these issues was beyond the scope of this review.

Finally, the continuous enrichment of knowledge on the pathogenetic mechanisms of this disease may be translated into new therapeutic strategies based on novel biological drugs; soon there may be therapeutic regimens with low doses of CCS or without CCS at all. Avacopan, a selective C5a receptor inhibitor, has proven to be an excellent glucocorticoid-sparing agent as showed in Phase II clinical trials.[51,53] However, these data now require confirmation by an ongoing Phase III trial.[52] Other agents are still under examination in promising preclinical studies.

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Mycophenolate Mofetil-Induced Colitis with Graft Versus Host Disease-Like Features in a Renal Transplant Recipient: Case Report and Literature Review

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Abstract

Diarrhoea is a common complication after renal transplant and has a significant impact on quality of life, graft function, and mortality. The main causes of post-transplant diarrhoea are infectious and pharmacological. Mycophenolate mofetil (MMF) is an immunosuppressive medication widely used in kidney transplantation patients. Gastrointestinal side effects of MMF, such as nausea, vomiting, diarrhoea, and abdominal pain, mostly occur during the first months of treatment; however, late-onset diarrhoea does not exclude the diagnosis of MMF-induced colitis. MMF-induced colitis is associated with a wide histological spectrum, including inflammatory bowel disease-like, graft versus host disease-like, and ischaemia-like changes, which may lead to misdiagnosis. The complexity and severity of histological features might explain the variation in treatment response. Given the differences in the therapeutic management and prognosis of these histological changes, it is crucial to consider the diagnosis of MMF-induced colitis. The aim of this paper is to report a rare case of late-onset MMF-induced colitis with graft versus host disease-like features in a renal transplant patient who did not respond to MMF therapy withdrawal, and provide a review of data on this rare complication of immunosuppression.

INTRODUCTION

Diarrhoea is a common complication after renal transplant, particularly within the first year,[1] and, although frequently overlooked, it has a significant impact on quality of life, graft function, and mortality.[1,2] The main causes of post-transplant diarrhoea are infectious and pharmacological, commonly due to immunosuppressive medications.[3] Mycophenolate mofetil (MMF) is an immunosuppressive treatment widely used in kidney transplantation patients due to its superiority in preventing rejection compared with azathioprine.[4] Both MMF and enteric-coated mycophenolate sodium have been associated with post-transplant diarrhoea and other gastrointestinal (GI) side effects, such as nausea, vomiting, and abdominal pain, mostly

occurring during the first 6 months of treatment.[5] The incidence of GI toxicity has been reported to be between 40% and 85%, and it is the most common cause of drug withdrawal, which can lead to graft rejection.[6]

The use of MMF has been associated with many histological patterns, such as Crohn's disease-like changes in the colon, erosive or ischaemic enterocolitis, and graft versus host disease (GVHD)-like colonic changes, which can make the diagnosis difficult.[7,8] The aim of this paper is to report a case of late-onset MMF-induced colitis with GVHD-like features in a renal transplant patient and provide a review of data on this rare complication of immunosuppression.

CASE REPORT

The patient was a 50-year-old Caucasian male who had end-stage renal disease due to diabetic nephropathy. He required peritoneal dialysis for 4 years and underwent kidney transplantation in 2009 from a deceased donor with three major histocompatibility mismatches. The induction therapy involved basiliximab, tacrolimus, MMF, and prednisolone. In the first 3 months, the patient had an acute cellular rejection (Banff 1A) and was treated with pulse steroids; he then had a renal artery stent inserted during the postoperative period due to renal artery stenosis. His creatinine concentration on discharge measured 1.6 mg/dL and remained at this level throughout the follow-up period. Maintenance therapy was with tacrolimus, MMF, and prednisolone.

Nine years after the transplant, the patient developed a history of watery diarrhoea, general weakness, and anorexia, and lost 9 kg over 3 weeks. He had no fever or skin rash and there were no reported recent infections and no history of prior blood transfusions. The patient was medicated with tacrolimus, MMF, prednisolone, carvedilol, amlodipine, furosemide, calcitriol, and insulin. The dose of immunosuppression was stable for many years.

