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Review of

ERA-EDTA 2017

Madrid, Spain

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NEPHROLOGY

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NEPHROLOGY 5.1
JULY 2017

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Welcome

Hello, and a warm summer's welcome to *EMJ Nephrology 5.1*, which provides a plethora of content from the field of nephrology. Inside, we feature a thorough review of the ERA-EDTA Congress 2017, which took place in Madrid, Spain. We also include a number of abstract reviews of research showcased at this event, penned by the presenters themselves. The second part of the journal is devoted to peer-reviewed papers provided by renowned members of the nephrology community, which cover topics ranging from acute kidney injury to kidney transplantation.

ERA-EDTA 2017, which took place over 4 glorious days in June, saw a myriad of research presented, and we showcase some of the most notable sessions in our congress review section. This includes a look at a biomarker of premature vessel ageing in chronic kidney disease patients, news of a potential first specific therapy for immunoglobulin A nephropathy, and a study analysing the impact of home-based exercise in dialysis patients.

Following on from this is the interviews section of the journal, in which three members of the *EMJ Nephrology* Editorial Board discuss their work, research interests, and general take on the current state of the field. These are not to be missed! There is also our abstract review section, which contains in-depth summaries of presentations made at the ERA-EDTA Congress. Amongst many fascinating reviews, there is a retrospective study evaluating the outcomes of acute kidney injury patients admitted to a nephrology department in Portugal, and an analysis of nutritional status and dietary habits among chronic kidney disease patients in conservative treatment.

> "The field of nephrology is in the midst of a very exciting period of growth and discovery..."

Turning to the articles section, our Editor's pick for this edition is provided by Dhanapriya et al., who have outlined the epidemiology, aetio-pathogenesis, clinical presentation, diagnosis, treatment, and prevention of community-acquired acute kidney injury in tropical regions. Additionally, van Doorn reviews particular issues associated with acute kidney injury in critically ill patients and Azim et al. discuss various types of intra-abdominal candidiasis. These are just a few of the papers that are contained in this edition of *EMJ Nephrology*.

We hope that you enjoy reading this journal, and that it will not only prove to be an interesting read, but also help you in your clinical practice and research. The field of nephrology is in the midst of a very exciting period of growth and discovery, and we hope that this is displayed throughout the journal.

Spencer Gore

Director, European Medical Journal

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References: **1.** Foley RN, Parfrey PS, Kent GM, Harnett JD, Murray DC, Barre PE. Long-term evolution of cardio myopathy in dialysis patients. *Kidney Int.* 1998;54(5):1720–1725. **2.** Rocco MV, Lockridge Jr. RS, Beck GJ, et al. The effects of frequent nocturnal home hemodialysis: the Frequent Hemodialysis Network Nocturnal Trial. Kidney Int. 2011;80(10):1080-1091. **3.** Nair S. et al. New European Evidence with Home HD Patients: 12 months follow-up in KIHDNEy cohort. Presented at 54th ERA-EDTA conference 2017, Madrid. **4.** Goffin E. et al. Mineral & Bone Disorders and Serum Phosphorus: we can free diet without increasing pill burden! Presented at 54th ERA-EDTA conference 2017, Madrid.

Foreword

Prof Norbert Lameire

Emeritus Professor of Medicine and Nephrology, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium.

Dear Readers,

It is a great pleasure to welcome you to this 2017 issue of *EMJ Nephrology.* As in the past, this issue contains a number of outstanding, high-level, educational contributions that will certainly attract the attention not only of nephrologists, but also of any other medical disciplines interested in acute and chronic kidney diseases. As always, all papers were externally reviewed, guaranteeing the scientific accuracy of their content.

A wide range of topics is covered, including the rather exceptional but fascinating group of diseases termed C3 glomerulopathies and more frequent kidney diseases, like polycystic kidney disease and acute kidney injury (AKI). The unravelling of the molecular pathways involved in the pathogenesis of cyst formation and the derived therapeutic possibilities of autosomal dominant polycystic kidney disease is elegantly described in this issue. AKI is associated, still, with poor short-term and long-term outcomes in critically ill patients, in the developed world, but has an even more dramatic impact in low income, mostly tropical, countries. This issue of the journal presents two in-depth reviews on several aspects of AKI. Two additional reviews cover the metabolism and clinical importance of vitamin D after kidney transplantation and the perplexing diagnostic and therapeutic consequences of intra-abdominal candidiasis.

“A wide range of topics is covered, including the rather exceptional but fascinating group of diseases termed C3 glomerulopathies and more frequent kidney diseases, like polycystic kidney disease and acute kidney injury (AKI).”

This issue is published shortly after the 54th, highly successful, congress of the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) held in Madrid, Spain.

Besides the traditionally outstanding invited plenary lectures, symposia sessions covering the broad field of nephrology, and numerous mini-lectures on several topics of recent interest, this congress offered, again, the opportunity for young, basic, and clinical investigators to present their results in the format of many oral and poster presentations. It was also rewarding to see, at this congress, the participation of a growing number of North American lecturers and Chinese investigators.

The *EMJ Nephrology* Editorial Board wishes you a pleasant reading experience.

Yours sincerely,

Prof Norbert Lameire

Emeritus Professor of Medicine and Nephrology, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium; Past Chairman of the European Kidney Health Alliance (EKHA).

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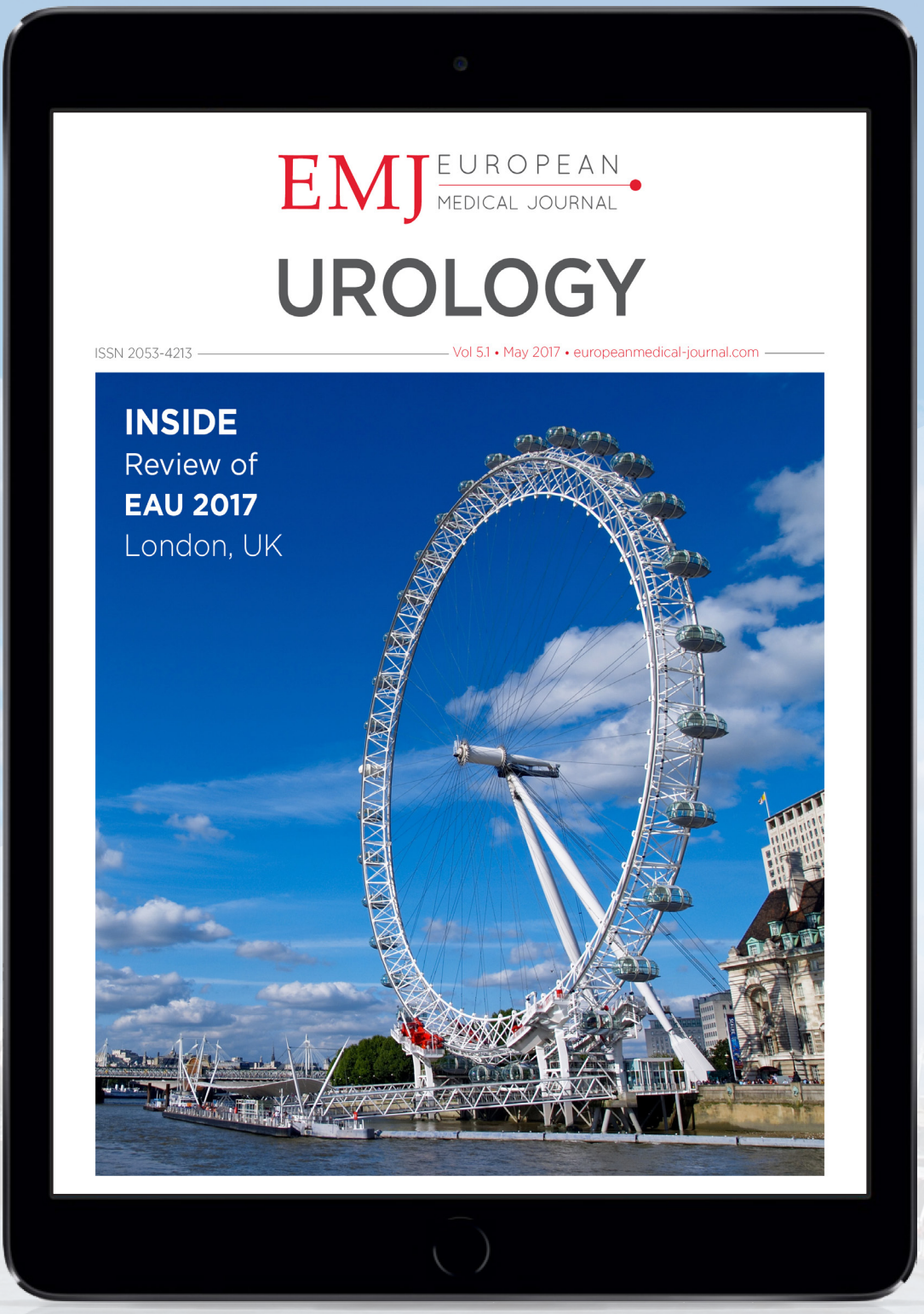

Featured inside:

CONGRESS REVIEW

Review of the 32nd Annual European Association of Urology (EAU) Congress, held in London, UK, 24th–28th March 2017

INTERVIEWS

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ERA-EDTA ANNUAL CONGRESS 2017

IFEMA FERIA DE MADRID,
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3RD–6TH JUNE 2017

Welcome to the European Medical Journal review of the 54TH Annual Meeting of the European Renal Association - European Dialysis and Transplant Association Congress

The 54th European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) Congress took place in the beautiful city of Madrid, and the Spanish capital was a truly fitting venue for this prestigious medical event. It is the place where the renowned Nobel Prize winning neuroscientist, Santiago Ramón y Cajal, made some of his most seminal findings, and, in keeping with Madrid being the highest capital city in Europe, as it is on a plateau 650 metres above sea level, participants were treated to some sky-high sessions during the 4-day event.

There were >300 expert speakers from >100 different countries who descended upon Madrid for the congress, which included 61 symposia, 4 plenary lectures, and 37 free communications sessions covering all aspects of the nephrological spectrum that kept the delegates engrossed in the proceedings. During an action-packed opening ceremony, ERA-EDTA President Prof Andrzej Więcek took some time to explain the enormous growth in popularity of the society and its congress: "The number of members of ERA-EDTA is continuously growing, and recently our number exceeded 7,400 members. With regards to the number of abstracts submitted to the congresses during the last 6 years, we received here in Madrid almost 2,500 abstracts, which is a quite similar number to the previous years, and the number of accepted abstracts is above 1,900, which is almost at the top of the list over the last 6 years." He also discussed some of the most prevalent topics that the abstracts covered, including an exciting new category: 'Patient Education, Research, and Training in Nephrology'.

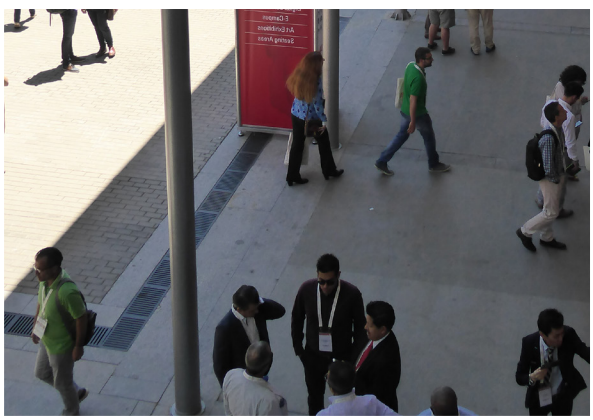
A number of prestigious awards recognising significant contributions to the field were given out at the opening ceremony. Prof Dontscho Kerjaschki (Vienna, Austria) took the prize for 'Outstanding Basic Science Contributions to Nephrology', and Prof Giuseppe Remuzzi (Bergamo, Italy) was presented with the award for 'Outstanding Clinical Contributions to Nephrology'. Prof Peter Stenvinkel (Stockholm, Sweden) was handed the prize for 'Outstanding Educational Contributions to Nephrology, Prof Jonathan G. Fox (Glasgow, UK) was acknowledged for 'Outstanding Contributions to ERA-EDTA', and the Stanley

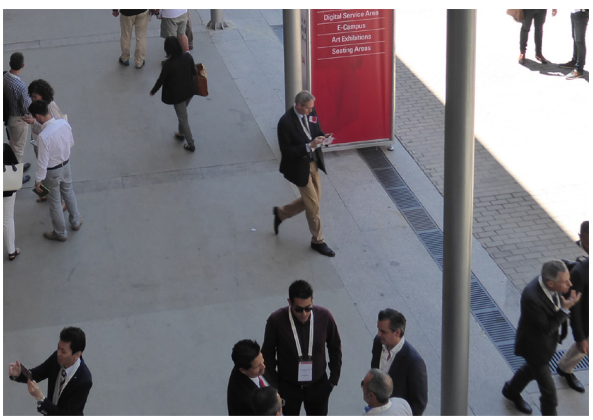
Sheldon Award for Young Investigators went to Dr Albertien van Eerde (Utrecht, Netherlands). Additionally, an ERA-EDTA Honorary Membership was awarded to Dr François Berthoux (St. Etienne, France). Attendees at the ceremony were also treated to a fascinating lecture by Prof Juan Carlos Izpisua Belmonte entitled: 'New approaches towards kidney regeneration'.

As expected, the medical science on offer was of the highest possible standard, with numerous sessions tackling some of the most prescient and challenging issues in the field. One session looked in depth at the topic of ageing in chronic kidney disease patients. These patients display significantly more discrepancies between chronological and biological age than those with most other diseases, and this is clearly a vital area for further research. Another looked at a particularly difficult challenge in Europe in the modern age: that of care for the elderly, with a focus on kidney care, including a discussion on the use of advanced care planning. There was also a fascinating session on the Dialysis Outcomes and Practice Patterns Study (DOPPS). This programme began in 1996 with the goal of understanding haemodialysis facility practices and informing people of the best practices in haemodialysis care and has grown hugely over the years, with 23 countries now participating. In this session, the important work of the programme and its recent research was explained to the audience.

We hope that you enjoy our review of this year's ERA-EDTA Congress, which was an informative and exciting event for all nephrology professionals in attendance. In this section, we review a number of studies that were presented on areas such as pathology and treatment options for conditions including lupus nephritis, chronic kidney disease, and glomerulonephritis. Next year's ERA-EDTA Congress takes place in Copenhagen, Denmark, and we hope to see you all there!

> "The number of members of ERA-EDTA is continuously growing, and recently our number exceeded 7,400 members."





Voclosporin Improves Complete Remission Rates in Lupus Nephritis Patients

COMPLETE remission in patients with lupus nephritis was found to be much more likely after treatment with low-dose voclosporin, a calcineurin inhibitor, in addition to standard immunotherapy, compared with placebo. These results were from the AURA-LV trial and were reported on in an ERA-EDTA press release dated 4th June.

This double-blind Phase II trial enrolled 265 patients who had active lupus nephritis and randomised them to either placebo, high-dose voclosporin (39.5 mg twice-daily), or low-dose voclosporin (23.7 mg twice-daily). In addition, patients in all study arms were treated with 2 g per day of mycophenolate mofetil and rapidly tapering steroid doses. The trial's primary outcome was the achievement of complete renal remission (defined as urine protein-creatinine ratio ≤0.5 mg/mmol and either an estimated glomerular filtration rate ≥60 mL/min/1.73 m^2 or no decrease in the baseline estimated glomerular filtration rate of ≥20% in the presence of low-dose steroids), which was assessed at Week 24. An assessment of the efficacy of voclosporin compared with placebo was made at Week 48 and was the secondary outcome.

The trial found that, at Week 24, 32.6% of patients treated with low-dose voclosporin achieved complete renal remission (odds ratio [OR]: 2.03; p=0.045). The corresponding figure in the placebo group was 19.3%. At Week 48, complete renal remission was higher in both voclosporin arms compared with the placebo arm (low-dose OR: 3.21; p<0.001; high-dose OR: 2.10; p=0.026). Also, at Week 48, no significant differences in renal function were identified. Overall, there were 13 deaths, and most of these deaths took place during the first 2 months of the study. Ten patients died in the low-dose group, 2 in the high-dose group, and 1 in the control group. The trial investigators believed that none of the deaths were related to voclosporin.

Speaking about the AURA-LV trial, the lead investigator, Dr James Tumlin, Southeast Renal Research Institute, Chattanooga, Tennessee, USA said: "This study demonstrates that voclosporin has positive additive effects on lupus nephritis with a rapid reduction of oral steroids. These promising data are a basis for a Phase III study to validate the efficacy of low-dose voclosporin in lupus nephritis."

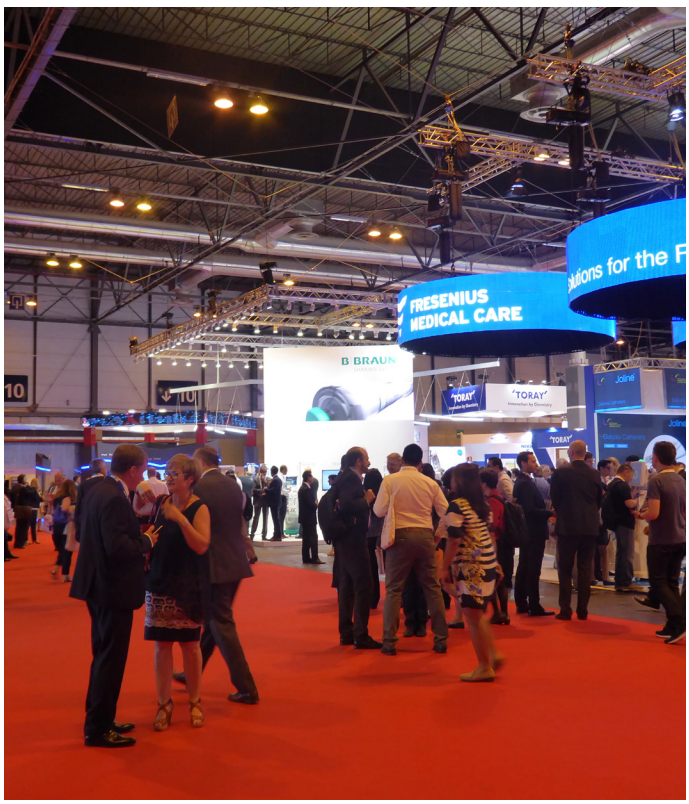
> "This study demonstrates that voclosporin has positive additive effects on lupus nephritis with a rapid reduction of oral steroids."

Biomarkers for Premature Ageing in Patients with Chronic Kidney Disease

ARTERIAL expression of the cyclin-dependent kinase inhibitor 2A/B (*CDKN2A/B*), and its related protein p16^{INK4a}, serves as a biomarker of premature vascular ageing in patients with chronic kidney disease (CKD), suggests a new study by researchers from the Karolinska Institute, Stockholm, Sweden, reported in an ERA-EDTA press release dated 5th June.

Patients with CKD exhibit a pronounced discrepancy between chronological age and biological age, more so than in all but a few other diseases, presenting an excellent opportunity to study premature vascular ageing. Furthermore, CKD patients present with a progeric vascular phenotype that is very difficult to model in animals. Several elements within the uraemic milieu are connected to premature ageing, including increased allostatic load (inflammation and oxidative stress); pro-ageing factors, such as hyperphosphataemia, angiotensin 2, and sodium; and defective anti-ageing protective mechanisms, such as vitamin D deficiency and nuclear lamina defects. Indeed, when CKD has advanced to end-stage renal disease, the risk of cardiovascular mortality is greatly increased, and occurs in much younger patients, because of vascular calcification and ageing.

> “Thus, *CDKN2A*/p16^{INK4a} is a biomarker of premature vessel ageing in CKD patients. Now we need to find out if it could also be a therapeutic target to address cellular senescence.”



Proteins coded by *CDKN2A/B* function as part of the mechanism to keep cells in a state of growth arrest. Therefore, because the expression of the gene increases as a function of increasing cellular stress and organismal ageing, and cellular senescence increases with age, *CDKN2A/B* appears to be an excellent biomarker for biological age. Now, by analysing arterial biopsies from 61 CKD patients undergoing living donor renal transplantation, researchers have observed that, in the uraemic milieu, increased expression of CDKN2A/p16^{INK4a} is associated with vascular progeria, independent of chronological age. A previous study, conducted on mice, had identified p16^{INK4a} as playing a role in the calcification and ageing of vascular smooth muscle cells, but this new study represents the first time such age-related findings were made in human arterial uraemic tissue.

"Thus, *CDKN2A*/p16^{INK4a} is a biomarker of premature vessel ageing in CKD patients. Now we need to find out if it could also be a therapeutic target to address cellular senescence," explained Prof Peter Stenvinkel, Karolinska Institute.

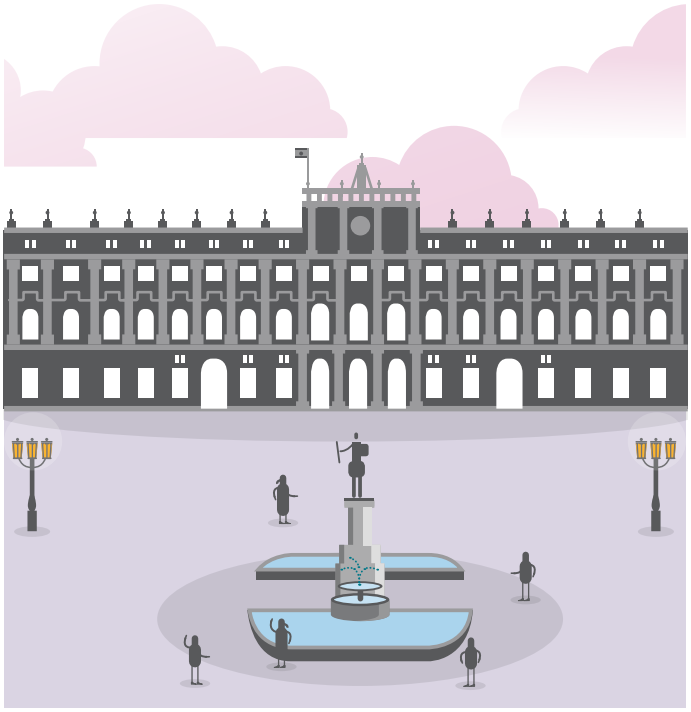
Decreasing Serum Phosphate Levels May Reduce Mortality

REDUCING serum phosphate levels could reduce relative mortality by 12%, according to the results of the COSMOS study, led by researchers from the Bone and Mineral Research Unit, Hospital Universitario Central de Asturias, Oviedo, Spain, and reported on in an ERA-EDTA press release dated 4th June. The proper functioning of the kidneys is integral to phosphate regulation, so patients with chronic kidney disease are particularly susceptible to the increased risk of cardiovascular complications associated with high phosphate concentrations.

> “For the first time, using a COSMOS analyses which mimics as much as possible what happens in randomised clinical trials, it was found that the reduction of serum phosphorus in dialysis patients may render the expected benefits, as it is associated to better survival.”

The study observed 6,797 haemodialysis patients, randomly selected from 227 centres across Europe, and sought to identify the association between reductions in serum phosphate levels and the relative risk of mortality. Patients were observed for six periods of 6 months, and researchers found that reducing serum phosphate (-1.1 mg/dL) towards a target range of 3.6–5.2 mg/dL, from a mean of 6.5 mg/dL, was linked to a 12% reduction in the relative risk of mortality.

This study also identified the significance of the timing of blood sample withdrawal, finding that samples taken post-weekend displayed significantly higher phosphate levels ($p>0.001$) than those taken midweek. Crucially, this aspect of the analysis also indicated an association between serum phosphate levels, including the safest ranges, and the lowest risk of mortality; this is an important discovery that is likely to influence the guidelines for clinical management of hyperphosphataemia.



“For the first time, using a COSMOS analyses which mimics as much as possible what happens in randomised clinical trials, it was found that the reduction of serum phosphorus in dialysis patients may render the expected benefits, as it is associated to better survival. In addition, the analyses showed that the time of blood withdrawal (related to the extent of the intradialytic period) matters as influences not only serum phosphate but also its association with survival. This aspect should be considered in future guidelines for its important clinical implications,” explained Prof Jorge Cannata-Andia and Dr Jose Luis Fernández, Hospital Universitario Central de Asturias.