The patient was dehydrated, with a blood pressure of 98/54 mmHg and a body temperature of 36.1°C. He was anaemic (haemoglobin: 8.9 g/dL), with a normal white blood cell count and negative C-reactive protein. His kidney function deteriorated (creatinine: 3.1 mg/dL, urea: 118 mg/dL) and had hypokalaemia and metabolic acidosis. The MMF dose was 500 mg twice a day and his serum tacrolimus trough level was 6.8 ng/dL. He underwent fluid resuscitation and electrolyte reposition. The investigation for watery diarrhoea revealed negative *Clostridium difficile* toxin, negative stool cultures, negative cytomegalovirus antigenemia assay, and negative serologies for adenovirus and Epstein–Barr virus. Serum liver function tests were normal and a computed tomography (CT) scan of his head, chest, abdomen, and pelvis was unremarkable.

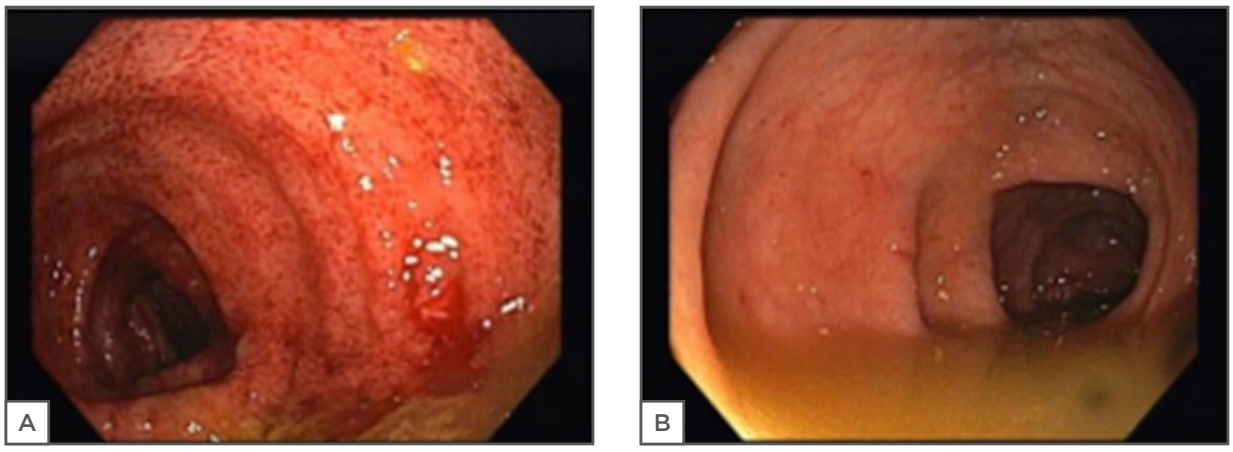

Figure 1: Colonoscopy findings in the patient.

A) The ascending colon with erythematous mucosa with multiple petechial lesions; B) The descending colon with normal mucosa.

Table 1: Mycophenolate mofetil-induced colitis morphological spectrum.

Histological characteristics	Incidence reported in the literature[7,8,16,20]
Normal or near normal	31–47%
Inflammatory bowel disease-like	28–83%
Graft versus host disease-like	8–19%
Self-limited colitis-like	16%

The patient's diarrhoea persisted despite MMF withdrawal and there was a clinical deterioration with severe prostration and hypotension. He developed pancytopenia with a haemoglobin count of 6.8 g/dL, white blood cell count of $1.23x10^9$ cell/L, and platelet count of $63x10^9$ cell/L. His renal function aggravated due to hypovolaemia, with a maximum creatinine of 3.8 mg/dL and urea of 250 mg/dL; furthermore, he had severe hypoalbuminaemia (albumin: 1.9 mg/dL) as a result of malnutrition. He maintained the need for intravenous electrolyte and albumin reposition. A kidney biopsy was not performed due to the clinical deterioration of the patient. A colonoscopy examination was negative for viral infections and demonstrated mucosal erythema and extensive haemorrhagic spots in the ascending colon. Colon biopsies revealed lymphocytic infiltration of the epithelium, multiple eosinophils, sloughing and apoptosis of epithelial cells, and multiple crypts with apoptotic cells, consistent with GVHD (Figure 1).

The patient was started on parenteral nutrition support and bowel rest, and was treated with intravenous methylprednisone 1 g/day for 3 days, followed by 500 mg for 3 days, and then prednisolone 2 mg/kg/day for 7 days, which was then tapered slowly. After 4 days of steroid pulses the diarrhoea ceased, and by Day 10 of steroid therapy the patient was restarted on oral alimentation. Human leukocyte antigen (HLA) typing was performed in a peripheral blood sample but did not reveal the presence of donor T lymphocytes in the recipient's blood, excluding GVHD in this patient.

This patient had two infectious complications related to his severe state of immunosuppression; namely, a *Staphylococcus aureus* methicillin-sensitive bacteraemia, which was treated with 3 weeks of flucloxacillin, and a nosocomial pyelonephritis to *Klebsiella pneumoniae*, which was treated with 3 weeks of cefuroxime. He was discharged after 2 months without diarrhoea and regained 50% of his lost body weight. He was maintained on tacrolimus and prednisolone only, with a kidney function that stabilised with a creatinine measure of 2.9 mg/dL.

DISCUSSION

MMF is widely used for the prevention of acute rejection following kidney transplantation.[9] The drug is absorbed and hydrolysed to its active metabolite, mycophenolic acid (MPA), which acts by inhibiting inosine monophosphate dehydrogenase in the *de novo* pathway of purine synthesis, thus effectively suppressing lymphocyte proliferation, which is dependent on this pathway.[10]

MMF has a low risk of causing nephrotoxicity, cardiotoxicity, and diabetes[10,11] but has the potential to affect both the upper and lower GI tract due to local and systemic disturbances.[11] The exact mechanism of GI toxicity is unclear since enterocytes are only partially dependent on the *de novo* pathway of purine synthesis for proliferation. It has been demonstrated that the acyl glucuronide metabolite of MPA may play a role in inflammation by stimulating the release of interleukin-6 and tumour necrosis factor-alpha, and through the formation of neoantigens and subsequent activation of the immune system, causing either a hypersensitivity reaction or an autoimmune response. Also, the antibacterial effect of MPA can cause changes in the GI tract flora, promoting anaerobic growth and tissue damage.[12-15]

Although most cases occur within the first 6 months of therapy, a long latency period does not exclude the possibility of MMF-induced

diarrhoea.[16] Indeed, there have been no studies focussing on the chronological relationship between duration of MMF therapy and symptom onset.[16] There have been sporadic reports of late-onset MMF-induced diarrhoea, with the latest in a heart transplant patient who presented after 13 years of stable MMF therapy.[17,18]

MMF-related GI mucosal injury may present with variable injury patterns, with the most common being a normal appearing mucosa.[19] In a study by Selbst et al.,[7] the histological changes in patients receiving MMF were categorised as normal or near normal (31%), inflammatory bowel disease-like (28%), GVHD-like (19%), ischaemia-like (3%), and self-limited colitis-like (16%). Calmet et al.[8] also demonstrated histological variability in MMF-induced colitis and reported a GVHD-like pattern incidence of 8.3%. Liapis et al.[20] further substantiated the wide spectrum of histological changes associated with MMF in 43 colon biopsies, with an incidence of 83% of inflammatory bowel disease-like changes and 18% of GVHD-like changes.[20] The study also documented variable timing of diarrhoea onset and showed the main histopathological features of MMF-induced colitis were apoptosis and crypt distortion: characteristics similar to GVHD and inflammatory bowel disease (Table 1).[20]