Targeted-Release Formulation Budesonide Reduces Proteinuria

A NEW target-release formulation (TRF)-budesonide may be the first specific therapy for immunoglobulin A (IgA) nephropathy. The formulation enables accurate delivery of budesonide to the intestine, where it selectively targets the mucosal immunity, upstream of disease manifestation, whilst restricting systemic glucocorticoid absorption. The findings of the NEFIGAN trial were reported in an ERA-EDTA press release dated 4th June 2017.

The NEFIGAN study was a randomised, double-blind, placebo-controlled Phase IIb trial investigating the addition of TRF-budesonide

(16 mg/day or 8 mg/day) or placebo. Patients were randomised 1:1:1 and stratified by baseline urine protein creatinine ratio (UPCR). The trial's purpose was to assess the safety and efficacy of delivery TRF-budesonide to the distal ileum of the intestine in patients with a confirmed diagnosis of IgA nephropathy.[1]

> "The observed beneficial effect was additive to optimised RAS blockade and supports the use of TRF-budesonide as adjunct therapy in patients with IgA nephropathy with persistent proteinuria."

Commenting on the study objectives, Prof Bengt C. Fellström, Uppsala University Hospital, Uppsala, Sweden, explained: "We wanted to know if the additional therapy with TRF-budesonide leads to a better disease control." He continued: "Our rationale was that this novel targeted therapy for IgA nephropathy patients that blocks disease manifestation could further improve outcomes."

At 9 months, results showed a 24.4% decrease in mean UPCR from baseline in both TRF-budesonide study arms. For patients randomised to the TRF-budesonide 16 mg/day arm, 24-hour urine protein excretion and proteinuria in the form of UPCR dropped by ~30%, in comparison to the control group assigned to placebo. A further meta-analysis indicated that there was a substantial association between end-stage renal disease outcome and reduction in proteinuria. Incidences of adverse effects were similar across treatment arms.

"The observed beneficial effect was additive to optimised RAS blockade and supports the use of TRF-budesonide as adjunct therapy in patients with IgA nephropathy with persistent proteinuria," concluded Prof Fellström.

REFERENCES

1. Fellström BC et al.; NEFIGAN Trial Investigators. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. Lancet. 2017;389(10084):2117-27.

Biomarkers for Immunosuppressive Treatment Investigated

GLOMERULONEPHRITIS, an inflammation of the kidneys and one of the most prevalent causes for young adults requiring dialysis, has been put under the microscope in a recent study reported on in an ERA-EDTA

press release dated 4th June. The aim of the study was to discover whether it is possible to ascertain which patients might respond well to the traditional immunosuppressive drugs and which could be treated with supportive therapy, which results in fewer side effects.

> “The findings suggest that patients with high Gd-IgA1 are high-risk patients and that the pre-treatment Gd-IgA1 level might be a good biomarker to stratify those patients who are in need of more intense treatment.”

Supportive therapy includes maximised antihypertensive and antiproteinuric medication and can be very effective for a lot of patients; however, immunosuppression has been shown to be more effective in regard to the higher percentage of patients who achieve clinical remission through this approach. Immunosuppressive treatment includes corticosteroids and sometimes also cytotoxic drugs and can lead to a higher risk of infection during treatment as well as a plethora of other very severe side effects including osteoporosis, a decrease in muscle function, and hyperglycaemia.

The team, led by Prof Jürgen Floege, Division of Nephrology, University of Aachen, Aachen, Germany, utilised data from the STOP-IgAN trial and demonstrated that higher levels of galactose-deficient immunoglobin (Gd-Ig) A1 was associated with a poor renal outcome from IgA nephritis. In the STOP-IgAn study, 104 patients did not respond to supportive therapy. Of these patients, the team found that those who went on to develop end-stage renal disease (ESRD), and those who did not achieve clinical remission had higher baseline Gd-IgA1 levels than those who did not develop ESRD. In the ESRD developing group, patients had an estimated glomerular filtration rate loss of >30 mL/min/1.73 m^2 at the end of the trial.

Prof Floege commented: "The findings suggest that patients with high Gd-IgA1 are high-risk patients and that the pre-treatment Gd-IgA1 level might be a good biomarker to stratify those patients who are in need of more intense treatment."

Home-Based Exercise Improves Functional Status in Dialysis Patients

FUNCTIONAL STATUS was improved in dialysis patients by a home-exercise programme, according to the results of the EXCITE trial, which were published in an ERA-EDTA press release dated 4th June. Prior to the EXCITE trial, the only studies carried out to analyse the impact of physical activity on haemodialysis patients had focussed on exercise that was supervised either at the dialysis session or in hospital. It was thought that if the exercise programme was home-based, this would enhance feasibility and patient adherence.

> "In conclusion, these results indicate that a simple, personalised, home-based, low-intensity exercise programme managed by dialysis staff improves physical performance and quality of life, and reduces short and long-term risk of hospitalisation in patients who maintain a high adherence."

This was the context of the EXCITE trial, which was conducted to investigate the impact of a home-based, personalised, walking exercise programme on the functional status of dialysis patients. The trial randomised 145 patients to walking exercise and 151 to a control group (N=296). Adherence to the exercise programme was defined as completing >60% of the exercise sessions during the first 6 months. The assessment of functional status was based on the Six Minute Walking Test and the Sit-to-stand-to-sit Test. A baseline assessment was carried out initially and a second assessment was made at Month 6. While the two study arms had comparable test scores at baseline, the Month 6 assessment found that the walking exercise group demonstrated significant improvements in either the Sit-to-stand-to-sit Test or the Six Minute Walking Test. However, no changes were found in the control group.

Furthermore, a per protocol analysis of time to first event demonstrated that the patients in the exercise arm had a significantly reduced risk of hospitalisation during the trial (hazard ratio [HR]: 0.46; 95% confidence interval [CI]: 0.22–0.97; p=-0.04). This analysis was also conducted after 36 months and found a 29% long-term risk reduction in hospitalisation (HR: 0.71; 95% CI: 0.50–1.003; p=0.05).

The trial's lead investigator, Prof Francesca Mallamaci, Division of Nephrology, Ospedali Riuniti, Reggio Calabria, Italy, spoke further about the findings, saying: "In conclusion, these results indicate that a simple, personalised, home-based, low-intensity exercise programme managed by dialysis staff improves physical performance and quality of life, and reduces short and long-term risk of hospitalisation in patients who maintain a high adherence."

Expanded Haemodialysis Therapy Effective When Paired with Dialyser

EXPANDED haemodialysis therapy (HDx) has been shown to be effective in the removal of toxins from the blood when used in conjunction with a novel THERANOVA dialyser (Baxter International Inc., Deerfield, Illinois, USA), as reported in a press release dated 5th June. The new therapy and dialyser combination boasts a range of features that could be beneficial to clinics treating patients for kidney failure. These include broadening the range of toxins that can be filtered from the blood, as well as having a straightforward interface for users and compatibility with existing haemodialysis technology. Two independent studies were presented at this year's congress that compared the therapy to haemodiafiltration (HDF), another type of dialysis that is not suitable for all patients because it requires ideal vascular access, with promising results.

The first of the studies assessed 10 patients over 12 months. The patients were treated initially with HDF for 6 months, followed by HDx with use of the THERANOVA 500 dialyser for a further 6 months. The team analysed the levels of urea, creatinine, beta-2 microglobulin, and myoglobin in the patients' blood every 2 months, which are just some of the toxins that haemodialysis is designed to filter from the blood. Results showed that HDx with therapy removed the toxins with a similar efficacy to high-volume HDF treatment and also maintained albumin levels.

> "We see the new HDx therapy as an excellent option for our patients, in particular in frail haemodialysis patients with a central venous catheter."

In the second study, pre and post-treatment samples were measured for levels of urea, creatinine, beta-2 microglobulin, myoglobin, haemoglobin, albumin, and total serum protein in eight patients over a period of 5 weeks. The team, from Garbagnate, Italy, found that removal rates of small and medium-sized molecules (beta-2 microglobulin, myoglobin) were comparable between HDx and high-volume HDF, with albumin levels maintained. Dr Ugo Teatini, ASST Rhodense, Garbagnate, Italy, commented: "We see the new HDx therapy as an excellent option for our patients, in particular in frail haemodialysis patients with a central venous catheter."

VDRA Treatment Did Not Reduce Risk of CVD Events in Dialysis Patients

RESULTS from the Japan Dialysis Active Vitamin D (J-DAVID) multicentre study indicated that treatment with oral vitamin D receptor activators (VDRAs) did not decrease risk of cardiovascular disease (CVD) events in haemodialysis patients, regardless of parathyroid hormone levels, according to a press release issued during the ERA-EDTA congress dated 4th June 2017.

Vitamin D activation is severely impaired in those with end-stage renal disease. Previous observational studies have indicated that all-cause mortality and cardiovascular risk is reduced in patients treated with VDRAs. The aim of the J-DAVID study was to test this hypothesis, assessing dialysis patients' risk of CVD events (primary study endpoint) and all-cause mortality (secondary study endpoint). Patients with a normal serum parathyroid hormone level (N=976) were randomised (ratio 1:1), across 108 trial sites, to receive either oral alfacalcidol treatment (starting dose 0.5 µg/day) or treatment without VDRAs; the follow-up duration was 48 months.

> "Based on our results there is no rationale for a VDRA therapy in dialysis patients with normal serum parathyroid hormone level."

During study follow-up (mean duration: 1,305 days) a total of 787 serious adverse events were reported. Twenty patients did not undergo primary analysis as they were lost to follow-up, 188 patients experienced the primary outcome, and 169 patients had the secondary outcome.

The lead study author, Prof Tetsuo Shoji, Osaka City University, Osaka, Japan, explained that the study showed no beneficial effect for this therapy. Contrary to the original hypothesis, intention-to-treat analysis actually indicated that cardiovascular risk increased, although this did not reach statistical significance (p=0.127).

Raised fibroblast growth factor 23 and calcium levels are known to be associated with increased cardiovascular risk; it is speculated that this may be the cause of the observed increase in cardiovascular risk. "Thus, these effects might have outweighed potential beneficial effects of the supplementation of active vitamin D," explained Prof Shoji. He concluded: "Based on our results there is no rationale for a VDRA therapy in dialysis patients with normal serum parathyroid hormone level."

Merits and Drawbacks of Risk Prediction Tools in Nephrology Debated

RISK prediction models in nephrology is a controversial topic, and two opposing views about the concept were aired during a lively discussion, which was described in an ERA-EDTA press release dated 3rd June 2017.

Strongly in favour of the use of predictive tools was Prof Navdeep Tangri, Seven Oaks Hospital, Winnipeg, Canada, whose working group created the Kidney Failure Risk Equations (KFREs) in 2011, with the aim of forecasting the need for dialysis and transplant in chronic kidney disease patients over the next 5 years.

To help make his argument, Prof Tangri presented a case study that made use of a threshold risk of 3% over 5 years as a criterion for nephrology referral. Within nephrology care, thresholds of 20% and 40% over 2 years were presented as criteria for starting access placement and dialysis modality education. He also showcased patient-focussed decision aids that seek to deliver improved information on kidney failure risk during the clinical encounter. It is hoped that these aids will enhance health literacy and shared-decision making, ultimately improving quality of life in such patients.

Opposing this point of view was Prof Friedo W. Dekker, Leiden University Medical Center, Leiden, Netherlands. He argued that most prediction models that have been created have not been utilised in clinical practice on a large scale, as the majority have been poorly reported and, in many cases, inappropriate methods have been used in their development. Additionally, he pointed out that it is a rare occurrence for impact studies to report improved clinical outcomes through the use of a prediction model. He therefore stated his preference for researchers to focus on validation and analysing the impact of existing tools instead of developing further models that are unlikely to ever be utilised in clinical practice.

"Predictive models based on clinical information and/or on old and new biomarkers have unquestionable potential in nephrology. More focus on this blossoming research area is desirable," noted Prof Carmine Zoccali, Ospedali Riuniti, Reggio Calabria, Italy.

> "Predictive models based on clinical information and/or on old and new biomarkers have unquestionable potential in nephrology. More focus on this blossoming research area is desirable."

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Juliette Hadchouel

INSERM UMRS 1155, Hôpital Tenon, Paris, France.

Q: What do your daily tasks and roles involve as a Research Director and Group Leader at INSERM UMRS 1155?

A: Like any full-time INSERM researcher, I have various tasks. The first is to perform experiments! I unfortunately do not have a lot of time to do this, but I try to conduct experiments as much as possible. The second, most important task, is to be available to answer questions and solve problems for the people working in my group. At the moment, I supervise a PhD student and a Master's student. Finally, I apply for grants, and I do a little bit of teaching for Master's and Bachelor's students.

Q: Could you provide us with details about your career path to date? In terms of your career choices and opportunities, how did you end up where you are today?

A: I was initially trained as a veterinary surgeon. I obtained my diploma from the National Veterinary School of Maisons Alfort, Paris, France, in 1994. I then chose to pursue a career as a researcher rather than a clinician. I did my PhD at the Pasteur Institute, Paris, France, in the laboratory of Prof Margaret Buckingham, 'Molecular genetic of Development', where I studied the transcriptional regulation of Myf5, a myogenic factor, during embryogenesis in mice. I then decided to do a postdoctorate in physiology in order to use some of the knowledge I acquired during my studies at the vet school. In 2001, I joined the laboratory of John Mullins, University of Edinburgh, Edinburgh, UK, where I studied the consequences of renin inactivation in mice. After 2 years, I obtained an INSERM permanent position as a full-time researcher in the team of Prof Xavier Jeunemaitre, College de France, Paris, France, where I initiated the project I am still working on: the characterisation of the roles played by the WNK1 kinase in renal physiology and pathology.

Q: Was there anything that particularly drew you towards studying renal physiology in the mouse model?

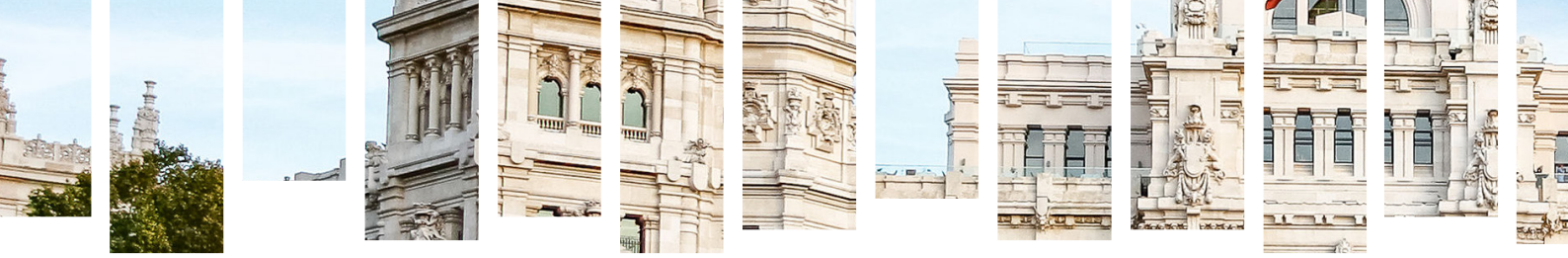
A: As I mentioned above, after spending 5 years studying mouse embryogenesis, I wanted to develop a project that would allow me to have a more integrated view of the animal and use some of the knowledge I acquired during my veterinary studies. I was also a bit frustrated to hear all these beautiful talks about the discovery of mutations in genes, the functions of which were unknown and were not always addressed by the geneticists. That is why I decided to change direction for my postdoctorate and went from developmental biology to physiology. I was then interested by the fact that we still could not fully explain why the chronic intake of a high salt diet leads to the development of hypertension in the population, a link clearly demonstrated by epidemiologists.

Q: What do you believe are some of the most pressing issues to be addressed in 2017 within the field of nephrology? How could these challenges be overcome?

A: Last year, I started a new project aimed at defining the roles played by WNK1 during kidney diseases, in addition to the physiology of ion transport by the distal nephron. I have thus discovered the world of acute kidney injury and chronic kidney disease. There are many research groups working on the subject, who all have identified new factors involved in these diseases. However, I have the feeling that a global picture is missing, which would bring together, and sometimes reconcile, all the data.

Q: How has the field of renal physiology developed since you began your career? Have there been any key changes or significant advancements?

A: My domain, which is the regulation of Na, C, and Cl in the distal nephron, has changed a lot.



In 2001, a collaboration between the groups of Prof Jeunemaitre and Dr Richard Lifton, Yale University, New Haven, Connecticut, USA, showed that familial hyperkalaemic hypertension, a rare form of human hypertension, is caused by mutations in the genes encoding two kinases, WNK1 and WNK4. Ten years later, the same groups identified two new genes that could be mutated in familial hyperkalaemic hypertension patients, *Cullin3* and *KLHL3*. At the time of their discoveries, there were no recorded data in the literature to indicate that any of these four genes could contribute to the regulation of ion transport in the distal nephron and thus blood pressure. Since then, we, and others, have shown that these four genes belong to the same pathway, with *Cul3* and *KLHL3* regulating WNK1 and WNK4. The two kinases regulate multiple ion channels and transporters, the most characterised being the co-transporter NCC. We now better understand how this transporter contributes not only to the maintenance of blood pressure through the regulation of Na and Cl balance, but also to K homeostasis.

Q: When designing an experiment using a mouse model, what factors need to be taken into consideration? Are there any particular challenges to account for?

A: Yes, we take into account that a mouse is a living being! It sounds obvious, but I sometimes have the feeling that researchers forget it. When working with an animal, it is essential to know its physiology and how it reacts to its environment. Any kind of disturbances to its habitat could change the outcome and results of an experiment, for example by inducing stress, which then has multiple repercussions on so many parameters, including the one you are studying.

Q: You have undertaken research in conjunction with international networks before. What opportunities arise from this type of collaboration?

A: One of the nicest opportunities is the opportunity to travel! Thanks to one of the networks, I visited Mexico 2 years ago. More seriously, the French renal physiology community is very small and the international one is not very big. It is therefore important to work together, to exchange ideas, and to criticise our own work (in a constructive manner) to ensure progression in our projects. Also, it is impossible for one lab to master all the techniques. You need the others to make your projects work.

Q: Could you tell us a little about any research you are currently undertaking or hope to undertake in the near future?

A: I am pursuing the characterisation of the roles played by WNK1 in Na and K homeostasis, as there are still some unanswered questions. But WNK1 is expressed in almost every tissue and we know very little about what it does outside the distal nephron. I am currently developing a project aimed at determining if WNK1 is involved in kidney disease.

Q: What has been your proudest achievement so far during your medical career?

A: All the PhD students I supervised have succeeded in obtaining a permanent position in research, which is quite a challenge in France nowadays. On a scientific front, I am particularly proud of an article my group published about the expression of WNK1 splicing variants. It started as a side project for a PhD student, and she took it further than I imagined. It led us to understand why research groups failed to show the activation of NCC by WNK1 *in vitro*, while it was clear *in vivo*. The WNK1 cDNA that everyone used carried a mutation which inhibited the kinase activity. Once we corrected it, the *in vitro* effects were the same as the ones observed *in vivo*.

Q: Finally, what advice would you give to up-and-coming clinicians or researchers with an interest in nephrology?

A: Be patient and be stubborn! But that is true for any research domain. For nephrologists, I would say that it is important to carry on research projects in this field even if they do not appear to be trendy and sexy. It is important for the patients!

> “When working with an animal, it is essential to know its physiology...”

Kathryn Garner

Bristol Renal, School of Clinical Sciences, University of Bristol, Bristol, UK.

Q: Could you tell us a little about your unusual route into specialising in the treatment of kidney diseases?

A: I loved both art and science when I was at school, but I chose to concentrate on art with the thinking that through art I could explore all corners of the universe. I attended Falmouth College of Arts, Falmouth, UK, now known as Falmouth University, at a time when the curriculum had been completely stripped out, allowing students to determine their own course of study. I found inspiration in the biology books in the library and consequently made a large body of work, entitled 'Cell Paintings', inspired by cell microscopy images and stained histology sections in books such as 'Gray's Anatomy'. The fascination with the images and the mysteries surrounding the unfamiliar words in the image captions led me to pursue jobs that enabled me to get close to biology; the first on an insect farm breeding crickets, and then working in an infertility clinic looking through a microscope to analyse human sperm. I studied biology in evening classes, and this eventually led to an undergraduate degree in molecular cell biology and a PhD at University College London, London, UK. A year ago, I seized the opportunity to work alongside world leaders in nephrology at Bristol Renal, University of Bristol, Bristol, UK, which enabled me to apply my expertise in high content imaging to the study and treatment of kidney diseases.

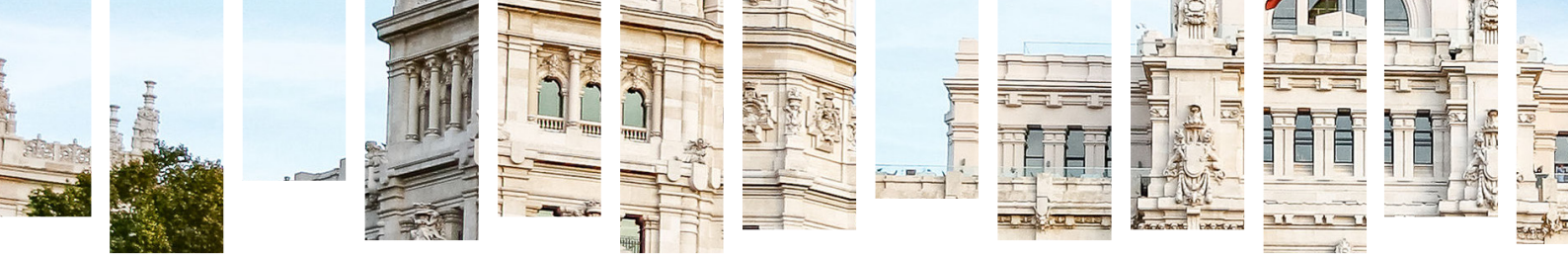
Q: Related to this, you are now using art to inspire and engage the public to take an interest in the treatment of kidney diseases. How has this increased public awareness of kidney disease and what are some future directions of your initiative to help promote awareness?

A: I have exhibited my Cell Paintings widely but have found it difficult to compete with interactive science displays in science fairs, and it is easy for people to walk past artwork in a hospital corridor. I am currently making some sculptures of the glomerulus as hands-on exhibits to accompany a 'Pint-of-Science' event hosted by a couple of my colleagues in Bristol. I am also keen to collaborate with other artists to develop an interactive art installation to discuss kidney disease. But I think art has the potential to reach even further than this, and I am therefore involved in developing a couple of projects that will use the activity of drawing and the making of art as a tool to teach and engage school children with more complex biological processes.

Q: What are the benefits of using interdisciplinary approaches to solve big problems in the healthcare sector? How does your background in fine art inform your current study?

A: I think interdisciplinary approaches are invaluable in solving big problems in the healthcare sector. It is so easy for us to stick to familiar methods within our own field. I think that innovation comes when researchers from different disciplines talk to one another, because their questions can at last be approached from a different perspective. My time at art school developed my skills of self-motivation, independent learning, and discovery. We were taught that art could be anything, that drawing was thinking, and that in this there were no boundaries. This means that if I do not know how to do something, I will figure it out, and if my research needs tools I do not have, my first thought is "How can I make it?". I have found an affinity for genetic engineering and am able to make reporter proteins for my automated fluorescence microscopy experiments and cell surface receptors that uniquely respond to light in the way that I choose.

> "We were taught that art could be anything, that drawing was thinking, and that in this there were no boundaries."



Q: In one of your blog posts, you discussed the idea that 'Science presents a picture of the world which is much richer in content than what the unaided eye discerns'. Could you tell us a bit more about this concept?

A: This is a quote from the philosopher Bas C. van Fraassen's book, 'The Scientific Image'. I like it because it reminds me that there is so much more to the world and to life than what can be viewed on its surface. He goes on to say: "But science itself teaches us also that it is richer than the unaided eye *can* discern." It tells us that through asking questions about how things work, scientists can tell us much more about the world and the way it works than can be imagined. To me the richness comes from having different researchers with different types of interests and experience asking questions. Amongst the Bristol Renal research team, we have clinicians treating patients with kidney diseases working side-by-side with cell biologists who are looking at how the cells of the kidney work and what happens in disease; we also have bioinformaticians, physiologists, and molecular biologists. Together we are providing a richer picture of how the kidney works and how kidney diseases are characterised so that more informed choices can be made when treating patients.