In 2003, Papadimitriou et al.[21] demonstrated similarities in the histological features of colitis secondary to MMF and GVHD. Likewise, Al-Absi et al.[22] described five patients who presented with variable onset and duration of MMF-induced diarrhoea with colonoscopy findings similar to GVHD. These findings were prominent crypt cell apoptosis, enterocyte cytologic atypia, increased neuroendocrine cells, and glandular architectural distortion.[21,22]

The distinction between MMF and GVHD-induced colitis is clinically important since not only the aetiology and natural history but also the management of these disorders are different. In GVHD, the donor's leukocytes dominate the recipient's immune system and induce an immune reaction that causes a multisystem disorder.[23] This is less common in solid organ transplantation than after haematopoietic stem cell transplantation. In kidney transplant patients, only six cases of GVHD have been described and these were associated with a high degree of HLA mismatch or donor HLA homozygosity; all cases were within the first year after transplantation, with a median time from transplant to GVHD of 111.2±90.4 days.[24-29] The diagnosis of GVHD is made by a tissue biopsy documenting epithelial cell apoptosis and mononuclear cell inflammatory infiltrate, and evidence of the presence of donor lymphocytes by serological HLA typing, polymerase chain reaction-based microsatellite markers, or fluorescence *in situ* hybridisation analyses.[23]

The immune dysregulation caused by MMF induces proliferation of donor lymphocytes, which can generate a GVHD-like phenotype. Star et al.[30] demonstrated that the presence and quantity of lamina propria eosinophils and endocrine cell aggregates, and the presence and degree of crypt distortion, apoptotic microabscesses, and hypereosinophilic crypts were features independently associated with MMF. Furthermore, the quantities of intraepithelial lymphocytes and endocrine cells were also significantly higher in patients with GVHD compared to those with MMF-induced colitis.[30]

The treatment for GVHD is based on increasing immunosuppression with corticosteroids and, depending on the severity of the symptoms, includes adding other immunosuppressive agents.[21] In most cases of MMF-induced colitis, dose reduction or withdrawal is sufficient; however, if symptoms persist, steroid therapy may be required. There are controversial data on GI symptom improvement after conversion to enteric-coated mycophenolate sodium, which decreases local adverse effects but has similar systemic toxic effects to MMF.[5,15,31,32] There is also one case report of MMF-induced ulcerative colitis with features of inflammatory bowel disease treated successfully with infliximab.[33] The complexity and severity of histological features might explain the variation in treatment response.

The case detailed in this report was a challenging diagnosis of late-onset MMF-induced colitis that was unresponsive to MMF withdrawal and treated successfully with pulse steroids. MMF-induced colitis has rarely been reported with such a late presentation on a stable dose of immunosuppression, and cases of GVHD after kidney transplant have only been described within the first year. The patient had been receiving MMF therapy for 9 years and had

tolerated it well up to symptom occurrence. Additionally, the biopsy findings of numerous eosinophils suggested a GVHD-like pattern of MMF-induced colitis, since GVHD was excluded by HLA typing. Although the diarrhoea persisted despite discontinuing MMF and a response was only possible with pulse steroids and high-dose prednisone, which is atypical for MMF-induced colitis, it was believed that the severity of the mucosal injury (similar to that seen in GVHD) was the cause of unresponsiveness to MMF withdrawal and the need for high-dose steroid therapy.

CONCLUSION

Diarrhoea associated with immunosuppression is a common complication after renal transplantation and has a significant impact on graft function and mortality. Although this adverse event commonly develops within the first year after kidney transplant, late-onset MMF-induced colitis must be considered as a differential diagnosis.

The wide morphological spectrum reported in MMF-induced colitis includes normal mucosa, inflammatory bowel disease-like, ischaemia-like, self-limited colitis-like, and GVHD-like features, which can result in misdiagnosis and a delay in the time to intervention. Given the differences in the therapeutic management and prognosis of these diseases, it is crucial to inform the pathologist of the clinical history of MMF therapy and to consider this diagnosis regardless of the duration of therapy. Treatment is complex and variable, ranging from MMF withdrawal to successful reports of specific immunosuppressive agents used to treat the histological pattern mimicked by MMF-induced colitis.

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Prolonged Intravenous Colistin Use Associated with Acquired Bartter-Like Syndrome in an Adult Patient: A Case Report

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Abstract

Colistin-induced nephrotoxicity has widely been identified through the elevation of serum creatinine level or a reduction of glomerular filtration rate, but tubulopathy associated with colistin use is poorly understood. Herein, the authors describe a unique case of a 32-year-old quadriplegic male who developed persistent hypomagnesaemia, hypokalaemia, and metabolic alkalosis >4 weeks into therapy with intravenous colistimethate sodium for the treatment of decubitus sacral osteomyelitis by extensively drug-resistant *Klebsiella pneumoniae.* This required daily aggressive intravenous repletion of electrolytes and fluids while on the treatment, but it was only after 6 days of finishing the treatment with the antibiotic that metabolic changes resembling acquired Bartter-like syndrome started resolving.

INTRODUCTION

In recent years, intravenous (IV) colistin has become one of the few available agents to treat multidrug-resistant and extensively drug-resistant Gram-negative bacterial infections.[1,2] Colistin exerts bactericidal activity against these agents by disrupting the bacterial cell membrane.[3] Nephrotoxicity has been the most worrying side effect of the medication; as a result, the systemic use of colistin was discontinued in the 1970s, shortly after being introduced.[2] However, with limited alternatives and recent studies showing a relatively lower incidence of nephrotoxicity associated with the use of more purified colistin (colistimethate instead of colistin sulphate), it has re-emerged as an important antimicrobial agent in a select group of patients.[2,4] Most studies have demonstrated colistin-induced nephrotoxicity as acute kidney injury or acute tubular necrosis and have described it in the form of increasing creatinine, decreasing glomerular filtration rate (GFR), or the need to undergo haemodialysis.[2,5-8] This paper, however, reports a unique case of acquired Bartter-like syndrome (BLS) after prolonged IV colistin therapy in an adult. Following a review of literature, only one case of BLS in an adult and one case in a preterm infant related to colistin use have been

reported.[3,9] The exact pathophysiology for this type of tubulopathy associated with colistin use remains unclear.

CASE REPORT

A 32-year-old African-American male with a history of quadriplegia secondary to a gunshot wound to the neck, Stage IV ischial and sacral decubitus ulcers, and a history of recurrent wound infections secondary to soiling by faeces, presented initially to the hospital after being referred by an infectious disease specialist for evaluation for diverting colostomy placement. The patient's medical history was also significant for chronic respiratory failure and ventilator dependence status post tracheostomy, percutaneous gastrostomy tube dependence secondary to oropharyngeal dysphagia, dysfunctional bladder with chronic Foley catheter, sick sinus syndrome status post dual-chamber pacemaker placement, and recurrent multidrug resistant infections of the urinary tract and decubitus ulcers.

At the time of admission, the patient's blood pressure was 110/60 mmHg, heart rate was 60 beats per minute, and respiratory rate was 22 breaths per minute. The patient had a temperature of 37.9°C and was found to be less alert than normal. A physical examination also identified a 3.5x4.2 cm sacral ulcer with foul smelling drainage and a 1.6x2.3 cm right ischial ulcer. A probe-to-bone test was positive for sacral decubitus ulcer. The Foley catheter was replaced. Blood, urine, and wound cultures were sent for further testing. IV vancomycin and piperacillin-tazobactam were started. The patient underwent a successful diverting colostomy placement the next day. Blood cultures remained negative while urine culture grew a *Klebsiella pneumoniae* carbapenamase (KPC)-producing strain. Sacral wound culture was polymicrobial and grew KPC-producing strain, *Proteus mirabilis*, *Providencia stuartii*, and *Escherichia coli* on MacConkey agar. The presence of KPC was confirmed by Hodge Test and KPC was found to be resistant to imipenem with a minimum inhibitory concentration of 8 mg/L and sensitive to polymyxin B with dilution of 0.25 µg/mL.