Q: Some of your particular interests lie in diabetic nephropathy and cystinuria. How far has our understanding of these conditions and their treatment developed since you began to study them?

A: In my research, I use automated fluorescence microscopy, which allows me to view lots and lots of cells very quickly. As a team at Bristol Renal, we have pioneered the development of immortalised podocytes that can be grown under laboratory conditions. By growing podocytes in 96-well culture plates, I can test their response to multiple concentrations of a drug or to different drugs in different wells of a plate. I then use computer algorithms to quantify the amounts of particular fluorescent signals in particular parts of individual cells. One characteristic of diabetic nephropathy is that misfolded proteins accumulate in the endoplasmic reticulum, affecting cell viability. I have developed an assay to measure this stress, with the view of carrying out large drug screens to identify novel compounds to prevent it. I am in the process of developing a similar assay for cystinuria. Patients with cystinuria commonly have a mutation in a subunit of an amino acid transport system preventing the channel subunits being trafficked to the plasma membrane of proximal tubular cells or to function properly once there, resulting in the formation of kidney stones in the urine. I hope that my research will aid the discovery of novel therapies to treat this debilitating disease.

Q: What, in your opinion, are the greatest challenges faced by nephrologists today? What developments would you like to see in the future to overcome these challenges?

A: I think that nephrologists are faced with lots of different types of data from many different sources, and knowing how to assimilate these is challenging. I would like to see a change in the way research is carried out and reported, moving further towards larger consortiums of multidisciplinary groups of researchers. This would reflect current improvements in technology, which are generating much larger datasets, requiring the input of lots of different researchers from different specialities. There can be such competition for first-author papers and to publish in leading journals that the true significance of the research findings can be lost. I think that by working together, rather than against one another, we can present a more curated and less subjective message to nephrologists.

Q: You are also involved in the processing of data using computer programs. What are your opinions on the problem of analysing vast amounts of data produced by patients and healthcare professionals alike through devices such as wearable technology?

A: It is becoming easier, now more than ever, to generate large quantities of data, and for this reason I think it is necessary to be very clear as to the purpose of the data collection, what the question is that needs to be answered, and what happens to the data once it has been collected. Methods for carrying out data analysis can be

subjective, and therefore education for researchers on the appropriate ways to analyse data is important. I think that data analysis should be standardised where possible and rigorously checked prior to publishing to prevent misleading messages being disseminated. Perhaps the submission of raw data along with analysed data is key.

Q: What advice would you give to medical students who are interested in pursuing a career in nephrology?

A: Nephrology is a fascinating subject, and I think that, if it is a field that interests them, they should go for it. We host many medical students and clinicians at different stages in their careers, so I would recommend they spend some time in a laboratory setting, carrying out research as part of their training to gain a different perspective on their work.

> “I am also keen to collaborate with other artists to develop an interactive art installation to discuss kidney disease.”

Q: Are there any areas of research that you have not yet had the opportunity to explore and would like to in the future?

A: I can see great scope for the use of high content imaging in nephrology so I am keen to continue to find different problems to solve using this technique. I would like to combine this with mathematical modelling to define new targets for therapeutic intervention in the coming years. I am particularly interested in how pulsatile hormones can affect their target tissues, and therefore would be interested in developing *in vitro* assays to analyse the effects of pulsatile hormones on podocytes in the future.

Q: Are there any specific avenues of research within chronic kidney disease that you feel are under-researched or overlooked that are now at a good stage to research further?

A: I think that now is the time to use systems biology approaches to research, high-throughput methods and ‘omics’ technologies combined with bioinformatics and mathematical modelling to consolidate and build on existing avenues of research.

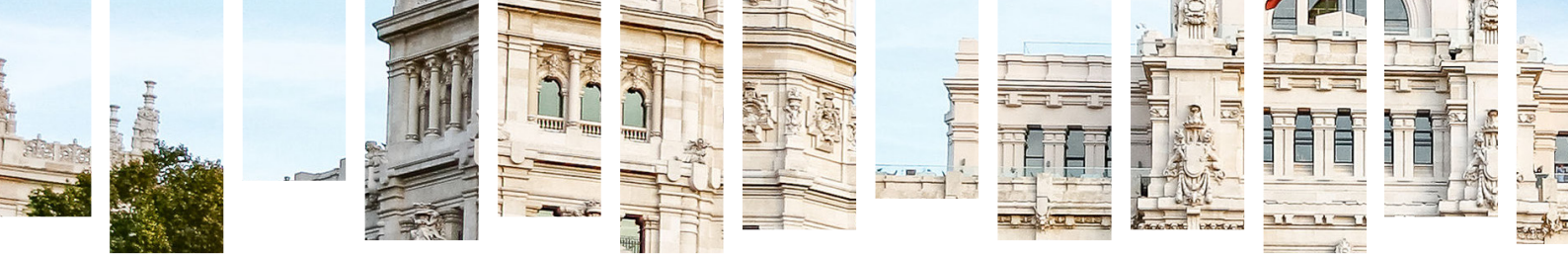
Djalila Mekahli

Pediatric Nephrologist, Pediatric Nephrology and Organ Transplantation, Department of Pediatrics, University Hospitals Leuven; Laboratory of Pediatrics, Department of Development and Regeneration, KU Leuven, Leuven, Belgium.

Q: Could you provide a brief overview of what your role as a paediatric nephrologist at the KU Leuven, Belgium, involves? What are your main responsibilities?

A: I have been a consultant paediatric nephrologist in Leuven University Hospitals since 2009. My work consists mainly of the follow-up of children with renal diseases, dialysis, and renal transplantation, and, also, counselling pregnant women who are carrying a fetus suspected to have a prenatal renal diagnosis. Our department is also responsible for the follow-up of children with liver, intestinal, and multi-organ transplantation. My specific interest and expertise is in the field of renal genetic diseases, more specifically renal cystic diseases. In our hospital, I lead the renal cystic disease programme and have a paediatric autosomal dominant polycystic kidney disease (ADPKD) clinic and I am part of the multidisciplinary clinic of autosomal recessive polycystic kidney disease (ARPKD) and tuberous sclerosis complex (TSC).

> “I have been a consultant paediatric nephrologist in Leuven University Hospitals since 2009.”



> “The ADPedKD requires teamwork and I am so lucky to have great collaborators such as Max Liebau and Stéphanie De Rechter.”

Q: What led you to specialise in paediatric nephrology? Was there a pivotal moment that influenced your decision to move into this field?

A: From a very early stage in my paediatric training, I was fascinated by electrolytes and renal genetic diseases. Moreover, nephrology represents a broad clinical spectrum from acute to chronic, acquired, genetic, and congenital diseases, dialysis, and transplantation. Most importantly, I have been blessed with some great mentors; I have had the chance to work with brilliant paediatric nephrologists, including Prof Pierre Cochat (Lyon, France), Prof Lesley Rees (London, UK), and Prof Franz Schaefer (Heidelberg, Germany), who supported my career and gave me a lot of inspiration. I am very grateful for their mentorship.

Q: Alongside your translational research, you are currently building an international registry; could you provide us with some more information regarding this project?

A: Indeed, my focus in clinical and fundamental research is on ADPKD. Together with my colleagues Max Liebau (Cologne, Germany) and Stéphanie De Rechter (Leuven, Belgium) and with the support of Prof Franz Schaefer, I initiated the ‘ADPedKD’ registry, which is an international web-based database for the longitudinal data registry of children with ADPKD. Its aim is to provide an observational evidence base for unified diagnostic, follow-up, and treatment approaches regarding modifiable disease factors in order to slow disease progression, for example factors such as hypertension and proteinuria. We also aim to establish the clinical presentation and/or bio-markers, predict the risk of early and progressive disease, and potentially lay the foundation for clinical trial patient selection. The scientific activities within ADPedKD will lead to a firm evidence base for the development of clinical practice guidelines and will help to harmonise the quality of care for this patient group.

Q: How have you approached the challenge of finding the time to combine your research with building the international registry? Is there any advice you would give young researchers regarding managing their priorities?

A: Helen Keller said: “Alone we can do so little; together we can do so much.”

The ADPedKD requires teamwork and I am so lucky to have great collaborators such as Max Liebau and Stéphanie De Rechter. It is a real pleasure to share this adventure with them.

But indeed, both time management and prioritisation are important challenges for each researcher. I was, and I am, often overwhelmed; however, over time I learned to manage my agenda in a better way and to devote a few hours per week to my academic and fundamental research tasks.

Q: There is much discussion around whether early genetic screening would be a useful diagnostic tool for ADPKD, as symptoms do not typically manifest until 30 years of age. Considering your interest in the paediatric population, what are your thoughts on this? Would it be feasible to introduce genetic testing of younger patients with a predisposition to developing the condition and what would be the benefits of early diagnosis, if any?

A: ADPKD is indeed the most common hereditary kidney disease and currently has no cure. Most patients progress to end-stage renal disease (ESRD) and require renal replacement therapy at mid-adulthood. Since most patients remain a- or oligo-symptomatic until adulthood, ADPKD is usually regarded as a late-onset disease. However, evidence is accumulating to suggest that renal injury starts early in life, with the formation of renal cysts *in utero*. Moreover, ADPKD patients may display symptoms from a young age. The spectrum of clinical characteristics and presentation in children and adolescents ranges from symptomatic presentation with gross haematuria and hypertension, to the incidental finding of renal cysts

due to other symptoms or screening with imaging, in at-risk asymptomatic individuals. Importantly, it has been shown that hypertension is the earliest and most prevalent systemic feature of ADPKD children occurring in 5–44%. It can present during the newborn or infantile period and correlates with the severity of structural renal disease despite normal renal function. Furthermore, long-term clinical outcomes in children with very early onset (VEO) ADPKD are worse compared to non-VEO ADPKD patients. Significant irreversible destruction of renal parenchyma will occur long before clinical symptoms develop or a loss in glomerular filtration rate is noted. The latter is masked by hyperfiltration and hypertrophy of residual nephrons.

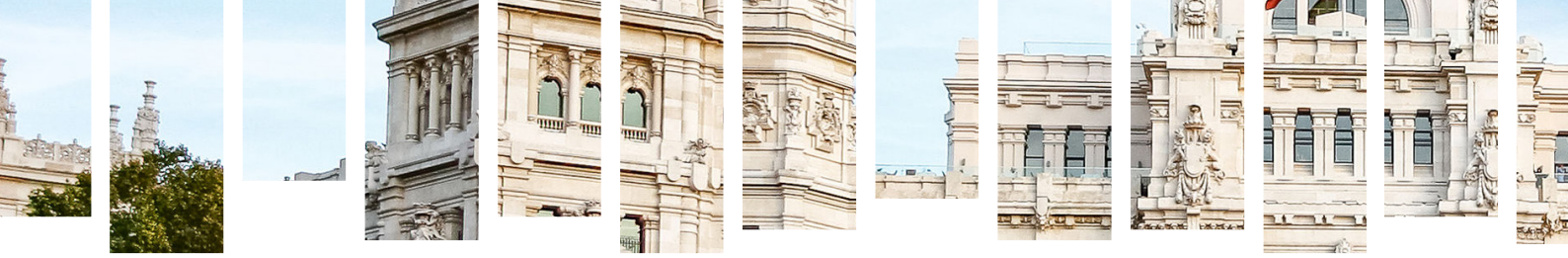
However, until now, it is controversial whether at-risk children should be tested for the presence of the disease and, if so, how this should be done. On the one hand, the absence of an effective cure, the potential psychological stress related to the diagnosis of a chronic progressive disease in the context of affected family members, and the potential financial and legal implications, such as the inability to obtain life or medical insurances, have been put forward against presymptomatic testing. On the other hand, early targeting of modifiable risk factors for disease progression, including hypertension, proteinuria, andurological complications increases the effectiveness of interventions to improve long-term renal survival. This is indirectly supported by the evidence of slower cyst growth, in number and size, in normotensive compared to hypertensive children with ADPKD. Effective blood pressure control from childhood onwards may also improve cardiovascular outcomes in this patient group, who are at high risk of early cardiovascular events.

Furthermore, the recent Kidney Disease: Improving Global Outcomes (KDIGO) recommended routine planning of medical check-ups, with blood pressure measurement and urinalyses in all at-risk children, as a standard of care. However, we recently performed a European survey among paediatric nephrologists, adult nephrologists, and geneticists in order to explore the clinical practices and beliefs towards ethical issues in the management of ADPKD patients. Although we demonstrated that most caregivers support clinical testing for at-risk minors and adults in ADPKD families, we revealed a great heterogeneity in attitudes towards genetic testing and issues related to family planning, such as preimplantation genetic diagnosis. Our present report is of high significance to the ADPKD field, as it demonstrates important differences in the care of ADPKD patients and their families. Our data support the need for a more standardised and multidisciplinary approach to management of ADPKD in order to avoid confusion in the counselling of this population.

Q: You recently published a paper analysing data collected from the European Society for Paediatric Nephrology/European Renal Association-European Dialysis and Transplant (ESPN/ERA-EDTA) registry of ARPKD patients with kidney or combined liver–kidney transplants; do you think that your findings, indicating that combined transplantation results in increased mortality, will affect the way transplantations are approached in the future?

A: Indeed, the finding of our paper on the transplantation strategy in ARPKD is of great importance. We demonstrated in the largest known ARPKD cohort that combined liver–kidney transplantation is associated with increased mortality compared to kidney transplantation and, moreover, it was not associated with improved 5-year kidney transplant survival. However, confirmation of the best transplantation strategy for ARPKD needs to be validated in this very rare condition with scarce data on systematic long-term monitoring of the natural history of both kidney disease and hepatic outcomes. The work of my colleague Max Liebau with his initiative of ARegPKD, an international registry on ARPKD, will be of great interest to better delineate the optimal management in this complex patient population and establish an evidence base for individualised treatment decisions in these patients.

> “From a very early stage in my paediatric training, I was fascinated by electrolytes and renal genetic diseases.”



> “As for my greatest achievement, I am still working on it!”

Q: In your opinion, what is the greatest achievement of your career to date?

A: I am a dreamer and an optimist. Antoine de Saint-Exupery said: “Let your dream devour your life, not your life devour your dream.” In addition, another saying is: “A pessimist sees the difficulty in every opportunity; an optimist sees the opportunity in every difficulty.” They are my main motivators. As for my greatest achievement, I am still working on it!

Vivekanand Jha

Executive Director, The George Institute for Global Health, New Delhi and Hyderabad, India; Professor of Nephrology and James Martin Fellow, University of Oxford, Oxford, UK.

Q: What was your main inspiration for deciding to specialise in the area of kidney disease?

A: Firstly, I was fascinated by the complexity of the renal physiology. Secondly, the speciality did not threaten to turn me from a physician to a practitioner of technology, and thirdly, at the time I was making this choice, it was already possible to transform the life of patients with end-stage kidney failure with dialysis and kidney transplantation, something that did not seem possible for other end-stage organ diseases. Finally, I had excellent role models.

Q: What are your main duties and responsibilities as Executive Director of The George Institute for Global Health? Could you give us a brief description of a typical working day?

A: The George Institute for Global Health is a healthcare research institute with the mission of reducing the burden of premature death and disability through discovery and implementation research, with a focus on disadvantaged populations worldwide. In India, the focus of research is in finding innovative solutions, using technology and manpower restructuring, and bringing essential healthcare to the community. We focus on chronic non-communicable diseases, mental health, trauma and injury, and the health of women and adolescents. We also analyse large datasets to identify gaps in healthcare delivery and trends.

Q: As a prominent member of a number of major international nephrology societies, how important would you say such bodies are in addressing global nephrological health problems?

A: The International Society of Nephrology (ISN) is very conscious of its unique position as the organisation that has a special responsibility towards regions where nephrology care or teaching is minimal or non-existent. With its goal of working towards a future where all people have equitable access to sustainable kidney health, the ISN takes a humanitarian view towards addressing this challenge through its programmes that help to build capacity through training and education; promoting partnerships between developing and developed world regions; improving research; and special programmes, such as the ongoing 0by25 that aims to eliminate all preventable deaths from acute kidney injury by 2025 through its Closing the Gaps initiative that envisages providing care for all patients with kidney disease, and the upcoming dialysis initiative that aims to lay out standards for improving access to ethical dialysis and transplants throughout the world.

> “In India, the focus of research is in finding innovative solutions, using technology and manpower...”

Q: Which World Health Organization (WHO) initiatives have you personally been involved in during your membership of the Expert Advisory Panel on Human Cell, Tissue and Organ Transplantation?

A: I have been involved with the World Health Organization (WHO) in its initiatives around the areas of organ and tissue transplantation, specifically its work on developing the Guiding Principles on Human Cell, Tissue and Organ Transplantation through the Declaration of Istanbul Custodian Group (DICG) and developing standard nomenclature for stem and progenitor cells. The DICG and WHO have been working together on promoting ethical transplantation around the world and preventing the exploitation of the poor in organ trafficking and transplant tourism.

Q: In a recent article that you co-authored, you discussed the increasing number of deaths caused by kidney failure in India in recent years. What are the main factors that are contributing to this?

A: The rising kidney failure deaths in India are due to a combination of factors, such as an increasing life expectancy, the increasing prevalence of common kidney disease risk factors, including diabetes and hypertension, poor access to treatment due to a broken primary healthcare system, and a lack of referral mechanisms in medical insurance, which hastens progression and leads to complications. The final reason is the expensive nature of treatment for advanced kidney failure, which leads to catastrophic out-of-pocket expenditure, forcing patients to stop treatment.

Q: What are the most prominent advances you have witnessed in terms of treatments for kidney disease in India since you began your career?

A: The most important advances have been increasing access to information and awareness of kidney disease, which causes patients to present to the medical community; the penetration of dialysis services to smaller towns; and an increasing number of nephrology training programmes. There has been progress, but we need more.

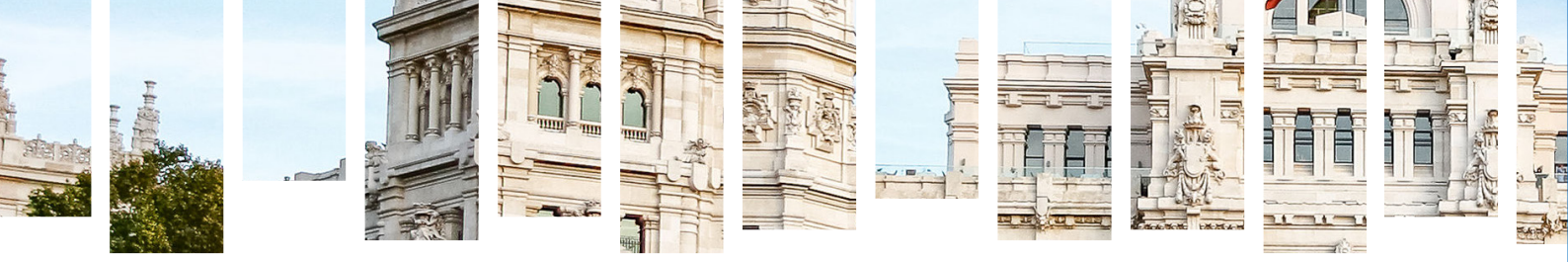
> “The International Society of Nephrology (ISN) is very conscious of its unique position as the organisation that has a special responsibility towards regions where nephrology care or teaching is minimal or non-existent.”

Q: What are the unique challenges posed by public health threats in a country as large and diverse as India? What strategies are currently being developed to ensure a co-ordinated approach across the many regions?

A: The biggest challenge is to ensure the delivery of equitable, good-quality, essential, evidence-based primary healthcare to all populations; development of an effective referral system; financial risk protection; and elimination of perverse incentives. The public-sector healthcare should adapt to the changing disease burden and address chronic non-communicable diseases while maintaining the pushing towards eliminating infections, and strengthening maternal health programmes. Innovation is needed in primary healthcare delivery, such as training the large cadre of non-physician healthcare workers for simple repetitive tasks, using technology to support their work, and focussing on guideline-based care delivery and quality measurement. Responsibility for healthcare delivery lies with the individual states in India, which accounts for heterogeneity in delivery. This needs to be minimised. Finally, healthcare financing needs a radical overhaul, both to ensure financial risk protection and to appropriately incentivise healthcare workers to improve efficiency.

Q: Are there any policies that you would like to see governments across the world implement that you believe would address many of the underlying causes of kidney disease?

A: The best policy to reduce kidney disease burden would include implementation of a cost-effective model of screening for early kidney disease



in high-risk populations, supplemented by opportunistic and workplace screening. This should be followed by the implementation of proved approaches to arrest or slow progression. Research should address areas where kidney diseaserisk factors are not known. Patients with advanced kidney disease should have the option to choose the most appropriate form of renal replacement therapy.

Q: Please tell us a little about your work tackling non-communicable diseases. Have there been any innovative approaches you have personally been involved in that have made a strong contribution in combatting such diseases?

A: The innovation that we are implementing is an integrated approach to managing kidney disease in the context of its risk factors, using electronic clinical decision support systems such as SMARThealth®, which is implemented in the community by Accredited Social Health Activists (ASHA). These are linked through a cloud-based electronic medical record with primary care physicians which allows a referral chain to be established and maintained. We are developing applications to support the process of behaviour change to ensure treatment adherence and continuation. Our aim is to develop a comprehensive set of patient-centred solutions that will address the top 10 causes of death and disability.

Q: If you could give one piece of advice to a medical student about to begin their career in the field of nephrology, what would it be?

A: My advice would be for students to retain their sense of curiosity no matter where they are in their careers, to always try to find out why things are the way they are, and how can we make them better.

> “The most important advances have been increasing access to information and awareness of kidney disease...”

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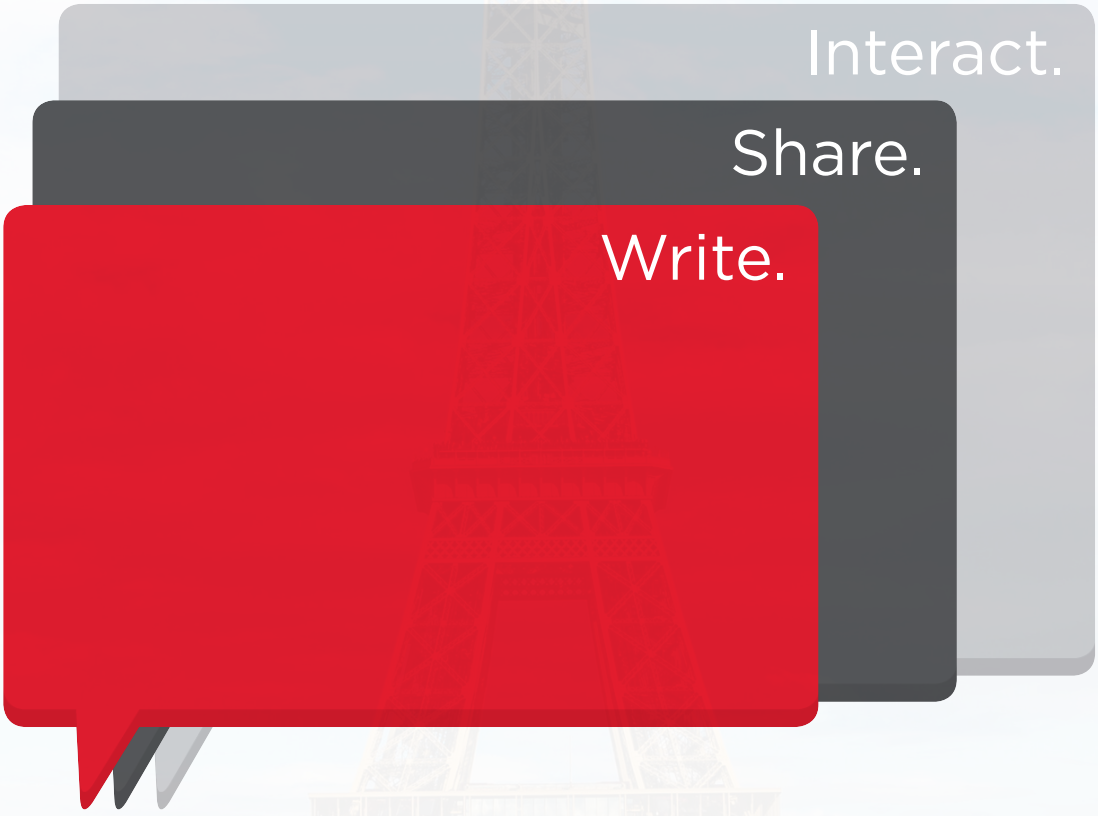

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MORE FREQUENT HAEMODIALYSIS IMPROVED OUTCOMES: THE WISH COMES TRUE AT HOME

This satellite symposium took place on 4th June 2017, as part of the 54th European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) congress in Madrid, Spain

Chairpersons

Maria Auxiliadora Bajo,[1] Natalie Borman[2]

Speakers

Sunita Nair,[3] Eric Goffin,[4] Matthew Herbert,[5] Kay Herbert[5]

1. Universitario La Paz, Madrid, Spain

2. Wessex Renal and Transplantation Unit, Portsmouth, Hampshire, UK

3. Shrewsbury and Telford NHS Trust, Shrewsbury, Shropshire, UK

4. Cliniques Universitaires Saint Luc – UCL, Brussels, Belgium

5. Patient representative, Waterlooville, Hampshire, UK

Disclosure: Dr Borman: Chair of the European medical board for NxStage and a paid speaker by NxStage. However, the clinical experience that is reflected in the manuscript and talks is from clinical practice at Wessex Kidney Centre, Portsmouth, UK. Dr Bajo is a paid speaker on behalf of NxStage and is also a member of the NxStage European Medical Board collecting the KIHDNEy cohort data. Dr Nair is a paid speaker on behalf of NxStage and is also a member of the NxStage European Medical Board collecting the KIHDNEy cohort data; Prof Goffin: Nothing to disclose; Mr and Mrs Herbert: Nothing to disclose.

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Important Information: All forms of haemodialysis, including treatments performed in-centre and at home, involve some risks. In addition, there are certain risks unique to treatment in the home environment. Patients differ and not everyone will experience the reported benefits of more frequent home haemodialysis. Talk to your doctor to see if more frequent home haemodialysis with NxStage® System One™ is right for you. Certain risks associated with haemodialysis treatment are increased when performing nocturnal therapy due to the length of treatment time and because therapy is performed while the patient and care partner are sleeping.

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MEETING SUMMARY

The symposium reviewed the challenges in providing dialysis to patients with kidney disease and outlined data supporting the effectiveness of home haemodialysis for improving clinical outcomes and patient quality of life. Prof Maria Auxiliadora Bajo opened the symposium by introducing the NxStage® System One™ for home-based dialysis. Dr Natalie Borman discussed the growing global burden of dialysis treatments and the ability of new technologies, such as the NxStage System One, to meet this need. Dr Sunita Nair then reviewed outcomes for patients using home-based dialysis in the Knowledge to Improve Home Dialysis Network in Europe (KIHDNEy) cohort. Prof Eric Goffin outlined the need to manage phosphorus levels in patients undergoing dialysis and compared phosphorus measures in patients undergoing different dialysis modalities. Matthew Herbert and his wife Kay then described their personal experience of using home-based dialysis and the impact this has had on their quality of life.

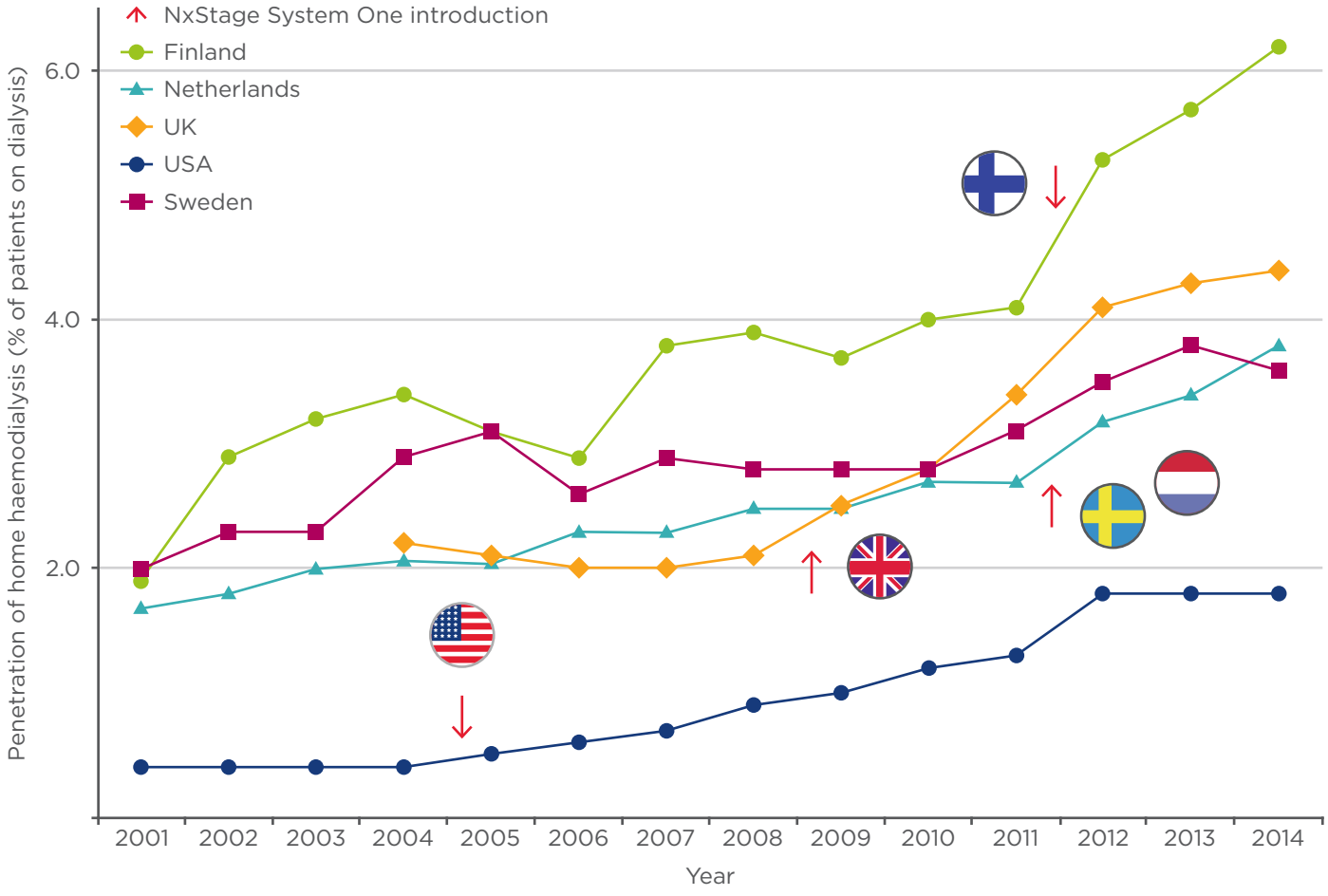

Figure 1: Penetration of home haemodialysis in countries where NxStage System One has been introduced.

Introduction

Doctor Natalie Borman

Chronic kidney disease (CKD) is estimated to affect 13.4% of the global population and is characterised by a progressive loss of kidney function.[1] CKD progresses with age and is often associated with cardiovascular (CV) comorbidities, premature mortality, and decreased quality of life.[1]

For patients with end-stage renal disease or acutely disturbed kidney function, the primary treatment option is augmenting impaired kidney function using haemodialysis (HD), i.e. removing waste and excess fluids by filtering a patient's blood through semi-permeable membranes integrated in an extra-corporeal circulation. However, as the incidence of CKD continues to rise worldwide, more effective and accessible dialysis treatments are required.[2] Indeed, the number of patients undergoing renal replacement therapies (RRT) is predicted to more than double by 2030.[3]

RRT becomes a central component of the lives of patients requiring dialysis, so patient preferences significantly influence treatment choices. Self-care or home-based dialysis is the preferred treatment for 56% of renal professionals and 56% of patients and includes options such as peritoneal dialysis (PD), home HD, and HD in self-care units.[4,5] Patients with impaired kidney function have more control over the timing and efficiency of their treatment and are able to clear greater volumes of water per week with home-based dialysis. More frequent HD allows patients to more closely mimic the fluid and toxin removal performed by healthy kidneys and allows them to avoid having to attend regular appointments at a dialysis unit. Home HD has offered a safe and reliable treatment option for approximately 50 years, with levels of patient survival surpassing those seen for hospital or satellite units.[6]

Despite the success of self-care, it is estimated that only between 2% and 4% of patients undergoing regular dialysis in the UK are engaging in home HD

therapy,[7,8] which is well below the National Institute for Health and Care Excellence (NICE) HD/PD target of 30%. This trend is reflected internationally, with many countries failing to grow their home HD programmes and instead experiencing flat, or even decreasing, levels of use.[9]

Specialist renal healthcare professionals report that the poor implementation of more frequent home HD is reflective of the barriers to implementation that exist, including installation costs, complexity, and concern regarding cannulation and risk of infection. However, considering the established benefits associated with this therapy, emerging technologies must be embraced to break through these obstacles.

The NxStage System One is a simple and portable home dialysis option, designed to fit easily into a patient's daily life, which utilises a drop-in cartridge-based system that contains a high-flux membrane to effectively remove waste products and permit more frequent, and even nocturnal, HD treatments at home. Compared with in-centre treatments three-times per week, more frequent HD with NxStage System One reduces the risk of mortality,[10-13] improves blood pressure,[14-16] and decreases cardiac stress,[14,17-20] while improving recovery time[21,22] and the overall quality of life reported by patients.[23-30] In countries that previously experienced stagnating levels of home HD modality, implementation of NxStage System One has significantly increased the penetration of home HD treatment (Figure 1).[31,32] However, strict adherence to training and system guidelines is necessary to fully realise the benefits of more frequent home-based HD using NxStage System One.

This symposium discussed data supporting the use of the NxStage System One from the KIHDNEy cohort and how home HD can improve outcomes and quality of life for patients requiring dialysis.

New European Evidence with Home Haemodialysis Patients: 12-Month Follow-Up in KIHDNEy Cohort

Doctor Sunita Nair

The KIHDNEy cohort is a collaborative effort undertaken by nine home HD programmes that enrolled 182 patients using the NxStage System One to dialyse at home across five western European countries (Belgium, France, Italy, Spain, and the UK).[31] Patients participating in the study had a mean age and BMI of 49.5 years (range: 15–84 years) and 26.1 (range: 13.3–50.8), respectively. Furthermore, approximately two-thirds of patients had at least one comorbid condition and the sample population had a mean comorbidity score (Charlson score) of 3.9.[31]

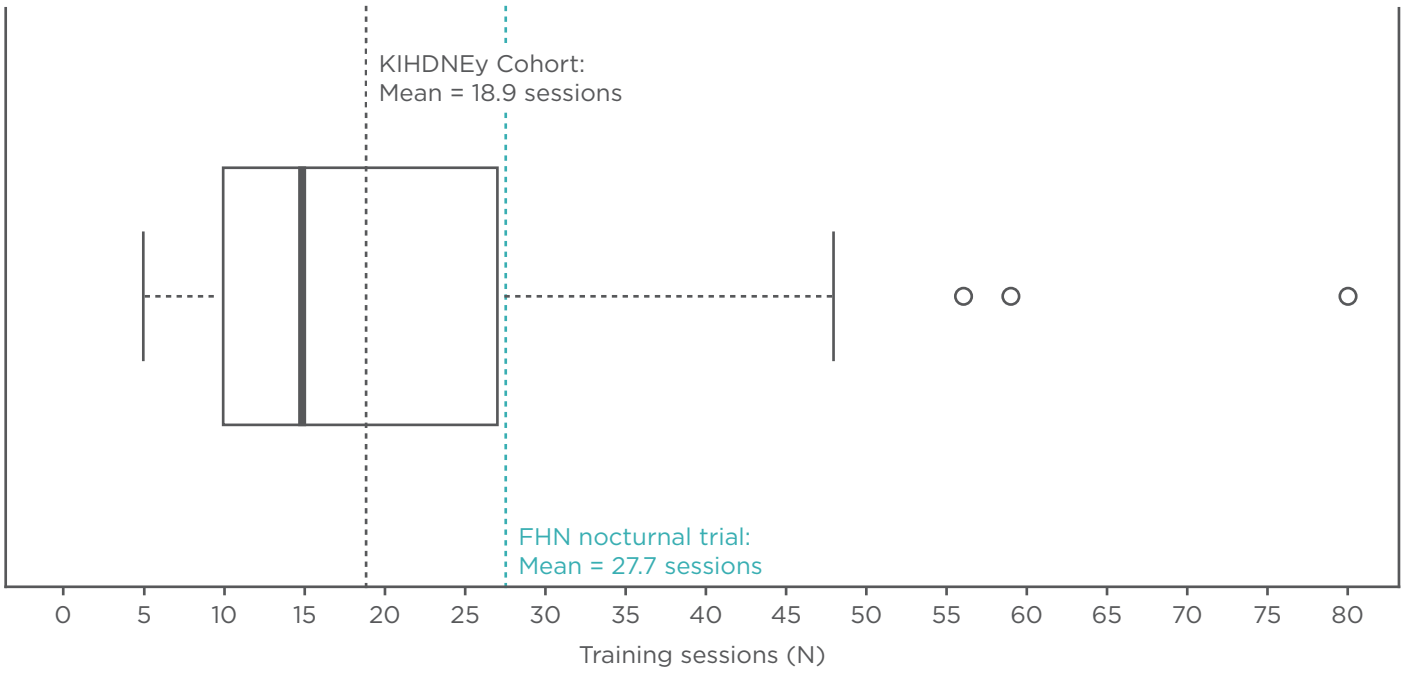

Figure 2: Short training times.
Number of training sessions before transition to home without supervision.

Prior to receiving home HD training, patients spent an average of 3 years on dialysis; 61% of patients were on conventional HD, 9% were on PD, 7% were kidney transplant recipients, and 17% were incident dialysis patients. The vascular access patterns of the patients showed that 74% used a fistula to dialyse, 24% used a catheter, and only 2% used a graft. Of the patients using a fistula, 76% used the button-hole technique to cannulate and 24% used the rope ladder technique.[31]

Compared with the previous Frequent Hemodialysis Network (FHN) study, patients in the KIHDNEy cohort took fewer sessions (18.9 versus 27.7) to complete training before being fully established to dialyse at home (Figure 2).[31,33] Furthermore, patients who initiated the programme being able to cannulate independently required approximately three fewer training sessions.[31]

The majority of patients dialysed across 5–6 sessions per week with each session lasting 2–3.4 hours.[31] On average, patients dialysed for 14.6 hours per week,[31] which was marginally higher than the Dialysis Outcomes and Practice Patterns Study (DOPPS); however, 16% of the patients in KIHDNEy dialysed for less than the conventional 12 hours per week.[34] Of the 30 patients who dialysed for <12 hours per week in this cohort, 28 had residual renal function (RRF), of whom 20 had a urine output of ≥1 L/day.[31] Four patients had an output of 500–900 mL/day and 4 patients had anuria.[31] Of the 4 patients with anuria, 3 weighed 40–56 kg and had a Kt/V of 2–2.6, while 1 patient weighed 67 kg and had a Kt/V of 1.2.[31]

The majority of patients used 20–30 L of dialysate per session or 100–175 L per week.[31] When comparing prescription patterns by patient BMI, it was found that increasing BMI positively correlated with mean sessions per week, time per session, and volume of dialysate used per session, providing evidence that a personalised prescription allowing tailoring of dialysis intensity was achieved with the NxStage System One.[31]

Patients had a mean ultrafiltration rate (UFR) of 6.8 mL/h/kg, with 84% of patients having a UFR of <10 mL/h/kg, indicating that patients were achieving a less intensive UFR per session with the higher frequency of sessions enabled by home dialysis.[31] Patients had a mean Kt/V of 2.61, which remained stable throughout the follow-up period.[31] The proportion of patients requiring two or more antihypertensive agents to maintain appropriate blood pressure significantly decreased from baseline.[31] Bicarbonate levels rapidly and significantly improved during the first 6 months and then stabilised, whereas potassium levels were stable throughout the 12 months of follow-up.[31] Haemoglobin also remained stable and adequate at 11.4 g/dL and did not require any incremental dose in erythropoiesis-stimulating agent (ESA).[31] However, there was a significant reduction in the use of anticoagulants.[31]

Of the 98 patients who provided data for RRF, 54 patients had RRF. Of these, 18% were rendered anuric at 12 months, compared with 50–67% of patients reported to be anuric in other studies of patients undergoing continuous ambulatory PD, automated PD, or intensive HD.[31,35,36] Finally, the cumulative proportion of patients who remained on home-based HD after 3 years was 40%, while 19% of patients were stopping the modality, 31% had received a kidney transplant, and the mortality rate was 10%.[31]

In summary, the KIHDNEy cohort demonstrated the effectiveness of the NxStage System One in delivering dialysis to a wide spectrum of patients, including patients with comorbid conditions. The NxStage System One provided patients with individualised prescriptions, which resulted in less intensive UFRs and reduced use of antihypertensive agents. Patients maintained stable biochemistry and haematinics, with no change in ESA dosing and a reduced use of anticoagulants. RRF was preserved in 80% of patients and overall excellent clinical outcomes, including a high rate of continuation on home-based HD, were achieved. NxStage System One was able to offer the right treatment, to the right patients at the right place, with good clinical efficacy.

Mineral and Bone Disorders and Serum Phosphorus: We Can Free Diet Without Increasing Pill Burden

Professor Eric Goffin

Phosphorus homeostasis is important in CKD, and mineral and bone disease (MBD) remains an ongoing issue in dialysis populations. Patients undergoing HD typically fail to achieve adequate phosphorus control,[37] and evidence suggests that increased phosphorus concentrations are toxic for endothelial cells, inducing arterial stiffness and vascular calcification. These changes are significant risk factors for CV mortality in patients undergoing HD.[37,38]

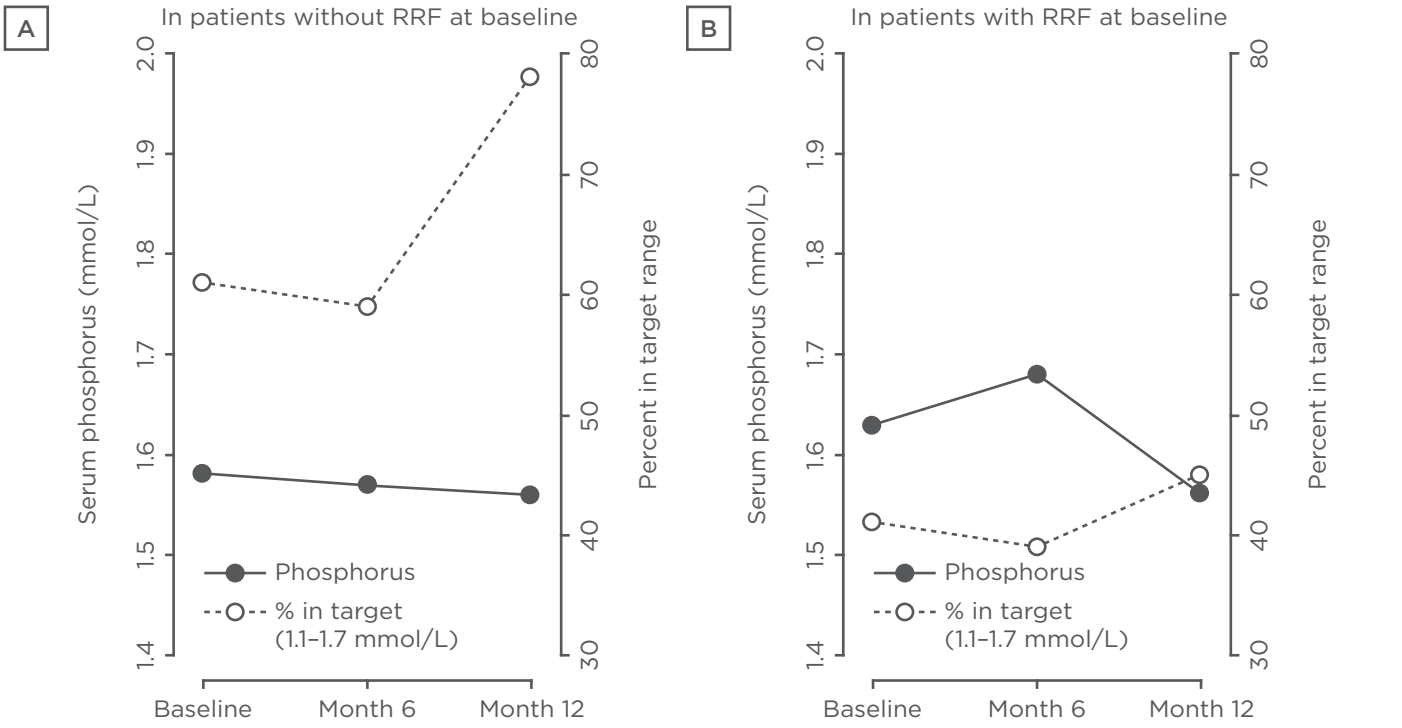

Figure 3: Serum phosphorus concentration and percentage of patients within target range at baseline, after 6 months and after 12 months on home haemodialysis.

A) Patients transitioning to System One without RRF at baseline; B) Patients transitioning to System One with RRF at baseline.

RRF: residual renal function.

Dietary and pharmacological interventions can help lower phosphorus intake and serum phosphorus concentrations.[37] Dietary counselling helps educate patients about phosphorus sources in food, such as food additives, and about how to reduce the phosphorus content when preparing meals. Supplemental phosphorus binders can be used to remove the excess of dietary phosphorus, but this therapy has limitations, including gastrointestinal side effects and a high pill burden, which can lead to poor adherence.[39] In addition, phosphorus-binding medication is associated with significant economic costs.[40,41]

Typically, conventional HD has limited effectiveness in eliminating phosphorus, despite its low molecular weight, with a rebound in serum phosphorus levels generally following conventional three-times per week in-centre dialysis sessions.[42] DOPPS found serum phosphorus levels in a population undergoing HD remained relatively unchanged over a 5-year period (2010–2015), and >36% of patients undergoing HD had serum phosphorus levels persistently above the target range.[43]

More frequent HD sessions, or longer sessions, offer improved phosphorus control. Furthermore, nocturnal HD improves the efficiency of phosphorus removal, reduces the phosphorus binder pill burden and is systematically better than conventional HD for CKD and MBD parameters.[44-47] The FHN Daily Trial demonstrated better control of phosphorus with intensive therapy compared with conventional therapy, with a 0.46 mg/dL decrease (95% confidence interval [CI]: 0.13–0.78 mg/dL) in serum phosphorus levels in the intensive group (1.5–2.75 hours of HD, six-times per week) compared with the conventional group (2.5–4.0 hours of HD, three-times per week).[45] In addition, patients treated with intensive daily dialysis experienced a 1.35 g/day reduction (95% CI: 0.20–2.50 g/day) in equivalent phosphorus binder dose at 12 months.[45]

The FHN Nocturnal Trial found that nocturnal HD sessions of 6–8 hours, six-times per week, were associated with a 1.24 mg/dL decrease (95% CI: 0.68–1.79 mg/dL) in serum phosphorus levels compared with the conventional HD group. Also, 73% of these patients did not require phosphorus binding medication at Month 12 compared with 8% of patients assigned to three sessions per week ($p<0.001$).[45]

Finally, preliminary results from the KIHDNEy cohort indicated that patients treated frequently with the NxStage One System maintain stable levels of phosphorus within the first 6 months.[48] Further examination of the KIHDNEy cohort data revealed a trend towards decreased MBD parameters in patients undergoing more frequent home-based HD, but changes were not statistically significant.[31] Even patients with high baseline phosphorus levels achieved good control of MBD parameters and a decreased phosphorus binder pill burden at 12 months, provided they were exposed to a longer duration of dialysis (≥15 hours).[31] Furthermore, there was significant improvement in the proportion of patients achieving target phosphorus ranges across groups with or without RRF.[31] There were also improvements in nutritional markers, including progressive gains in post-dialysis body weight and serum albumin concentrations, indicating that patients were eating more protein (Figure 3).[31]

My Dialysis Journey

Matthew and Kay Herbert

Coming to terms with a lifelong dependency on dialysis treatment can be an enormously daunting prospect. After being diagnosed with focal segmental glomerulosclerosis at 15 years of age, Matthew had to endure several in-centre dialysis treatments per week, which took a significant toll on his life and wellbeing. Here, his journey towards a life with greater control over dialysis treatment is described.