Osteomyelitis could not be confirmed by MRI given the patient's history of pacemaker reliance and the patient was not able to tolerate nuclear bone scan. Since the patient's clinical picture was highly suggestive of decubitus sacral osteomyelitis, the infectious disease specialist decided to treat the patient with 6 weeks of IV antibiotics. Following the U.S. Centers for Disease Control and Prevention (CDC) recommendation, the patient was started on on a 5 mg/kg daily dose of IV colistin, divided into 3 doses throughout the day, in combination with IV meropenem at 1 g every 8 hours for 6 weeks due to the synergistic action of colistin with carbapenem. A peripherally inserted central catheter was used for the administration of IV antibiotics. The patient's mental status improved, haemodynamics stabilised, and the patient was discharged back to a long-term acute care (LTAC) facility.

After 22 days, the patient was readmitted to the hospital from the LTAC facility for hypotension and fever. Initially, the patient's condition was suspected to be secondary to sepsis and, as a result, Gram-positive coverage with IV vancomycin was added to his ongoing regimen of IV colistin and meropenem. However, the cultures remained negative and the patient was noted to have recurrent early morning hypoglycaemia. Serum cortisol levels were 2.2 µg/dL, confirming adrenal insufficiency. The patient started IV stress dose hydrocortisone, which improved his overall clinical condition. IV vancomycin was discontinued, but the patient remained on IV colistin and IV meropenem. After 30 days on IV colistin, the patient started developing significant electrolyte disturbances. Laboratory analysis of serum constituent concentration revealed serum sodium 143 milliequivalents (mEq)/L, serum potassium 2.8 mEq/L, serum bicarbonate 29 mmol/L, serum magnesium 1.4 mg/dL, serum calcium 8.6 mg/dL, and serum creatinine of 0.25 mg/dL. On subsequent days, despite daily aggressive electrolytes repletion, the patient was noted to have persistent hypomagnesaemia, with levels as low as 1.1 mg/dL; persistent hypokalaemia, with levels between 2.5 and 3.4 mEq/L; metabolic alkalosis, with serum bicarbonate levels between 29 and 32 mEq/L; and polyuria, with urine output of around 4.0–4.5 L daily. Serum creatinine remained

within the normal range of 0.25–0.60 mg/dL. The patient did not have any diarrhoea or vomiting. Urine studies were carried out, and the patient's fraction excretion of magnesium was calculated to be 24%, confirming renal wasting. Urine potassium, urine calcium, and urine chloride concentrations were not obtained. The nephrology department followed the patient. In the absence of any other medications, including diuretics or aminoglycosides, unexplained electrolyte disturbances were most likely suggestive of tubulopathy associated with prolonged colistin therapy with resultant acquired BLS. However, due to the patient's complex medical history, the infectious disease specialist and nephrologist decided to complete the full 6-week course of IV colistin. The patient was kept in the hospital for close monitoring of his metabolic panel during therapy. The patient finished the 6-week course of IV colistin and IV meropenem and was discharged back to the LTAC facility on oral supplementation of magnesium and potassium for 3 days, along with close monitoring of blood work. Six days after the conclusion of therapy, repeat blood work at the LTAC facility started to show stabilisation of electrolytes levels.

DISCUSSION

Bartter syndrome is a hereditary, renal tubular salt-wasting disorder resulting from defective sodium chloride reabsorption in the medullary thick ascending limb of the loop of Henle and is characterised by hypokalaemia, metabolic alkalosis, hypochloraemia, and hyperreninaemia with normal blood pressure.[10-12] Based on the various genetic defects causing defective sodium chloride reabsorption, Bartter syndrome has been classified in to type I, II, III, IV, IVb, and V.[12] Acquired BLS has also been described, especially following the use of aminoglycoside antibiotics.[9,12,13] Certain diuretics and other medications, including amphotericin B, cyclosporine, and cisplatin, have also been associated with BLS.[9,13] It is unclear how prolonged use of colistin can cause such tubulopathy.