Initially, Matthew had to undergo two in-centre dialysis sessions every week. Initially, each session lasted 5 hours, before he progressed to three 4-hour sessions. After treatment, he often felt weak and fatigued, which made it difficult to complete daily tasks. Despite these obstacles, he continued persevering, successfully completing college, becoming a qualified chef, and meeting his wife in the process.

Over the following 10 years, Matthew had to co-ordinate life around work and family commitments and around appointments for in-centre dialysis treatment. A typical day would involve waking up at 05:30, travelling to the clinic for a 4-hour dialysis session, then heading straight to work for his morning shift at a restaurant. Matthew would then travel home to rest over his lunch break and return for the evening service. As it is not unusual for chefs to work 60–65 hour weeks, he was left exhausted.

Three years ago, at the suggestion of Dr Borman, Matthew began nocturnal home HD using NxStage System One. As he was already experienced with self-cannulation, training was straightforward and completed in ˜5 days. Almost immediately, he felt a sense of rejuvenation, gaining back the energy that he felt was wasted during in-centre visits.

NxStage System One has allowed Matthew to more effectively balance his work schedule, while offering time to pursue activities that he was previously restricted from participating in, such as running, cycling, international travel, and even the occasional skydive for charity. After the birth of their son Oliver, he was able to lend a hand with night-time feedings, an activity that would have been exceedingly difficult alongside his in-centre dialysis schedule.

For Matthew, the transition from in-centre to home-based dialysis has changed his life, and he would recommend that any healthcare professional treating patients undergoing HD seriously consider this treatment option, as it has helped him a great deal both mentally and physically.

Summary

RRT is placing an increasing burden on healthcare systems around the world. Data from the KIHDNEy cohort indicate that home HD, when performed more frequently with the NxStage System One, is an effective RRT option, potentially offering improved clinical outcomes compared with other RRT.[11,14] Furthermore, home HD can help improve quality of life for patients with renal disease.

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NEW BIOCOMPATIBLE HAEMODIAFILTRATION MEMBRANE TO ENABLE MAXIMUM SUBSTITUTION FOR SENSITIVE PATIENTS

This symposium took place on 5th June 2017, as part of the 54th European Renal Association – European Dialysis and Transplant Association (ERA–EDTA) Congress in Madrid, Spain

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MEETING SUMMARY

In many European countries, high-volume online haemodiafiltration (OL-HDF) is becoming the method of choice for treating patients with chronic kidney disease. The high convective (Qs >20 L/session) and diffusive properties of this treatment have been shown to be beneficial for patient survival. For optimum outcomes, the dialyser membrane must be able to cope with high transmembrane pressures. For this reason, the most widely-used membranes for this technique are synthetic and asymmetric in structure, making it easier for the membrane to divert the pressure away from its surface. However, patients allergic or sensitive to synthetic molecules, cannot access these high convective volumes (CV) reached in high-volume HDF, because alternative semi-natural membranes for allergic patients, such as cellulose acetate-based membranes, do not have adequate pressure-handling properties for high-volume HDF.

At this symposium, a new type of cellulose triacetate (CTA)-based membrane that is biocompatible, able to perform high-volume OL-HDF, and suitable for sensitive patients was introduced.

Anaphylactic Reactions to Haemodialysis Membranes

Professor Rafael Selgas

The hypersensitivity responses are categorised into two types, Type A and B. Type A response is a severe reaction that occurs within the first 30 minutes after the start of dialysis, it includes angioedema, dyspnoea, hypotension, cardiac arrest, and potentially death. This type of reaction requires immediate disconnection of the patient without returning the extracorporeal blood. The best-documented Type A reactions in dialysis are the reactions against ethylene oxide, hydrogen oxide (from dialyser reuse), formaldehyde, heparin, latex, or the combination of AN69 and angiotensin-converting enzyme inhibitors.[1-4] The Type B response, also referred to as the unspecific response, is more common than the Type A response, but less severe. The symptoms include the aforementioned pulmonary leukostasis, leucopoenia, and hypoxaemia, and normally occur

late on in dialysis, starting from around 15–30 minutes after the beginning of dialysis, or even later.[5-7] These symptoms generally resolve during the session, and do not require patient disconnection.

Case Reports on Hypersensitivity Reactions in Dialysis

In 1988, it was reported that 4 out of 100,000 treatments lead to an anaphylactic reaction. In 2014, six case reports were published in which the patient had an allergic response against a synthetic dialyser membrane component.[7] Patients were switched to a semi-natural CTA membrane and no longer experienced hypersensitivity reactions. It was suggested that the unknown factor activating these responses was one of the components present in the capillaries of the synthetic dialysis membrane, which was absent in the capillaries of the CTA membrane.[7]

To investigate the mechanisms involved in polysulfone (PS) hypersensitivity, basophil, T cell, and complement activation, were measured in acute-phase samples from two patients with anaphylactic reactions to PS-based membranes. Basophil and T cell activation, as well as higher serum tryptase levels, were detected in acute-phase samples compared with basal levels, suggesting the activation of mast cells and basophils. Complement levels (C3 and C4) were decreased in acute-phase samples from PS-allergic patients to a higher extent than in samples from control donors. In an *ex vivo* setting, basophils from PS-allergic patients exhibited increased degranulation, and T cells showed significantly increased activation after contact with PS-based membranes primed with low volumes of saline. No activation was detected in leukocytes from non-allergic patients under the same experimental conditions. Membrane priming with high volumes of saline abrogated activation of basophils and T cells; however, basophils from allergic donors showed significantly higher responses to FcεR stimulation after contact with PS membranes. Basophil degranulation in allergic patients and serum tryptase levels during acute reactions support the activation of mast cells and basophils during hypersensitivity reactions to PS-based membranes.[7]

With these results in mind, this symposium discussed the implications of hypersensitivity reactions for patients undergoing haemodialysis (HD) and the possibility of keeping these patients on high convective therapies like high-volume OL-HDF.

Comparison of Old Versus New Generation Cellulose Triacetate Membrane in HD and HDF Treatment

Doctor Francisco Maduell

Several studies show that high-volume OL-HDF, when compared with HD, achieved better removal of uremic toxins, better control of hyperphosphataemia, anaemia, and nutrition; greater reductions in neurological symptoms and cardiovascular risk; as well as improved haemodynamic stability and survival.[8-11] The ESHOL study, one of the most recent studies, was the first randomised controlled trial to demonstrate the superiority of OL-HDF over HD for all-cause mortality,[9] a finding that was subsequently verified in other clinical trials. A pooled analysis of results from four studies involving a total of 2,700 patients found that OL-HDF versus HD reduced the risk of all-cause mortality and cardiovascular mortality by 14% and 23%, respectively.[3] These benefits have further been demonstrated in several meta-analyses that reported significant risk reductions in all-cause and cardiovascular mortality with OL-HDF compared with HD.[9,12,13] Further support for the reduced risk of mortality came from a French registry, which enrolled nearly 30,000 HD patients between 2008 and 2011. Of these patients, >5,000 participated in at least one HDF session and >2,000 were treated exclusively with HDF. All-cause mortality, cardiovascular mortality, and non-cardiovascular mortality were all reduced with OL-HDF compared with other forms of HD.[14] A secondary analysis of three trials found that improved mortality rates were associated with a higher CV,[9,15-17] suggesting that patients should receive a minimum of 21 L replacement volume and 23 L total CV. To achieve high-volume throughput and ultimately achieve higher survival rates, synthetic, high-flux membranes or cellulose triacetate membranes are required. All these results indicate that high-volume OL-HDF is more beneficial for patient outcomes.[8-11]

A literature review of the membranes capable of performing high-volume OL-HDF revealed several findings. In an experiment comparing the attributes of 11 dialyser membranes made of different materials, 11 patients received 11 dialysis sessions in which only the dialyser was changed.[18] Observed blood flow rates were similar for all membranes, but transmembrane pressures were higher, and β2-microglobulin removal rates significantly lower for Tricea 190G (cellulose acetate) and BK-21P (polymethyl methacrylate [PMMA]) membranes.

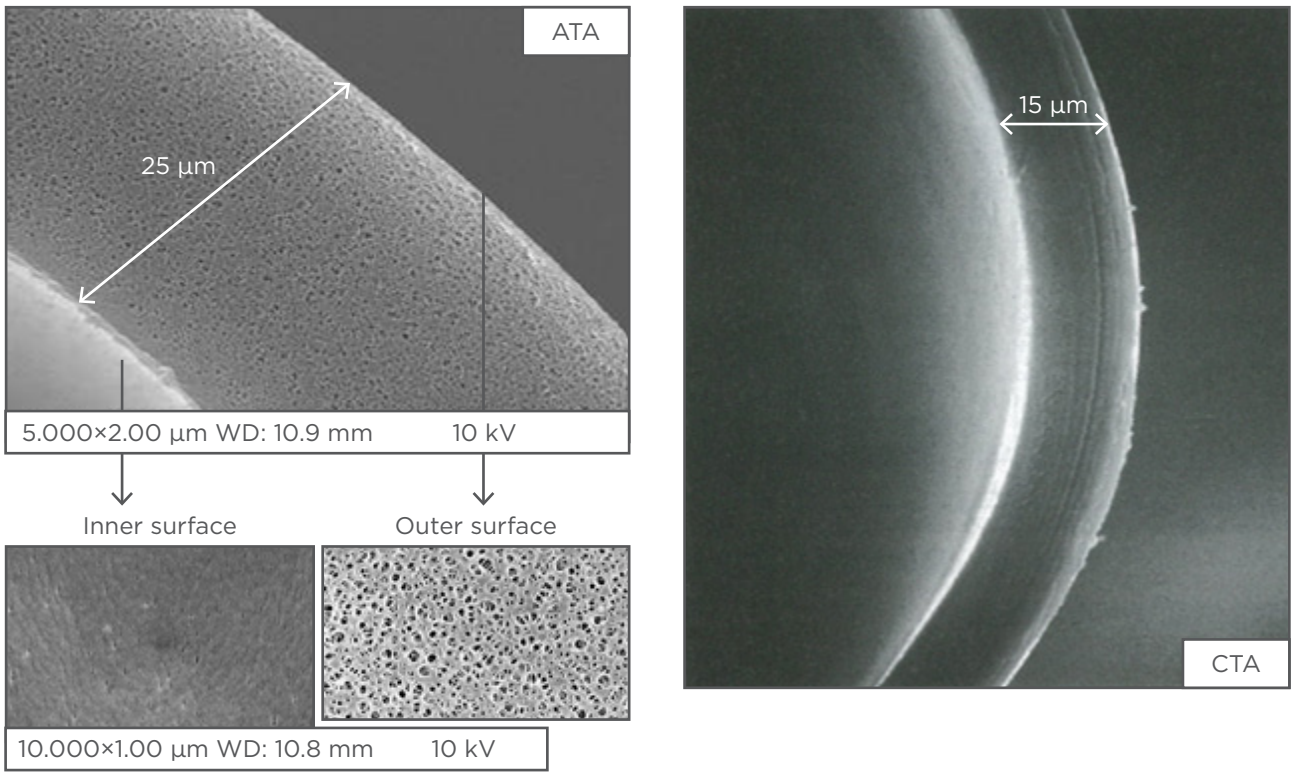


Figure 1: Asymmetric triacetate and cellulose triacetate membrane structure.
ATA: asymmetric triacetate; CTA: cellulose triacetate.
Adapted from Sunohara and Masuda.[21]

The investigators concluded that cellulose triacetate and PMMA membranes were of limited use for OL-HDF.[18] A French study analysed 19 synthetic dialysers (not including PMMA) to assess their compatibility with the CVs recommended for post-dilution OL-HDF.[19] The investigators observed a direct relationship between CV, β2-microglobulin, and myoglobin reduction rates. When the amount of albumin lost in the dialysate was analysed, however, they found that 6 dialysers (Phylther HF 22SD [Bellco Srl, Mirandola, Italy], FDX-210GW, FDY-210GW [Nikkiso KK. Osaka, Japan], TS-2.1UL, (Toray Medical Company Ltd., Tokyo, Japan) FX 1000 HDF (Fresenius Medical Care, Bad Homburg vor der Höhe, Germany) and Rexeed-21A [Asahi Kasei Medical Co., Ltd., Tokyo, Japan]) were associated with albumin loss of >5 g per session, which they considered excessive. As a result, recommendations against the use of these 6 dialysers for OL-HDF were made. These studies show that, currently, the membrane chosen for high-volume OL-HDF is a synthetic membrane that is able to withstand high CV throughput but does not leach too much albumin.

The concerns with synthetic membranes are hypersensitivity reactions observed in some patients. Sànchez-Villeneuva et al.[7] investigated six cases and found that hypersensitivity disappeared when synthetic membranes were replaced by CTA membranes. These findings were reviewed by Alvarez-de Lara and Martín-Malo,[1] who reported the disappearance of hypersensitivity symptoms after a switch from synthetic membranes, which often contain polyvinylpyrrolidone, to CTA membranes. In their opinion, the fact that all clinics have seen at least a few hypersensitivity cases indicates that such reactions cannot be considered to be rare and should be monitored carefully. One of the current disadvantages of using a CTA membrane is that these membranes are less capable of performing high-volume OL-HDF. This is due to the uniform cross-sectional structure, which has a similar pore size on the blood-facing surface and the dialysate-facing surface. On the other hand, CTA membranes have a low electrical charge and minimal adsorption,[20] excellent antithrombotic properties, and little residual blood loss after clinical HD. Furthermore, they have been associated with decreased triglyceride and increased HDL-cholesterol levels with long-term use, as well as decreased homocysteine and advanced glycation end products peptide levels.

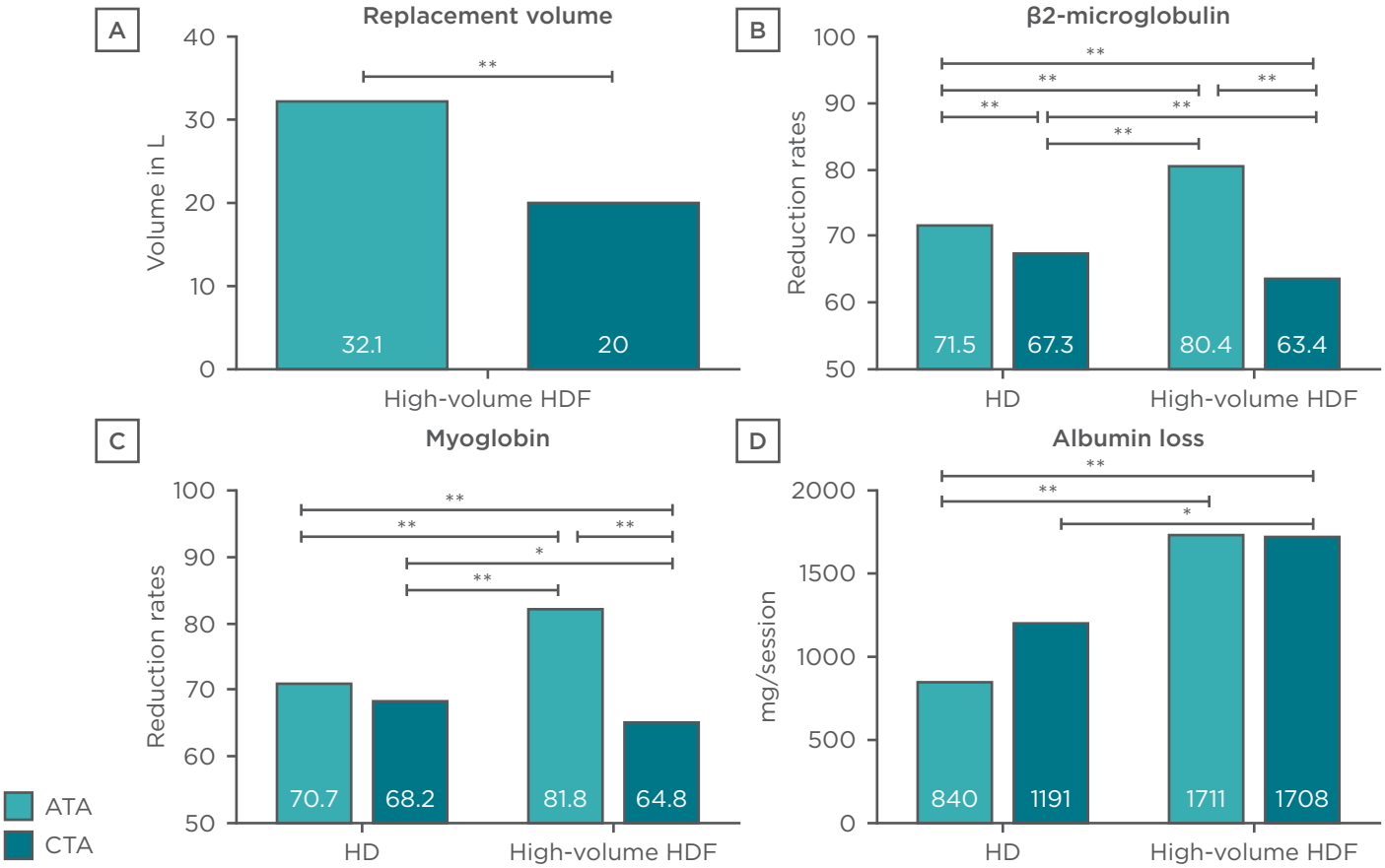


Figure 2: Performance comparison of the cellulose triacetate and asymmetric triacetate membrane.
Comparison of the replacement volume in high-volume OL-HDF between the ATA and the CTA.
A) reduction rates of β2-microglobulin; B) and myoglobin; C) and the loss of albumin; D) between the ATA and CTA membrane in HD and high-volume OL-HDF.
*p<0.05; **p<0.01.
ATA: asymmetric triacetate; CTA: cellulose triacetate; HD: haemodialysis; HDF: haemodiafiltration; OL-HDF: online haemodiafiltration.

These properties, in addition to the lack of hypersensitivity, make them excellent dialysers in many ways; however, it implies that patients on high-volume OL-HDF might have to return to HD or low-volume HDF treatments.

Up until now, there was an unmet need for a dialyser that combines the high-flux capability required for high-volume OL-HDF with reduced risk of hypersensitivity reactions. A new generation CTA membrane, the asymmetric triacetate (ATA) membrane, has been developed and has been proven suitable for high-volume OL-HDF. On the blood-facing side a smooth surface optimises pore distribution, whereas on the dialysate-facing side an asymmetric support layer, reduces pressure build-up in the membrane (Figure 1).[21] The ATA membrane is similar to the CTA membrane in all characteristics except for a slightly increased wall thickness (25 µm versus 15 µm) and its asymmetric structure. An important advantage with this new membrane compared with the old CTA membrane is the reduction in transmembrane pressure. The ATA membrane has a lower baseline pressure in high-volume OL-HDF, which remains fairly constant throughout the dialysis session, while the pressure across the CTA membrane increases.[21]

In a head-to-head comparison of the ATA and CTA membranes,[22] the patient received two HD sessions with each of the two membranes, and two high-volume post-dilution OL-HDF sessions with each of the membranes. In all cases, dialysis time was approximately 5 hours; the mean blood flow was reported as 462 mL/min and dialysate flow as 500 mL/min. Performance was evaluated by measuring markers such as urea, creatinine, β2-microglubulin and myoglobin. Of particular interest to the investigators were the differences in albumin loss across the four dialysis sessions.

Table 1: Comparison of cellulose triacetate and asymmetric triacetate performance under haemodialysis and online haemodiafiltration conditions.[8]

	Haemodialysis			Online haemodiafiltration		
	CTA	ATA	p value	CTA	ATA	p value
Initial weight (g)	72.4	72.3	NS	72.3	72.8	NS
Final weight (g)	69.9	70.0	NS	69.8	70.0	NS
Interdialytic weight gain (g)	2.5	2.3	NS	2.5	2.8	NS
Haematocrit (initial)	-	-	-	29.8	29.8	NS
Haematocrit (final)	-	-	-	37.2	37.6	<0.01
Replacement volume (L)	-	-	-	20.0	32.1	<0.01
Dialytic volume (L)	152.1	152.0	NS	171.8	184.6	<0.01
Dialysis dose (L)	72.1	68.9	<0.01	74.8	76.3	NS
Reduction rates (%)						
Urea	85.4	83.0	<0.01	85.8	85.6	NS
Creatine	78.6	76.3	<0.01	78.3	79.3	NS
β2-microglobulin	67.3	71.5	<0.01	63.4	80.4	<0.01
Myoglobulin	68.2	70.7	NS	64.8	81.8	<0.01
Prolactin	65.2	61.1	NS	63.2	74.4	<0.01
α1-microglobulin	17.3	13.6	NS	16.5	23.5	<0.01
α1-acid glycoprotein	3.8	3.7	NS	6.9	11.5	<0.01
Albumin	6.4	4.2	NS	5.9	8.1	NS
Albumin loss in dialysate (g)	1.2	0.8	NS	1.7	1.7	NS

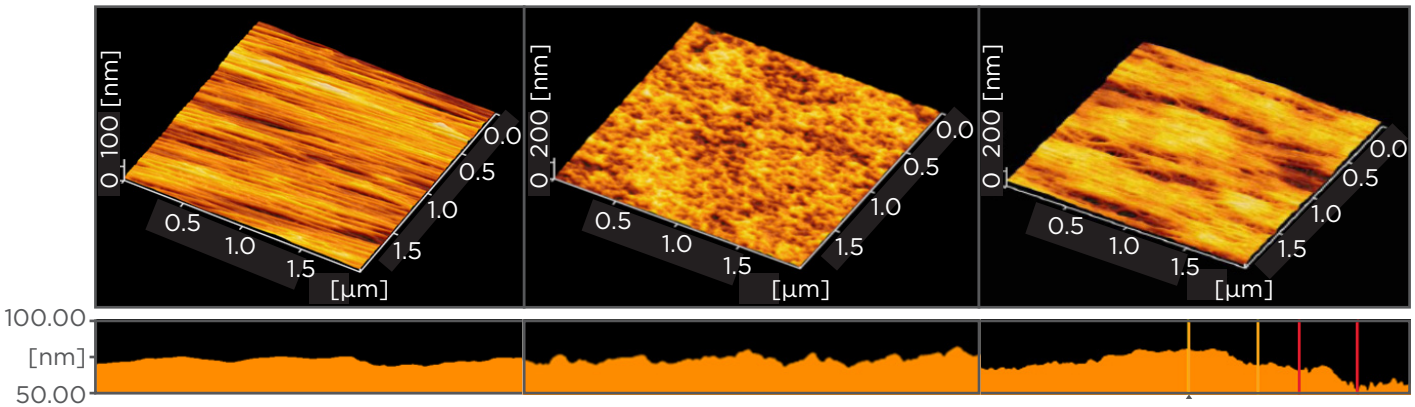
ATA: asymmetric triacetate; CTA: cellulose triacetate; NS: not significant.

The study found no differences in initial, final and interdialytic weight, and no differences in initial and final haematocrit concentrations for high-volume OL-HDF (Table 1). The recommended minimum replacement volume (21 L/4 hours) was not achieved with the CTA but was comfortably achieved with the ATA membrane. Under HD conditions, the dialysate volume was similar for both membranes, but was significantly higher for the ATA membrane with high-volume OL-HDF (Figure 2A).

The results obtained for removal rates of larger molecules (β2-microglobulin [Figure 2B], myoglobin [Figure 2C], prolactin) were unexpected based on a previous study that reported increased CV with CTA membranes.[23,24] The reduction rate of α1-microglobin was close to the cut-off point with the CTA membrane during HD, but nearly doubled during high-volume OL-HDF. Reduction rates of α1-acid glycoprotein were similar with both membranes in HD, while a significant reduction during OL-HDF was observed only with the ATA membrane. Albumin removal rates increased with OL-HDF compared with HD.[10] Albumin loss was close to 1 g with ATA and >1 g with CTA in HD, and 1.7 g for both membranes in OL-HDF (Figure 2D).

Other studies comparing the ATA and CTA membranes are ongoing in Madrid, Spain (NCT03105817)[25] and London, UK (NCT02546037).[26] A recent study comparing the ATA membrane and the polynephron membrane, presented at the ERA-EDTA 2017 congress, found no differences in dialysis load, β2-microglobin, myoglobin, and albumin reduction rates in a small study population of six patients. Albumin loss was 1 g with a CV of 26 L.[15]

The newly developed ATA membrane is a suitable membrane for high convective therapies reaching a CV well above 20 L/session. Performance-wise, it demonstrated benefits across all markers analysed, including the middle molecular weight molecules, without losing large amounts of albumin, making it a good alternative for current synthetic high-volume HDF membranes.



Averaged roughness	ATA membrane	CTA membrane	PS membrane
Ra (nm)	4.5	5.5	9.2

Figure 3: AFM analysis of the surface roughness of the asymmetric triacetate, cellulose triacetate, and polysulfone membranes.[21]

AFM: atomic-force microscopy; ATA: asymmetric triacetate; CTA: cellulose triacetate; PS: polysulfone.

Biocompatible Characteristics of a Newly Developed Smooth Surface Membrane

Doctor Tadashi Tomo

HD and other similar processes have many bioincompatible factors. These presumably induce inflammation, which can lead to the development of complications (e.g. atherosclerosis); hence the need to reduce micro-inflammation. Biocompatibility of the treatment is influenced by the materials and chemicals used in the treatment but also the type of treatment provided.

When we look at the treatments provided, data from the Japanese J-DOPPS III study indicate that increased baseline levels of the inflammatory molecule C-reactive protein (CRP) is associated with increased death risk, which implies that techniques that reduce CRP levels could reduce chronic inflammation and ultimately death.[27] Several studies have demonstrated that dialysis with OL-HDF results in lower CRP levels and lower mortality rates than with HD, making the HDF technique an attractive technique that is able to reduce micro-inflammation.[8,28,29] To understand some of the concerns around biocompatibility, differences between pre-dilution HDF and post-dilution HDF were assessed.[30] In pre-dilution HDF, some fluid is injected into the inlet of the haemodiafilter so that contact between the white blood cells, monocytes, and membrane is decreased, but linear velocity and shear stress increase. The opposite is true for post-dilution HDF, where linear velocity is decreased and contact between white blood cells, monocytes, and membrane are increased due to haemoconcentration.

Alongside the dialysis technique used, the dialyser membrane used has a major impact on biocompatibility of the treatment, because the body continues to recognise it as a foreign substance. In the long term, even small inflammatory reactions between the dialysis membrane and blood cannot be overlooked. An improvement in the general biocompatibility of membranes and a reduction in contact between membrane surface and blood cells are pivotal in preventing micro-inflammation.

The new ATA membranes are designed to perform well in both sections: achieve good clearances in high-volume HDF and have as little as possible interaction with blood cells to minimise micro-inflammation. Figure 3 shows the differences in the surface roughness of ATA, CTA, and PS membranes with the ATA membrane at the smooth and the PS membrane at the rough end of the spectrum. The build-ups of the membranes are also different. The CTA membrane is symmetrical, limiting its capabilities in high-volume treatments, and the ATA and PS membranes are asymmetrical, making them capable of withstanding higher convective therapies than the CTA membrane.

To investigate the inflammatory properties of different membranes and treatment types, the ATA, CTA and PS membranes were investigated in an *ex vivo* study. Micro modules consisting of fifty fibres from three membranes (CTA membrane from FB-U [Nipro Corporation Osaka, Japan], ATA membrane from FIX-210Seco [Nipro Corporation, Osaka, Japan], and PS membrane from FX-180 [Nikkiso KK. Tokyo, Japan]), each 16 cm in length, were exposed to blood collected from healthy volunteers under HD, pre-dilution haemofiltration (HF)/HDF and post-dilution HF/HDF conditions. Blood flow rates, dialysis flow rates, and substitution-flow rates were adjusted to be equivalent with those of liner velocity used in clinical practice. After 15 mins of exposure, neutrophils were separated from the blood samples and neutrophil counts were adjusted to $1.5x10^6$ /mL by dilution with phosphate buffered saline. After 10 µL luminol and 100 µL t-buOOH were added to 200 µL of this sample, the free-radical content was measured. The concentration of platelet-derived micro particles (PDMP) in the plasma was measured by the ELISA method.

Neutrophil-induced free radical formation is a good indicator for micro-inflammation. When tested in circulated blood that passed through the *ex vivo* circuit containing the different dialysis membranes and applying different treatment modalities, it was found that the ATA membrane in comparison with the CTA and PS membranes (tested under blood circulation without dialysate) had the lowest amount of free radical induction and PS had highest. In the HD condition, the amount of free radical induction from ATA and PS does not show a significant difference, and CTA had the highest. The variation in results between the two conditions was considered to be caused by dialysate or back filtration. In the pre-dilution HF and HDF, and the post-dilution HF and HDF conditions, ATA had the lowest amount of free radical induction and PS had highest. These results might be explained by the ATA membrane inducing less radical stress, usually caused by blood concentration or shear rate, under HF and HDF conditions.

The formation of PDMPs play an important role in the clotting process by stimulating platelets and monocytes leading to aggregation of platelets and potentially hypercoagulability, as well as promoting secretion of adhesion molecules. PDMP may act as a biomarker of the biocompatibility of dialysis membranes. When assessing this marker, PDMP levels were lower with the ATA membrane under HD, pre-dilution HDF and post-dilution HDF conditions, however, these results were not demonstrated during the blood flow assessments under pre-dilution HD and post-dilution HD conditions. Further investigations are required to assess the impact of PDMP levels on membrane compatibility in more depth as current assumptions are based on limited data.

In conclusion, poor biocompatibility of dialysis membranes is implicated in promoting micro-inflammation in the blood vessels of the patient. The newly developed ATA membrane appears to have an improved biocompatibility profile in high convective therapies compared with earlier membranes.

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OUTCOMES OF ACUTE KIDNEY INJURY IN A NEPHROLOGY DEPARTMENT

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Keywords: Acute kidney injury (AKI), end-stage renal disease (ESRD), cardiovascular mortality, mortality.

Acute kidney injury (AKI) is a global problem that occurs in the community and in the hospital, both in the intensive care unit (ICU)[1] and outside this environment. The in-hospital mortality rate is ~20–50%.[2] AKI also increases the risk of chronic kidney disease (CKD) and end-stage renal disease (ESRD) and may result in damage to non-renal organs.

This was a retrospective study to evaluate the outcomes of patients admitted to a nephrology department with the diagnosis of AKI. Patients admitted to our service with a diagnosis of AKI, according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification for 5 years, were evaluated. The following endpoints were evaluated in the follow-up period: progression to ESRD, all-cause mortality, in-hospital admission for stroke, acute coronary syndrome (ACS), or heart failure (HF). Data were collected from medical records. Patients without records or with an unknown serum creatinine value in the 12 months prior to this AKI episode, and those who needed treatment in the ICU, were excluded. Survival analysis was carried out by the Kaplan–Meier method and potential risk factors for ESRD by Cox regression.

We included 191 patients, 113 (59.2%) were male, the mean age was 73.83±12.49 years, and 137 (71.7%) patients had a history of CKD. Comorbidity distribution based on the Charlson comorbidity index was <3 points (n=22; 11.5%), 4–5 points (n=32; 16.8%), 6–7 points (n=59; 30.9%), and >8 points (n=78; 40.8%). The median length of stay was 12 days. Pre-renal AKI was assumed in 128 patients (67%), while intrinsic AKI occurred in 45 (23.6%), and post-renal AKI was seen in 15 (7.9%). In three patients (1.6%), the cause of AKI was undetermined. Thirty-three patients (17.3%) had AKI Stage 1, 11 (5.8%) had AKI Stage 2, and 147 (77%) had AKI Stage 3.

Renal replacement therapy (RRT) was needed for 124 patients (65%), 65 (34%) received only pharmacological treatment, and 2 (1%) needed surgery. At discharge, 107 patients (56%) had recovered renal function to the values they presented before the AKI episode, 41 (21.6%) presented serum creatinine levels above the basal values but without need of RRT, 25 (13%) evolved to ESRD, 16 (8.4%) died, and 2 (1%) had unknown outcomes. Four patients were lost to follow-up. Overall, the median survival time free of RRT was 74 months and 69 months (38.24–99.76) in the group of patients with a history of CKD; in patients without previous CKD, it has not yet been reached ($p<0.05$). The only factor associated with progression was history of CKD (hazard ratio: 2.37; 95% confidence interval [CI]: 1.23–4.56) (Table 1). The median survival time in this sample was 34 months (95% CI: 23.3–44.7) and the mortality rate was 18 deaths/100 patient-years. After the AKI episode, 22 patients (11.5%) had at least one hospital readmission for HF, 5 (2.7%) were rehospitalised for ACS, and 6 (3.1%) were readmitted due to stroke. The incidence of a composite cardiovascular endpoint of HF, ACS, and stroke, was 6 events/100 patient-years.

The outcomes of the patients admitted in our service with AKI were different to those we find in the literature. We confirmed that patients with a history of CKD are prone to ESRD after an admission for AKI. The rate of admission for a cardiovascular event in our study was lower than that described in the literature because the median survival time of

our patients was similar to the median survival time of a cardiovascular event.

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Table 1: Hazard ratio of possible factors associated to progression from acute kidney injury to end-stage renal disease.

	Unadjusted	
	HR (95% CI)	p value
Age (years)	1.009 (0.99–1.029)	0.361
Female sex	0.765 (0.455–1.287)	0.313
Charlson comorbidity index >4	2.059 (0.972–4.363)	0.059
History of renal disease	2.379 (1.230–4.565)	0.010
Cause of renal disease	1.089 (0.753–1.575)	0.649
History of smoking	1.551 (0.762–3.158)	0.227
HD treatment during AKI	1.319 (0.761–2.288)	0.324

HR: hazard ratio; CI: confidence interval; HD: haemodialysis; AKI: acute kidney injury.

THE INTRODUCTION OF A NOVEL SMARTPHONE APP TO TACKLE ACUTE KIDNEY INJURY IN NORTH WEST ENGLAND

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Citation: EMJ Nephrol. 2017;5[1]:53-54. Abstract Review No. AR2.

Keywords: Acute kidney injury (AKI), technology, renal failure.

The AKI Care App (Extravision, Manchester, UK) was chosen for an oral presentation at the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) meeting, Madrid, Spain. The app was developed through collaboration with the local Strategic Clinical Networks and designed to improve the investigation and management of acute kidney injury (AKI). It acts as an educational and reference tool for the different stages of AKI, their complications, and when it is necessary to refer. Not only can it be used as a point of care calculator and for risk assessment, it also provides contact information for local renal unit referrals and links to Think Kidneys, the National Institute For Health and Care Excellence (NICE) AKI Guidelines, and the NICE Fluid Prescription Guidelines.

The app was analysed for user demographics and usage statistics in order to understand the current reasons for use and to improve user experience. As the majority of AKI incidence occurs outside

the renal department,[1] it is important to engage non-nephrologists and use accessible non-specialist language. Whilst this is not a compulsory input by app users, some demographic detail can be analysed; 85% of downloads were by doctors (34% junior doctors; 28% consultants) and 9% by nursing staff. Ten percent of the total downloads were from outside the North West of England.

The data for potassium, pH, symptoms of renal failure, and AKI stage were then collated. The median potassium in mmol/L (n=281) was 6 (Q1: 5; Q3: 6.35) and median pH (n=237) was 7.2 (Q1: 7; Q3: 7.4). The number of patients at each AKI stage was as follows: Stage 1: 189, Stage 2: 33, and Stage 3: 154. The over-representation of AKI Stage 3 in comparison to epidemiological studies[1] is likely to represent either increased use for more severe stages of AKI or for educational inquiry. Patients reported symptoms of confusion (n=123; 33%), flap (n=75; 20%), pericardial rub (n=59; 16%), and oedema (n=82; 22%). The e-alert has superseded the app for alerts about AKI Stages; however, the app remains a crucial educational and reference tool for symptoms recognition, safe transfer assessment, and signposting to appropriate services.

Discussion was generated at the conference around the intended target audience. Should tech-savvy medical students be encouraged to use this app or is it targeted at the older physician? Undoubtedly, this simple interface and user-friendly app lends itself to both and has multidisciplinary appeal. Overall, it can deliver valuable information to users for further investigation of AKI and management of its complications, with signposting to appropriate services for onward referral.

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EVALUATING PHARMACIST MEDICATION INTERVENTIONS IN EMERGENCY ADMISSIONS WITH COMMUNITY-ACQUIRED ACUTE KIDNEY INJURY IN A LARGE TEACHING HOSPITAL

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Keywords: Acute kidney injury (AKI), pharmacist, sick day guidance.

This study, selected for presentation as a poster at the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) meeting, Madrid, Spain, looked at key initial recommendations and interventions by a pharmacy team for patients with community-acquired acute kidney injury (CA-AKI). Over 60% of AKI starts in the community.[1] The National Health Service (NHS) England's AKI programme 'Think Kidneys' supports patients in understanding the risks of AKI and educating them in protection against it.[2] This includes medication management known as 'Sick Day Guidance'. The aim of this study was to evaluate the role of secondary care pharmacists in the management of community acquired AKI and to explore the dissemination of sick day guidance.

Prospective data were collected from 50 consecutive emergency medical admissions with AKI <48 hours from admission over a 4-week period in 2016 using a piloted data collection form and interview questions. Using the electronic patient records, patients' pre-admission medications were screened and split into five categories: angiotensin converting enzyme inhibitors, angiotensin receptor blockers, nonsteroidal anti-inflammatory drugs, diuretics, and metformin. These were considered to

have nephrotoxic potential or pose further risk to patients' health in AKI, and the following elements were reviewed:

1. The number, nature, and timing of recommendations made by pharmacists via the AKI Pharmacy Review document.
2. The number of patients with AKI admitted with a history of taking medicines that have nephrotoxic potential.
3. The proportion of pharmacist recommendations implemented by the medical team.
4. AKI progression after the medication intervention.
5. The number of patients with AKI who have been given sick day guidance.

1. Pharmacist AKI reviews were indicated for 46 patients of the 50 admitted with CA-AKI. Pharmacists reviewed 44 of these patients (96%); 35 (76%) within 24 hours and 42 (91%) within 48 hours of the AKI alert. Dose adjusting or withholding of medications was recommended for 38 (80.9%), of which 34 recommendations (89.5%) were to withhold the medication. Changes were also recommended for 14 'other' medications.
2. The study found 29 patients (63%) were taking ≥1 medication from 1 of the 5 categories. Diuretics were the most common category, with 4 (14%) patients on 2 diuretics.
3. Pharmacist recommendations were adhered to for 36 medications (95%); recommendations for 'other' medications were followed for 11 (79%).
4. Results showed that 34 patients (77.3%) showed no AKI progression following pharmacist review.
5. Finally, 35 patients were identified as suitable for interview and 28 were interviewed. No patient in this group recalled sick day guidance or had been counselled that any medications they were taking could affect their kidneys.

This study suggests that the dissemination of sick day guidance to at risk patients has not been maximally implemented thus far, a point which, in particular, was discussed at the poster presentation. At the congress, there was debate over the formation of the agreement for sick day guidance itself and then the subsequent responsibility for tailoring advice and restarting medication. Pharmacist reviews in AKI are crucial in the early recognition and cessation of potentially nephrotoxic mediations. Reviews could be fundamental to optimal medical management of AKI and preventing AKI progression.

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PREDICTORS OF OLIGURIC ACUTE KIDNEY INJURY DUE TO LEPTOSPIROSIS IN AN ALBANIAN POPULATION

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Keywords: Leptospirosis, acute kidney injury (AKI), oliguria, hypoalbuminaemia, creatinine, bicarbonate.

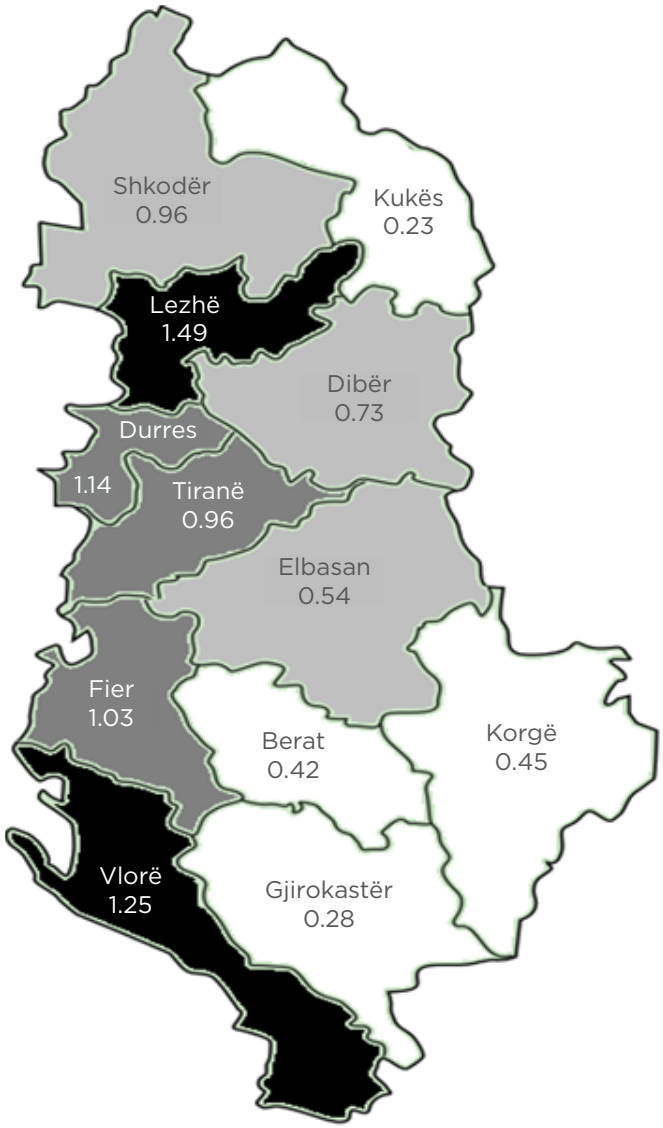

Figure 1: The distribution of leptospirosis in Albania.

Leptospirosis is an endemic zoonosis that is encountered more frequently in warm and tropical areas; Albania is considered to be an endemic zone.[1] Acute kidney injury (AKI) is one of the most serious complications associated with this infection. The severity of AKI is closely related to mortality in this context.[2,3]

Therefore, we investigated 119 consecutive adult patients diagnosed with leptospirosis from 2010–2015 and treated in a tertiary referral centre. The map in Figure 1 shows the distribution of leptospirosis in Albania, which will help in structuring better preventive public health measures. The majority of patients came from the western areas on the Adriatic coast.

In our study, 95 patients developed different degrees of AKI during the course of the disease. Patients were statistically analysed to identify predictors of oliguric-AKI. Patients were classified into two groups: oliguric (18 patients; 18.9%) and non-oliguric (77 patients; 81.1%). Receiver operating characteristic (ROC) curve analysis identified albumin level (area under the curve [AUC]: 0.854; cut-off value ≤2.7 g/dL; sensitivity 90%; specificity 71.1%), serum creatinine (AUC: 0.769; cut-off value ≥3.84 mg/dL; sensitivity 83.4%; specificity 64%), and HCO_3^- (AUC: 0.769; cut-off value ≤18.4 mmol/L; sensitivity 68.7%; specificity 79.1%) (Figure 2).

In our study, hypoalbuminaemia, elevated serum creatinine, and low serum levels of HCO_3^-, were indicators for oliguric-AKI in leptospirosis upon admission. The evaluation of such simple tests in patients with leptospirosis can help a physician determine early risk for the development of oliguria.

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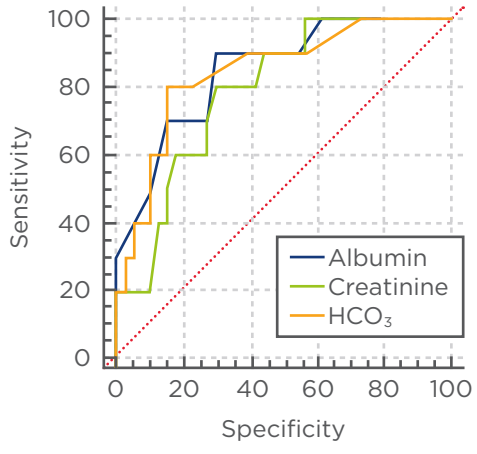

Figure 2: Receiver operating characteristic curve comparison.

BLOOD PRESSURE AND OUTCOMES IN STAGE 3–5 CHRONIC KIDNEY DISEASE PATIENTS: LESS IS MORE?

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Keywords: Blood pressure (BP), chronic kidney disease (CKD), J-shaped relationship, malnutrition, inflammation.

This presentation focussed on J-shaped relationships between time-averaged blood pressure (BP) and outcomes in advanced chronic kidney disease (CKD) patients, who are usually excluded in clinical trials. Several observational studies demonstrate that low BP levels seem to be related to higher risk of cardiovascular (CV) events, end-stage renal disease (ESRD), or mortality in patients with CKD. The latest results from the SPRINT trial show that targeting a systolic BP (SBP) <120 mmHg among 2,646 patients with CKD was not as beneficial as for those without CKD.[1,2] These studies raise concern that J-shaped relationships may exist in patients with CKD. This prospective observational study enrolled 2,340 CKD Stage 3–5 patients between November 2002 and May 2009 and followed them until July 2010 or death. Standardised BP measurements were obtained by a standard mercury sphygmomanometer or a validated automated device in seated patients after a 10-minute rest. The average of the first two BP readings was recorded at each visit. The BP records of each patient were averaged during the study period. Demographic, clinical, laboratory, and disease variables were measured. Three outcomes were assessed: ESRD, cardiovascular events, and all-cause mortality. The definitions of each outcome were the same as our previous study.[3]

The results of this study showed that, in fully-adjusted Cox regression, a J-shaped relationship existed between time-averaged SBP and ESRD: the hazard ratio (HR) of time-averaged SBP <110 mmHg was 2.01 (95% confidence interval [CI]: 1.14–3.57), and the HR of time-averaged SBP ≥160 mmHg was 2.82 (95% CI: 2.07–3.84), compared with the reference group (time-averaged SBP 120–129 mmHg). A J-shaped relationship also existed between time-averaged SBP and cardiovascular events or all-cause mortality. The association between time-averaged SBP and malnutrition-inflammation, defined as albumin <3.5 g/dL and C-reactive protein (CRP) >10 mg/dL, was also J-shaped. The odds ratio of time-averaged SBP <110 mmHg was 2.63 (95% CI: 1.31–5.27), and the odds ratio of SBP ≥160 mmHg was 1.63 (95% CI: 1.10–2.41), compared with the reference group. As for diastolic blood pressure (DBP), a J-shaped relationship also existed between time-averaged DBP and CV events and all-cause mortality. For CV events, the HR of time-averaged DBP <60 mmHg was 1.59 (95% CI: 1.14–2.22), compared with the reference group (time-averaged DBP 70–79 mmHg). For all-cause mortality, the HR of time-averaged DBP <60 mmHg was 1.50 (95% CI: 1.03–2.17), compared with the reference group (time-averaged DBP 70–79 mmHg). However, there were no J-shaped relationships between time-averaged pulse pressure and clinical outcomes. Malnutrition-inflammation complex syndrome could be a possible factor associated with the impact of low BP in advanced CKD patients. A schematic representation of protein-energy wasting and its complex inter-relationships in CKD patients has been proposed by Fouque et al.[4] These factors include chronic inflammation, malnutrition, uraemic toxin, acidosis, ageing, oxidative stress, diabetes, cardiovascular disease, and atherosclerosis. Our findings may add another factor, low BP, to this complicated puzzle. Low BP may lead to hypoperfusion and end-organ damage. At the

same time, it may be a result of inflammation. Therefore, low BP may be a cause, an effect, or both, of malnutrition-inflammation complex syndrome. Further analysis is warranted.

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NUTRITIONAL STATUS AND DIETARY HABITS AMONG PATIENTS WITH CHRONIC KIDNEY DISEASE IN CONSERVATIVE TREATMENT: A LONGITUDINAL STUDY IN BRAZIL

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Keywords: Chronic kidney disease (CKD), nutrition, obesity, diet.