In vitro electrophysiological studies have demonstrated that prolonged exposure to colistin can directly damage mammalian urothelium by interfering with transepithelial conduction.[2,9,14] Also, similarly to aminoglycosides, colistin may directly activate the calcium-sensing receptor in the medullary thick ascending loop of Henle, resulting in hypokalaemic metabolic alkalosis and hypomagnesaemia.[2,9,13] This may also result in hypercalciuria and lower-than-normal serum calcium levels.[2,9,13]

In the 5th week of IV colistin treatment, started on the 30th day of treatment, the patient started to develop persistent severe hypomagnesaemia, hypokalaemia, metabolic alkalosis, and polyuria, but serum calcium level, corrected for albumin, was normal. The patient was not taking any diuretics or other tuberculostatic medications. During readmission, the patient received IV vancomycin for 7 days from the 22nd to the 28th day of IV colistin therapy. However, the patient developed the aforementioned electrolyte disturbances 2 days after vancomycin was stopped. In addition, a review of the literature revealed that vancomycin-induced nephrotoxicity has been described as acute kidney injury resulting from acute interstitial nephritis or acute tubular necrosis.[15,16] The authors were not able to find any data suggesting tubulopathy associated with vancomycin use in the absence of elevation of creatinine or reduction in GFR. Colistin has been associated with hypokalaemia,[9,17] while other electrolyte disturbances are not well associated. In the patient, fraction excretion of magnesium was 24%, suggestive of urinary magnesium loss, along with polyuria with around 4.5 L of urine output daily. Urine potassium, calcium, and chloride were not analysed, which is a limitation of the case; however, there was no evidence of electrolyte loss from the gastrointestinal tract and no change in frequency or consistency of stools. Aggressive daily IV repletion of electrolytes and IV hydration were required to maintain metabolic balance. It was only after the cessation of IV colistin use after 6 weeks of treatment that the patient's metabolic panel started showing consistent improvement.

Colistin-induced nephrotoxicity is shown to be dose and duration dependent.[2,7,18,19] As noted, the nephrotoxicity associated with colistin has mainly been reported as renal failure and deteriorating renal function in the form of an increase in serum creatinine, or decrease in GFR.[2,5-8] Studies have also focussed on the need for renal replacement therapy.[2,5-8] Tubular dysfunction or tubulopathy associated with

colistin use is not well described. In this case, the patient received colistin for 6 weeks, while in another two reported cases of colistin-associated acquired BLS, the adult patient received the treatment for 23 days and the preterm infant received the drug for 26 days.[3,9] This may indicate that prolonged use of IV colistin, especially for >3 weeks, can result in tubulopathy. Patients may experience symptoms related to electrolyte disturbances, such as muscle cramps, fatigue, paraesthesia, or muscle spasms. Signs of volume depletion from polyuria may be present. Some patients may also develop ileus from hypokalaemia, and dyselectrolytaemia can predispose the patient to dysrhythmias. Therefore, the metabolic panel should be analysed periodically in those receiving IV colistin therapy for >2 weeks.

Reducing duration of treatment in certain infections can decrease the incidence of tubular dysfunction associated with colistin use.[9] Additionally, the dosage of colistin administration should be adjusted for tubulopathies beside serum creatinine level and/or GFR.[9] Finally, the decision to stop colistin treatment based on renal dysfunction must be weighed against the consequences of withholding a potentially life-saving antibiotic.[2,9] In this case, due to the patient's complicated and advanced medical problems, the infectious disease specialist decided to finish the course of antibiotics for 6 weeks despite the tubulopathy that developed in the 5th week of therapy.

CONCLUSION

Renal tubular dysfunction associated with IV colistin use should be kept in mind, especially while administrating the antibiotic for a prolonged period. More pharmacological studies are needed to determine the optimal dosing regimen with colistin use to achieve adequate antibacterial activity while minimising associated toxicities.[3,9] Finally, mild and reversible side effects developing with the medication administration should not preclude the patients from receiving the treatment for the course, as it may be the best option available against certain life-threatening infections.

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