Metabolic disturbances are common in patients with chronic kidney disease (CKD). A longitudinal study is being conducted in Fortaleza, Brazil, to evaluate nutritional status and dietary habits among CKD patients in conservative treatment. The study began in May 2015 and, during the initial evaluation, a complete anthropometric assessment was completed and dietary habits were recorded through a 24-hour food recalling. Patients were re-evaluated every 3 months. A total of 93 patients were included, the majority of whom were female (54.8%), and their mean age was 67±14 years, which points to an ageing population with CKD. The majority of patients had Stage III CKD (51%). According to BMI, the majority of patients (53.8%) had excess weight and, according to waist circumference, 81.7% had high cardiometabolic risk. Most of the studied patients had low socio-economic status, which limits access to a proper diet and regular exercise. This resulted in the participants being overweight. A recent study with elderly women concluded that nearly 50% of the cohort were classified as overweight, and 36% were classified as obese. Increased central fat distribution was found in 91.7%. Participants with CKD were older and had higher prevalence of either diabetes or hypertension.[1]

Our study provided evidence that abdominal obesity is an important predictor of CKD, as suggested in previous studies.[2] Associations between BMI and CKD were found in a study in the UK, which provided evidence that being overweight increases the risk of advanced CKD, that being obese further increases such risk, and that this remains true for those with and without diabetes, hypertension, or cardiovascular disease.[3] In our study, mean daily energy intake was 1,312±504 kcal. Evaluation of macronutrient intake evidenced mean daily consumption of carbohydrate at

51±5.5%, lipid consumption at 28±14%, and protein intake at 43±14 g/day. Mean daily fibre intake was 13.2±8.5 g/day.

According to a study that analysed the macronutrients and energy prescribed to CKD patients on conservative treatment, the diets analysed had, on average, 1,393 kcal less than the value contained in the diet manual used by the hospital nutrition service.[4] The diets studied were always inadequate, with respect to the nutrients evaluated, and carried an insufficient amount of energy. CKD patients in conservative treatment present nutritional risk, as they have excess weight, high cardiometabolic risk, and a diet with a high amount of carbohydrates and lipids and low amounts of fibre. Nutritional intervention is very important to this group of patients, and dietary modifications could have a positive impact on slowing CKD progression. Further results of this longitudinal study will be available soon and may highlight novel aspects of nutrition in CKD.

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ACUTE INTERMITTENT PORPHYRIA IN ELDERLY PATIENTS UNDERGOING CHRONIC HAEMODIALYSIS: RESOLUTION OF TETRAPLEGIA WITH SYSTEMIC HAEMIN AND REHABILITATION

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Keywords: Acute intermittent porphyria, tetraplegia, haemin, chronic kidney disease (CKD).

Porphyrias are inherited defects in the biosynthesis of haem. Attacks in acute intermittent porphyria are characterised by abdominal pain, neurological disturbances, and psychiatric disorders; in severe cases, they may lead to respiratory paralysis and coma. The disease carries a 5-year mortality rate of 20–25%, mostly in young adults and especially in females in their second and third decade of life. The condition is less frequent in males (mostly taking place during the third–fourth decade of life), is rare in children, and even rarer after the fifth decade of life.

Patients experienced renal colic-like pain, with pallor, nausea, vomiting, fever, acute urinary retention, and hyperchromic urine emission (urine may turn dark red). There are multiple inducing factors:

drugs, alcohol, stress, fasting, menstruation, and infections. The incidence of acute porphyria is rated 0.54/100,000 (according to Orphanet, November 2016).[1,2] Renal involvement in acute porphyrias is represented by hyponatraemia, urinary retention, tubulo-interstitial nephropathy, hypertension, and chronic kidney disease (CKD).

A 68-year-old woman, undergoing haemodialysis three-times a week since January 2011 (32 months) for CKD due to undiagnosed nephropathy, has been diagnosed with acute intermittent porphyria through biomolecular analysis performed as part of a family screening. In September 2013, she was admitted to the Nephrology Unit for abdominal pain, constipation, and uncontrolled hypertension. Since she had no diuresis, plasma porphyrins were measured, peaking at 619 nm. The patient reported depression and progressive muscle weakness in her legs and then, the following day, in her arms, defining a medical case of flaccid tetraparesis. Supposing she had polyradiculoneuritis, a lumbar puncture was made and was negative. Two days later, she was given haemin (Normosang®, Orphan Europe, Puteaux, France), at a dose of 3 mg/kg/24 hours for 4 straight days, and then twice a week for the following 2 months, during which time she was moved to the Rehabilitation Medicine Unit, where she started a rehabilitation plan.

Functional evaluation was assessed by the Barthel scale (BS) (values from 0–100), while muscular strength of involved paretic muscles was assessed by the Medical Research Council (MRC) scale (values from 0–60; 0–5 for muscle bundle for three muscle groups for the four limbs), respectively, at admission, 2 weeks, 4 weeks, and at discharge. The patient underwent rehabilitation including electrical stimulation and occupational therapy.

At admission, BS score was 25, which indicated severe disability. Likewise, neurological imaging showed severe impairment of strength characterised by tetraplegia. MRC score was 0 in both upper and lower limbs.

After haemin administration and rehabilitation treatment, muscular deficit progressively improved and MRC scores were 24, 36, and 50, at 2 weeks, 4 weeks, and at discharge, respectively. Likewise, good functional outcome was also observed, with BS scores of 45, 65, and 90 at 2 weeks, 4 weeks, and at discharge, respectively. After 40 months, the patient had no more abdominal pain or constipation. Blood pressure, motor skills, and muscle strength are back to normal values, after mild weakness. Currently, the patient is taking haemin every 4 months and, given her good state of health, it is likely she will be given haemin every 6 months until total discontinuation. The patient will keep on following a normocaloric, hyperglucidic diet with maltodestrins.

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COMPARISON OF FLUID STATUS IN A PREVALENT HAEMODIALYSIS AND PERITONEAL DIALYSIS COHORT: A RETROSPECTIVE ANALYSIS

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Citation: EMJ Nephrol. 2017;5[1]:60-61. Abstract Review No. AR8.

Keywords: Overhydration (OH), peritoneal dialysis (PD), haemodialysis (HD), pro-brain natriuretic peptide (pro-BNP), echocardiogram.

INTRODUCTION

Euvolaemia is a major issue in chronic kidney disease, as volume overload (VO) is related to cardiac dysfunction, inflammation, and mortality.[1] Guidance on how to achieve and maintain euvolaemia in dialysis patients is hampered by the absence of factors associated with VO.[2] The aim of this study was to compare volume status between haemodialysis (HD) and peritoneal dialysis (PD) patients and to identify factors associated with hypervolaemia.

METHODS

The study included 47 HD patients and 21 PD prevalent patients. Baseline characteristics and comorbidities were evaluated. For each patient, blood pressure, pro-brain natriuretic peptide (pro-BNP), bioimpedance analysis, and echocardiographic variables were evaluated. In HD patients, the values were recorded pre-session. Overhydration (OH), extracellular water (ECW), and OH/ECW were used as volume indices; an OH/ECW >15% was the cut-off used to define OH.

RESULTS AND DISCUSSION

The characteristics of the population are summarised in Table 1.

Table 1: Overall characteristics of the population.

	PD (n=21)	HD (n=47)	p value
Male sex	71.4%	66.0%	NS
Mean age (years)	55.3±14.5	72.7±12.9	<0.001
Diabetes mellitus	14.3%	44.7%	0.013
Chronic obstructive pulmonary disease	9.5%	10.6%	NS
Hypertension	85.7%	74.5%	NS
Coronary artery disease	14.3%	25.6%	NS
Stroke	0%	23.4%	0.011
Peripheral vascular disease	14.3%	17.0%	NS
Mean dialysis vintage	19.2±16.1	27.5±30.8	NS
OH/ECW	7.6±8.9%	12.4±8.1%	0.037
OH/ECW >15%	33.3%	42.6%	0.049
OH (L)	1.2±1.6	1.7±1.4	NS
pro-BNP (ng/L)	4,260.0±8,992.8	8,282.5±8,903.4	<0.001
Systolic blood pressure (mmHg)	137.3±34.7	132.5±22.7	NS
Diastolic blood pressure (mmHg)	85.3±13.4	65.0±16.6	<0.001
Left atrium diameter (cm)	3.6±0.8	4.5±0.7	<0.001
Left ventricular end-diastolic diameter (cm)	4.4±1.6	5.1±0.9	0.042
Posterior septal thickness (cm)	0.9±0.2	1.0±0.2	NS
Ejection fraction	60.3±12.4%	58.2±9.8%	NS

OH: overhydration; ECW: extracellular water; pro-BNP: pro-brain natriuretic peptide; HD: haemodialysis; PD: peritoneal dialysis; NS: not significant.

Fluid overload is frequently present in dialysis patients and leads to adverse clinical outcomes; thus, ensuring dialysis patients are euvolaemic is essential.[1] Despite the fact that VO is a preventable and treatable condition, managing fluid balance and achieving true dry weight is still a major challenge in both HD and PD patients. However, indices obtained from bioimpedance analysis are useful for the assessment of fluid status. The different dialysis modalities have different effects on fluid volume control. PD is believed to provide better fluid control due to its continuous ultrafiltration and the fact that residual renal function is better preserved.[3] The findings of our study corroborate this explanation. Although the HD patients were older and had a higher incidence of diabetes and stroke, they were also more overhydrated compared to PD patients and had higher pro-BNP values and echocardiography measurements, such as left atrial diameter and left ventricular end-diastolic diameter (LVEDD). Overall, 27 of 68 (40%) patients had OH/ECW >15%, and this ratio was positively correlated with pro-BNP (r: 0.79; p<0.001), left atrial diameter (r: 0.64; p=0.002), and LVEDD (r: 0.73; p<0.01). This indicates that fluid overload has an effect not only on cardiac remodelling, but there also seems to be an effect with a well-established cardiovascular laboratory parameter, pro-BNP, indicating that it is not only a marker of cardiac dysfunction but is also associated with VO. There were several independent factors (p<0.05) associated with OH in multivariate logistic regression analysis: higher systolic blood pressure (odds ratio [OR]: 1.05; confidence interval [CI]: 1.01–1.09) and higher LVEDD (OR: 1.99; CI: 1.09–3.06).

CONCLUSION

Excess fluid may lead to adverse events, especially in cardiac conditions. So, finding tools to achieve euvolaemia is of the utmost importance. In this cohort, fluid overload was more common among HD patients, although they were older and had more severe diabetes. Globally, OH was associated with higher pro-BNP, systolic blood pressure, and worse cardiac parameters, especially LVEDD.

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MALNUTRITION IN CHRONIC HAEMODIALYSIS PATIENTS: EFFECTS OF INTRADIALYTIC PARENTERAL NUTRITIONAL THERAPY ON SERUM ALBUMIN AND TOTAL PROTEIN, BMI, AND PHASE ANGLE IN SELECTED PATIENTS

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Keywords: Intradialytic parenteral nutritional therapy (IDPN), malnutrition, nutritional medicine, haemodialysis.

Malnutrition is a common problem that is associated with unfavourable clinical progression, more frequent hospitalisation, and increased mortality in patients on dialysis. For dialysis patients with diabetes mellitus (DM) or tumour patients, the risk is especially high. In order to improve nutritional status, different therapeutic approaches are followed; intradialytic parenteral nutritional therapy (IDPN) is one of them. We herein compared the effects of IDPN on protein metabolism, BMI, and

phase angle in dialysis patients with DM or tumour disease to patients without DM or malignancy.

We analysed single-centre data from 57 chronic haemodialysis patients with malnutrition (17 with DM, 20 with malignancy), who were treated with IDPN for ≥6 months between January 2013 and December 2015. An individualised IDPN infusion regime containing 800–1,000 kcal per application was administered three-times a week. Assessments of laboratory parameters, phase angle, and BMI were performed every 3 months. In contrast to tumour patients with a low BMI (22.2±7.0), patients with DM showed a normal BMI (24.7±7.8). These significant differences remained during the study period (22.8±6.7 versus 25.6±7.8). Interestingly, the values of the phase angle in DM patients were lower (3.5±1.3) during the study period compared with patients with tumour disease and control patients (3.5±1.3 versus 3.7±1.1, 3.5±1.3 versus 3.8±1.1). In contrast to published data, this study showed that IDPN was unable to improve BMI and phase angle in treated patients with DM or malignancy but was effective at improving the BMI of controls (22.8±9.6 versus 23.8±6.7). Moreover, serum albumin in patients with tumour disease increased (3.5±0.5 versus 3.7±0.4 g/dL). Although our study failed to demonstrate a significant IDPN-dependent improvement in the dietary status of chronic haemodialysis patients with DM or tumours, IDPN effectively prevented further deterioration of those patients with malnutrition. Even though meta-analyses point to the low quality of many IDPN studies,[1] a positive influence of IDPN on food-related parameters can nevertheless be assumed.[2] A clear statement on the long-term effects of IDPN cannot be made at present due to the lack of studies.[1]

The various approaches suggested to avoid malnutrition in haemodialysis patients point to the fact that, because of multifactorial causes,[3] there are still insufficient therapeutic measures to identify patients at risk and start prevention; moreover, it is still under debate how to diagnose malnutrition. As discussed in the recent literature, and as our study shows, a range of parameters needs to be assessed for determination of nutritional status, because single-parameter assessment might lead to misclassification of patients. The biochemical laboratory parameters prealbumin, serum albumin, anthropogenic measurements, BMI, and the bioelectrical impedance analysis with phase angle determination should be assessed and assessment instruments that have been proven valid (subjective global assessment, Mini Nutritional Assessment short-form, and malnutrition, inflammation and atherosclerosis) should be utilised.[3] In the opinion of the authors, dialysis patients should be regularly screened for malnutrition, and IDPN could be useful to prevent further nutritional deterioration in selected patients, despite its high costs.

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KIDNEY VOLUME EVALUATION IN AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE PATIENTS' RENAL OUTCOMES

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Keywords: Autosomal dominant polycystic kidney disease (ADPKD), kidney volume, estimated glomerular filtration rate (eGFR), height adjusted total kidney volume (HtTKV).

Autosomal dominant polycystic kidney disease (ADPKD) patients show end-stage renal disease (ESRD) progression, which requires suitable biomarkers to identify. While estimated glomerular filtration rate (eGFR) remains in normal ranges for several years before renal impairment, there is a direct negative correlation between kidney volume (normalised according to the patient's height adjusted [HtTKV]) and eGFR. This has recently highlighted a HtTKV-based classification to stratify patients according to their risk of developing kidney failure. Five patient classes have been identified (1A–1E), in which eGFR decline ranges from 0.23–4.78 mL/min/1.73 m^2/year (males) and 0.03–4.58 mL/min/1.73 m^2/year (females).

We have conducted a prospective study enrolling 29 APKD patients (12 males and 17 females). Renal function and HtTKV were evaluated by CKD-EPI formula and kidney nuclear magnetic resonance, respectively. HtTKV values were between 224 and 3,091 cc/m, and patients were therefore divided into five groups according to the classification previously described (see Table 1). In the patients' cohort, eGFR was found to range from 12–107 mL/min/1.73 m^2 (15 patients showed a CKD-EPI eGFR >60 mL/min/1.73 m^2, while 14 patients had an EPI eGFR <60 mL/min). Among Class D patients, three-quarters of patients had eGFR <60 mL/min/1.73 m^2, as did 6 out of 7 Class E patients. Among Class B patients, only 1 patient showed an CDK-EPI eGFR <60 mL/min/1.73 m^2, as did 4 out of 10 Class C patients. Early-onset hypertension was exhibited in 20 out of 29 patients <35 years old. In this hypertensive group, an HtTKV >600 cc/m was observed in 16 patients. An ESRD-familiar history was observed in 9 patients <55 years old (3 Class C, 1 Class D, and 5 Class E patients). For each patient a prognostic evaluation was performed according to a 'slope' model derived by Mayo Clinic classification; 10-year progression towards Stage 3 CKD was estimated in 6 out of 15 patients with eGFR >60 mL/min/m^2. At the same time, 6 out of 14 patients with eGFR <60 mL/min/m^2 were estimated to develop ESRD in a 5-year period, with 6 more predicted to develop the disease over a 10-year period. The last 2 patients were estimated to develop Stage 4 CKD over a 10-year period.

Although conducted on a small sample size, our data suggest the clinical utility of kidney volume assessment in ADPKD patients, especially for prognostic evaluation, allowing the identification of patients at higher risk of developing ESRD.

Table 1: Classification of autosomal dominant polycystic kidney disease patients.

Class (n)	eGFR >60 mL/min	Hypertension/ HtTKV >600 cc/m	Family history for ESRD onset <55 years
A (3)	3	0	0
B (5)	4	0	0
C (10)	6	7	1
D (4)	1	3	1
E (7)	1	6	4

eGFR: estimated glomerular filtration rate; HtTKV: height adjusted total kidney volume; ESRD: end-stage renal disease.

NEOPTERIN, MCP-1, AND MCSF AS NEW MARKERS OF TUBULAR DAMAGE IN CHILDREN WITH CHRONIC KIDNEY DISEASE ON CONSERVATIVE TREATMENT

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Keywords: Fractional excretion (FE), inflammation, tubular dysfunction.

Chronic kidney disease (CKD) is characterised by enhanced migration of immunocompetent cells to the sites of inflammation, renal fibrosis, and irreversible tubular damage. Monocyte chemoattractant protein (MCP)-1, macrophage colony stimulating factor (MCSF), and macrophage migration inhibitory factor (MIF) control early-stages of cell migratory activity, such as the movement of monocytes to the sites of inflammation and their transition into macrophages. However, these have not been put into the focus of CKD progression in children. Neopterin was the only parameter in this group produced by monocytes and macrophages upon stimulation. Thus, it may mirror cellular immune response; however, it has never been analysed as a marker of inflammation or macrophage activity in children with CKD.

The analysis of fractional excretion (FE) as a substitute for tubular dysfunction in CKD patients was studied in the case of heat shock protein (Hsp)-27 in adults[1] and concerned markers of epithelial-mesenchymal transition in children from our previous study.[2] The aim of this study was to analyse the usefulness of FE of MCP-1, MCSF, MIF, and neopterin as pluripotent markers of inflammation, monocyte-macrophage interplay, and tubular damage in the course of CKD. The study group consisted of 20 children at CKD Stages 1–2, 41 pre-dialysis patients at CKD Stages 3–5, and 23 age-matched controls. The serum and urine concentrations of MCP-1, MCSF, MIF, and neopterin were assessed by enzyme linked immunosorbent assay (ELISA). The FE of analysed parameters was then calculated according to the formula: ([parameter urine concentration] x [creatinine serum concentration])/([parameter serum concentration] x [creatinine urine concentration]) x 100%.

The serum and urine concentrations of MCP-1, MCSF, MIF, and neopterin were significantly elevated in CKD children versus controls, although no correlations were noticed. The values of MCSF and neopterin in urine were higher than those in serum, both in CKD and control groups. In healthy controls, the FE of MCP-1 and MIF did not exceed 1%, whereas it reached ≤5% in the case of MCSF and neopterin. FE MCP-1 remained <1% in children at CKD Stages 1–2 and FE MIF <1% was seen in all children with CKD. Only FE MCP-1 and MCSF values were significantly elevated in children at CKD Stages 1–2 versus controls, whereas all FE values were higher in patients at CKD Stages 3–5 than in CKD Stages 1–2.

The values of FE MCP-1 in CKD Stages 1–2 were significantly higher in comparison to controls but did not exceed 1%, which seemed to confirm the early inflammatory process in the tubules, preceding their damage. The increase in FE MCSF values, together with the decline in MCSF urine levels in CKD Stages 3–5, could signify early macrophage overactivity in renal parenchyma of CKD Stages 1–2 and progression to tubular damage in CKD Stages 3–5. Elevated FE neopterin values, accompanied by increasing neopterin urine concentrations in advanced CKD, suggested tubular damage due to persistent inflammation.

FE of the examined markers may serve as a useful tool in the assessment of CKD related to tubular dysfunction and may help distinguish between early inflammatory and late destructive processes in renal parenchyma of children with CKD.

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EDITOR'S PICK

This particularly comprehensive and realistic review of the epidemiology, pathogenesis, and management of AKI in a tropical country like India is highly recommended reading.

Prof Norbert Lameire

ACUTE KIDNEY INJURY IN TROPICAL COUNTRIES

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ABSTRACT

Acute kidney injury (AKI) in tropical countries is strikingly different from that in countries with a temperate climate. Tropical regions are characterised by year-round high temperatures and the absence of frost, which supports the propagation of infections that can potentially cause AKI. The aetiology and presentation of AKI reflects the ethnicity, socioeconomic factors, and ecological conditions in tropical countries. Apart from infections, other causes of AKI include exposure to animal toxins, ingestion of plant toxins or chemicals, poisoning, and obstetric complications. The low income status, poor access to treatment, and sociocultural practices (use of indigenous medicines) contribute to poor outcomes of patients with AKI. The exact aetiologic diagnosis often cannot be made due to lack of appropriate laboratory services. The epidemiology of AKI in tropical regions is changing over time. Renal replacement therapy is inaccessible to the majority and late presentation with delayed treatment add to the risk for future development of chronic kidney disease. AKI is often the primary cause of chronic kidney disease in the developing world, which increases demand for renal replacement therapy and transplantation. Most causes of AKI in developing countries are preventable and strategies to improve the public health and increased access to effective medical care are the need of the hour. This review offers comprehensive ideas about epidemiology, aetio-pathogenesis, clinical presentation, diagnosis, treatment, and prevention of community-acquired AKI in the tropics, with special reference to the Indian subcontinent. AKI is an under-recognised cause of morbidity and mortality in developing countries and even small, simple interventions could have an impact on its outcome.

Keywords: Acute kidney injury (AKI), chronic kidney disease (CKD), haemodialysis, infection, mortality.

INTRODUCTION

The lack of a uniform single definition, absence of multicentre studies, and under-reporting of acute kidney injury (AKI) in the tropics has led to difficulties in defining true epidemiology. The most recent definition of AKI proposed by the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines workgroup retains the Acute Kidney Injury Network (AKIN) and Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) staging criteria[1,2] (Table 1). In the developed temperate countries, AKI usually occurs as a part of multi-organ involvement, especially

in elderly patients; while in tropical countries it is usually community acquired, affecting the younger individuals.[3] The published data on AKI incidence in developing countries are scarce[4,5] and the risk of progression to chronic kidney disease (CKD) is unknown.[6]

EPIDEMIOLOGY

The epidemiology of AKI is largely influenced by environmental factors and climatic conditions in tropical regions. Most published data are from single-centre studies conducted in urban areas and might not reflect the true prevalence of AKI. Approximately 0.1–0.25% of all admissions or 6.6 out of 1,000 admissions were for the management of AKI.[7,8] The population of patients with AKI in developing tropical countries is younger (30–40 years of age) than that reported in developed temperate countries (60–70 years of age).[9] The incidence of AKI is usually about 5–9% inwards and 30–36% in intensive care units. The incidence of AKI was predominantly seen during the months of July–September.

AETIO-PATHOGENESIS, DIAGNOSIS, AND TREATMENT

The causes of AKI in tropical countries can be due to infections, animal and plant toxins, drugs/poisons, or obstetric complications.[10] There are some newly emerging and rare causes for AKI that we commonly encounter. Figure 1 gives the overall aetiology, pathomechanisms, renal histology, and outcome of AKI in the tropics. Table 2 gives the detail regarding diagnostic tests, treatment, and outcome of common aetiologies of AKI.

Infection

The usual presentation of tropical febrile illness is fever with headache, severe myalgia, jaundice, intravascular haemolysis, and thrombocytopenia to variable extent.[11] However, the similarity of the clinical presentations of the various forms of infection-associated AKI causes difficulty in diagnosis based only on clinical grounds.

Malaria

Most cases of malaria-associated AKI occur due to *Plasmodium falciparum* infection, although a few cases with *Plasmodium vivax* infection have been reported. About 50% of confirmed cases reported annually in India were due to *P. falciparum*. Severe parasitaemia, children aged <5 years, pregnant women, and immunosuppressed individuals have an increased risk of AKI.[12] The pathomechanisms include cytoadherence of parasitised erythrocytes to the vascular endothelium, sequestration and obstruction of small vessels, immune-mediated glomerular and tubular damage, alterations of renal haemodynamics, and proinflammatory monocyte activation with release of tumour necrosis factor-α.[13] The risk factors for high mortality include late referral, high parasitaemia, oliguria, hypotension, multisystem involvement, hepatitis, or acute respiratory distress.[14,15]

In a study involving 59 patients, *P. falciparum* malaria was seen in 76.3%, *P. vivax* in 16.9%, and mixed infection in 6.8% of patients. Dialysis was undertaken in 92% of patients, 81.3% of patients had complete renal recovery, 11.8% succumbed to malaria, and 6.9% progressed to CKD.[16]

Leptospirosis

Leptospirosis is a zoonosis caused by *Spirochete leptospira.* There are >200 pathogenic serovars with rodents as major reservoirs.[17] Classic leptospirosis consists of two phases: the initial lepto-spiraemic phase lasting 4–7 days followed by the immune phase, characterised by an increase in immunoglobulin M (IgM) antibodies, and the development of disease manifestations in various organ systems.[18] The pathogenesis includes direct nephrotoxicity, hyperbilirubinaemia, rhabdomyolysis, and hypovolaemia.[19] The major histological findings are acute interstitial nephritis (AIN) and acute tubular injury (ATI).[20] The leptospirosis laboratory, first established in July 1994 at the Institute of Nephrology, Madras Medical College, Chennai, India, is where microscopic agglutination tests, IgM enzyme-linked immunosorbent assay (ELISA), and macroscopic slide agglutination tests are carried out.[21] In the recent past, leptospirosis-associated AKI at the centre had significantly declined from 31% in 1987–1991 to 7.5% in 1995–2004 due to greater awareness of disease, availability of better diagnostic facilities, and widespread use of antibiotics. Faine had evolved criteria for diagnosis of leptospirosis on the basis of clinical, epidemiological, and laboratory data (World Health Organization [WHO] guidelines).[22] Certain necessary modifications had been set (Modified Faine's Criteria) to make the diagnosis early and simple.[23] A 2007 study from Sri Lanka followed-up 44 patients with leptospirosis-associated AKI for at least 1-year, of which 9% showed progression to CKD. [24]

Table 1: Acute kidney injury classification and staging.

Stage	Urine output common to all	KDIGO	AKIN staging	Class	RIFLE criteria	GFR
		Serum creatinine	Serum creatinine		Serum creatinine	
1	<0.5 mL/kg/h for >6 h (6–12 h in KDIGO)	1.5–1.9 x baseline or ≥0.3 mg/dL increase	Increase of 0.3 mg/dL or increase of 150–200% from baseline	Risk	Sr creatinine x 1.5	Decrease of >25%
2	<0.5 mL/kg/h for ≥12 h	2–2.9 x baseline	Increase of >200–300% from baseline	Injury	Sr creatinine x 2	Decrease of >50%
3	<0.3 mL/kg/h for ≥24 h or anuria ≥12 h	3 x baseline or increase to ≥4 mg/dL or initiation of RRT or <18 years with decrease in eGFR to <35 mL/min/1.73 m^2	Increase of >300% from baseline or ≥4 mg/dL with an acute increase of ≥0.5 mg/dL or on RRT	Failure	Sr creatinine x 3 or >4 mg/dL with an acute rise of >0.5 mg/dL	Decrease of >75%
-	-	-	-	Loss	Persistent acute renal failure = complete loss of kidney function >4 weeks	-
-	-	-	-	ESRD	ESRD >3 months	-

AKI: acute kidney injury; eGFR: estimated glomerular filtration rate; RRT: renal replacement therapy; ESRD: end-stage renal disease; KDIGO: Kidney Disease: Improving Global Outcomes; AKIN: Acute Kidney Injury Network; RIFLE: Risk, Injury, Failure, Loss, and End-stage kidney disease.

Scrub typhus

Scrub typhus is caused by an obligate, intracellular gram-negative bacterium *Orientia tsutsugamushi* which is maintained by transovarian transmission in trombiculid mites.[25] It presents with fever, eschar at the site of mite bite, maculopapular rash, and multiorgan involvement (interstitial pneumonia, meningitis, and hepatitis). Prerenal azotaemia is the main cause of AKI, though direct invasion of bacterium, systemic vasculitis, interstitial nephritis, and pigment nephropathy due to rhabdomyolysis can occur.[26-28] In a study of 35 children with scrub typhus, an eschar was observed in 11%. Complications included myocarditis with cardiogenic shock in 34% and AKI in 20%.[29] Creatine phosphokinase was raised in 55% and haemodialysis was undertaken in 10%. Independent predictors of AKI were intensive care unit requirement and thrombocytopenia.[30] Renal failure was found to be an independent predictor of mortality.[31]

Dengue

Dengue is caused by an arbovirus, transmitted by *Aedes aegypti* female mosquitoes and about 40% of the world's population are living in areas of increased risk of dengue infection. In addition to climatic conditions, uncontrolled and unplanned urbanisation, and migration of people are important factors for epidemics of dengue.[32] The spectrum of dengue infection may be asymptomatic or classic dengue symptoms, such as fever, headache, retro-ocular pain, myalgia, arthralgia, and skin rash or dengue haemorrhagic fever (DHF), or dengue shock syndrome (DSS). AKI is an unusual complication of dengue, frequently associated with hypotension, rhabdomyolysis, or haemolysis, immune complex mediated-acute glomerulonephritis, or sepsis. The indicators of mortality were severe dengue, oliguria AKI, respiratory failure, and prolonged prothrombin or activated partial thromboplastin greater than twice the normal values. Lee et al.[33] reported a 4.9% incidence of AKI in 81 patients suffering from DHF/DSS. Based on the AKIN criteria, the results revealed that 5.4% had mild AKI, 3.1% had moderate AKI, and 2.2% had severe AKI.[34] Mallhi et al.[35] reported a high incidence of AKI (14.2%) among dengue patients with mortality rates of 1.2%.

HIV

In patients with HIV, AKI occurs with sepsis, hypotension, dehydration, exposure to nephrotoxins, and toxic effects of antiretroviral therapy (ART).[36] The most common nephrotoxic effects associated with ART include crystal-induced obstruction, mainly indinavir and atazanavir, and proximal tubule damage related to tenofovir. The combination

of tenofovir with didanosine should be avoided because of its potentially addictive toxicity. Severe immunosuppression (CD4+ count <200 cells/mm^3 and HIV RNA level >10,000 copies/mL) means a greater risk of AKI development.[37,38] AKI was noted in 138 (3.9%) patients in a study. Hypovolaemia (44.2%) and sepsis (14.5%) contributed to AKI in the majority of cases. Acute tubular necrosis (ATN) was the most common histology, followed by AIN and diffuse endocapillary proliferative glomerulonephritis. In hospital mortality was 24.64%. A lower CD4 count decreased serum albumin levels, and Stage 4 WHO disease were associated with higher mortality.

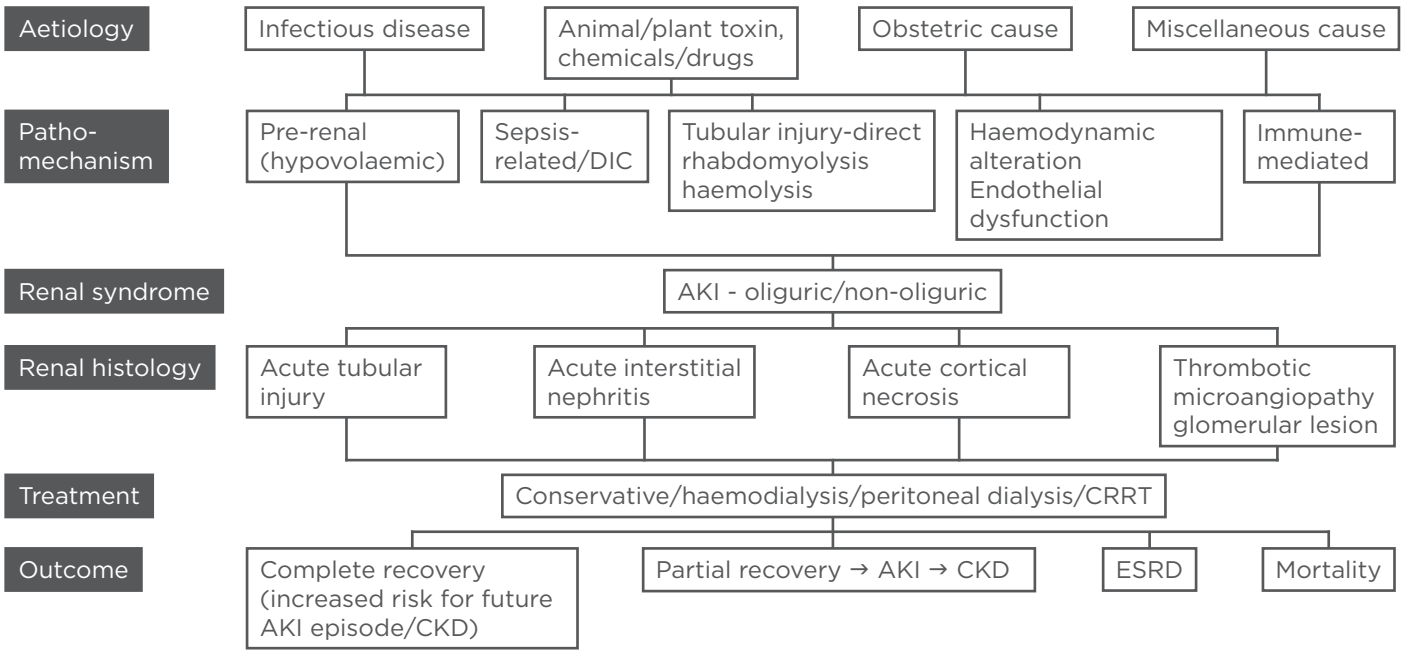

Figure 1: Schematic chart of pathomechanisms, renal histology, and outcome of various aetiologies of acute kidney injury.

AKI: acute kidney injury; CKD: chronic kidney disease; ESRD: end-stage renal disease; CRRT: continuous renal replacement therapy; DIC: disseminated intravascular coagulation.

Table 2: Incidence, diagnostic tests, treatment, and outcomes of common causes of acute kidney injury.

Aetiology	Incidences of AKI	Diagnostic tests	Treatment	Dialysis	Mortality
Malaria	Endemic: 1–4% Non-endemic: 25–30%	Quantitative buffy coat (sens/spec >95%) Peripheral smear	Artesunate Quinine Mefloquine	15–80%	6–50%
Lepto-spirosis	10–85%	Microscopic agglutination test (sens 30–60%, spec 97%) Nucleic acid tests	Penicillin Doxycycline Cefotaxime	30%	4–20%
Scrub typhus	9–53%	ELISA for IgM and IgG antibodies (sens/spec >90%	Doxycycline Azithromycin	6–10%	30%
Dengue	10.8%	Non-structural 1 protein antigen detection (sens 70–90%, spec 97%)	Supportive measures	5–40%	15–30%
Snake bite	1.4–38%	History/clinical examination	Early referral and initiation of dialysis	60%	1–20%
Bee/wasp	1–2%	History/clinical examination	Early referral	10%	5%
Obstetric causes	10–12%	History/relevant investigations	Early referral and initiation of dialysis	30%	1–15%

AKI: acute kidney injury; Ig: immunoglobulin; ELISA: enzyme-linked immunosorbent assay.

At 3 months, complete recovery of renal function, CKD Stages 3–5, and progression to end-stage renal disease (ESRD) were noted in 58.69%, 14.5%, and 2.2% of cases, respectively.[39] Rarely, thrombotic microangiopathy (TMA) caused by HIV infection can present with AKI.[40]

Acute diarrhoeal disease

AKI secondary to acute diarrhoeal disease (ADD) is still a major health problem in rural areas of tropical countries, though the dialysis requirement of ADD-associated AKI has recently decreased to 17% in the paediatric population.[41] Rotavirus infection is the most common cause followed by *Escherichia coli, Vibrio cholerae*, *Shigella*, or *Salmonella*.[42] However, the mortality rate associated with diarrhoea-related AKI remains high. The mortality rate was 2.1 in 1,000 admissions in a study conducted by Kumar et al.[43]

Acute Pyelonephritis

Renal infection can range from mild acute pyelonephritis (APN) to renal abscesses or emphysematous pyelonephritis (EPN).[44] APN and EPN were seen in 75.2% and 24.7% of patients, respectively. *E. coli* was the most common organism. The mortality rate was 12.4% and the presence of shock and altered sensorium were associated with poor outcome in patients.[45] It was found that about 121 patients were admitted with pyelonephritis in 22 months in our institute; about 67.7% were diabetics and 42.9% were in AKIN Stage 3 at presentation. Bilateral involvement was present in 55 patients (45%) and EPN was seen in 11 patients (9%). *E. coli* (27%) was the commonest organism, followed by *Klebsiella*. Around 60 patients were supported with renal replacement therapy (RRT). The mortality rate was alarmingly high at about 11% (unpublished data).

Drugs and Native Medications

Easy access to over-the-counter medications and dispensing drugs, including antibiotics, without proper prescriptions results in increasing incidence of AKI due to drug use. The common drugs that cause AKI include angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs, amino glycosides, anti-cancer, and lithium.[46] Indigenous medical systems based on remedies derived from local plants and animals flourish in tropical countries. Anti-tuberculous treatment also contributes to drug-induced AKI by causing direct tubule-toxicity.[47] Potentially toxic substances, such as paint thinners, turpentine, copper sulphate, and potassium permanganate, added to the plant extracts to increase their effect, cause AKI. The kidney is the usual route of excretion; the high blood flow rate and large endothelial surface area of the kidneys results in high concentration in the medulla resulting in AKI. Recently, there have been an increasing number of AKI reports among young people who are amateur body builders in tropical countries due to the use of creatine supplements, vitamin D overdosage, and anabolic steroids.[48]

Chemical Toxins

Accidental, intentional, or occupational exposure to chemicals that induce AKI is well documented in tropical regions. AKI occurs after the ingestion of chemicals, such as dimethyl bipyridinium dichloride and organo-phosphorus containing pesticides, copper sulphate, and mercuric chloride for suicidal purposes. There is a rise in AKI due to paraquat poisoning.[49,50] We reported a patient who consumed mercuric chloride used for folk remedies with suicidal intent, and presented with AKI, gastrointestinal erosion, and disseminated intravascular coagulation.[51] Diethylene glycol is present in brake oil and is used as an illegal adulterant in ethanol spirits or in medications. Ingestion of brake oil causes acute abdomen, dialysis-requiring renal failure, hypertension, deafness, and multiple neurological deficits due to poisoning.[52] We published our experience of 32 cases that developed AKI in a toxicology unit.[53] The risk of developing AKI was greater among the poisoning caused by bites and stings (6.15%) than by chemical poisoning (0.9%). Copper sulphate and rat killer poisonings were the most common causes of chemical-induced AKI.

Plant Toxins

Starfruit (*Averrhoa carambola*) juice is popular in India as an indigenous medicine and fruit drink, and contains a high oxalate concentration. Taking this fruit juice in large quantities on an empty stomach and in a dehydrated state causes nephrotoxicity. In a case series of five patients, all became symptomatic 10–12 hours after eating and developed AKI. Renal biopsy revealed ATN and all improved with complete renal recovery.[54] Consumption of uncooked beans from the djenkol plant, especially in individuals with a low fluid intake, can cause dysuria, lumbar pain, hypertension, haematuria, and oliguria secondary to the intratubular formation of djenkolic acid crystals.

Animal Toxins

Snake envenomation is the most common cause of animal toxin-induced AKI. Stinging insects, such as honeybees, wasps, yellow jackets, and hornets are also common in tropical regions.

Snake bite

Of the 2,000 species of snake found worldwide, 450 are venomous. The highest number of snake-bite-related deaths, about 45,900 every year, is reported in India. Onset of AKI can occur within 4–6 hours after the bite, or may be delayed for 3–4 days. The pathogenic mechanisms involved are haemodynamic alterations induced by cytokines and vasoactive mediators leading to renal ischaemia, haemolysis, disseminated intravascular coagulation, rhabdomyolysis, and direct nephrotoxicity caused by metalloproteases and phospholipase A in the snake venom. Renal biopsy showed ATN with pigment casts in 70–80% of patients.[55] Other changes include TMA, mesangiolysis, interstitial inflammation, glomerulonephritis, vasculitis, and renal infarction.

In about 115 cases (1990–2014) of AKI, RRT was required in 106 (92.17%) patients. Complete recovery was seen in 51.30%, 13.04% expired during acute phase of illness, 3.47% developed CKD, and 9.56% required dialysis beyond 90 days.[56] Prolonged snake bite to hospital time, hypotension, albuminuria, and raised bleeding time and prothrombin time were significant independent predictors of AKI.

Bees and wasps

Bees and wasps can cause human injury by allergic reactions, occurring after one or several stings, or direct envenomation when a massive attack with hundreds or thousands of stings occurs. We published a case series of 11 patients with wasp sting. All patients had evidence of rhabdomyolysis and three among them also had haemolysis. Ten patients required haemodialysis with a mean haemodialysis session of 8.7±2.8. Renal biopsy was carried out in 4 patients, which showed AIN in 1 patient, ATN in 2, and 1 patient had both AIN and ATN. Two patients with AIN were given steroids, others were managed with supportive measures. 1 patient died within 48 hours of presentation due to shock. At mean follow-up of 24 months, 1 patient progressed to CKD.[57]

Obstetric

After legalisation of abortion and improvements in antenatal care, incidence of obstetric AKI in India decreased from 22% in the 1970s to about 8% in the 1990s. Pregnancy-related AKI (PRAKI) however, continues to be prevalent and has a poor prognosis in India even today. We prospectively studied 130 patients (2010–2014) with PRAKI.[58] The mean age was 25.4±4.73 years. The incidence of AKI in pregnancy was 7.8%. The aetiology was sepsis (39%), pre-eclampsia (21%), placental abruption (10%), ADD complicating pregnancy (10%), TMA (9%), postpartum haemorrhage (2%), and glomerular diseases (9%). Renal biopsy carried out in 46 patients showed renal cortical necrosis (n=16), TMA (n=11), ATI (n=9), AIN (n=1), and glomerular disease (n=9). Thirty-four patients were managed conservatively while 96 required dialysis. Complete recovery occurred in 56% and about 36% had persistent renal failure at 3 months. The mortality rate observed was 8%. Low mean platelet count, higher peak serum creatinine, dialysis dependency at presentation, and histopathologically presence of cortical necrosis and TMA predicted the progression to CKD.

Miscellaneous Causes

Post-infectious glomerulonephritis,[59] rapidly progressive glomerulonephritis, and natural disasters are various other causes of AKI in the tropics. Liver disease-related AKI is on a rise. In total, 87 patients were included in 1-year, of which 85 were male. Hepatorenal syndrome was seen in 37 patients, sepsis in 25, hypovolaemia in 20, and other causes (native medicine and IgA nephropathy) in 5 (unpublished data). The raw gallbladder freshwater carp/grass carp are used for medicinal purposes in rural areas of India. Acute hepatic failure and AKI has been reported after consumption of these items. AKI with oliguria develops within 48 hours and lasts 2–3 weeks.

RENAL REPLACEMENT THERAPY

The choice of RRT can be intermittent haemodialysis, continuous RRT (CRRT) and acute peritoneal dialysis according to the availability and haemodynamic stability of patients. The indications include uraemic symptoms, symptomatic volume overload, uraemic pericarditis, severe metabolic acidosis, and hyperkalaemia. The clearance of urea and other molecular waste products is much faster with haemodialysis compared to peritoneal dialysis,

but peritoneal dialysis does not need a special set-up as it can be started immediately and can be utilised in the case of haemodynamic instability.[60]

FOLLOW-UP, OUTCOME, AND PREVENTION

AKI is independently associated with new onset CKD, ESRD, cardiovascular disease, and all-cause mortality.[61] The risk of CKD is exacerbated by the late presentation of AKI. Among patients who survive an episode of AKI, 10% had developed ESRD at 3.0–3.5 years.

Studies suggest that patients who receive follow-up by a nephrologist after an episode of AKI have improved outcomes compared with patients who did not.[62] Only a minority of patients come for follow-up after an episode of AKI in the developing world, and the optimal strategies to promote rehabilitation after AKI are not well-defined. A retrospective study showed that 15% of AKI survivors were discharged on RRT, 12.5% remained dialysis-dependent, and 19–31% had CKD at long-term follow-up.[63] We urge healthcare providers to consider intensive follow-up for every patient who survives an episode of AKI. Establishing national and regional registries for data collection, processing, and reporting data availability will confer public and political prominence on AKI.

Interventions such as lifestyle changes, medication reconciliation, blood pressure control, and education could have significant population-level effects, and promote renal recovery. More research is needed to identify the highest-risk patients with AKI and to determine the components of evidence-based rehabilitation after AKI. An integrated approach to reduce the disease burden, requires a change in public policy and a change in focus away from hospital-based care and towards improvement of basic health needs. Vector control is the most effective way to prevent transmission of vector-borne-diseases. Public awareness of the need for use of safe water, safe handling, and use of pesticides and other nephrotoxins should be increased.

OUR DATA

Between January–December 2016, 1,003 patients were admitted to Rajiv Gandhi Government General Hospital, Chennai, India, with AKI (unpublished data). In respect to AKIN staging, 91 patients were in Stage 1, 271 in Stage 2, and 644 in Stage 3. Medical causes constituted 89%, surgical 7.6%, and obstetric 3.4%. Of the medical causes, sepsis was the most common (19.5%) followed by glomerular disease (10.7%), tropical febrile illness (9.14%), liver disease-related (8.64%), snake bite (6.6%), malignancy-related (6%), and acute poisoning (5.3%). Around 532 were managed conservatively, 367 received haemodialysis, and 119 received peritoneal dialysis. Of these patients, 70.4% improved with therapy, dialysis dependence was seen in 3.3%, 5.2% patients discharged against medical advice, and 20.8% died. Compared to our previous data,[64,65] the incidence of AKI due to sepsis (especially urosepsis), liver disease, and scrub typhus is increasing while there is a decline in the incidence of AKI due to leptospirosis, malaria, ADD, and obstetric causes similar to other published data. Mortality is also relatively low.

Comparison of Acute Kidney Injury Between Developing Tropical and Developed Nations

It is estimated that 85% of AKI episodes occur in developing countries with a tremendous impact on their public health. The male-to-female patient ratio of AKI in the developed world is close to 1:1 but is skewed in developing countries to between 1.8:1 and 5:1. In the developed world, intrinsic renal disease due to shock and sepsis predominates as a cause of AKI while volume-responsive.[66] In the developing world, RRT is often only available in large cities, with cost and difficulties in transportation being the main limitations.[67] In spite of marked improvements in the care of critically ill patients with AKI, mortality remains high in developed countries (40–70%), but mortality in developing countries seems to be lower, ranging between 10% and 40%.[68] As effective therapies are less accessible and with resource limitations, early preventive and therapeutic measures are essential to decrease mortality and cost. The major difference in AKI in tropical countries is due to poor health awareness and sanitation, overcrowding, unavailable/deficient prompt diagnostic tests, poor healthcare, less availability of dialysis resources, and professional experts. This may be improved by health education and awareness that has to be incorporated in school education, educating the public through media, increasing the GDP spent on health by political commitment, strengthening primary and referral health sectors, and finally to create awareness in the general public of the importance of seeking treatment early.

CONCLUSION

Community-acquired AKI is a major health problem in tropical countries. Need for intensive care and multisystem involvement carries poor prognosis. Recovery of renal function after an episode of AKI is an important determinant of further survival and life expectancy. The long-term renal prognosis is usually poor in AKI survivors. Timely referral of patients and early initiation of treatment will improve outcomes.

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VITAMIN D AFTER KIDNEY TRANSPLANTATION: METABOLISM AND CLINICAL IMPORTANCE

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ABSTRACT

Vitamin D (VD) is a key factor in calcium-phosphorus metabolism. In addition, it has increasing popularity due to its pleiotropic effects: renal protection, antineoplastic properties, and diabetes mellitus and hypertension control. The VD axis is severely impaired in chronic kidney disease. The changes are present even in the earliest stages and progress as kidney function worsens. Significant changes in VD occur after successful kidney transplantation, as different factors interplay, leading to widespread VD insufficiency in kidney transplant recipients. The aim of our review is to demonstrate the changes in VD metabolism after kidney transplantation and to reveal their full impact on graft and patient survival in the post-transplant setting. Furthermore, current strategies for VD supplementation and their efficacy will be discussed.

Keywords: Vitamin D (VD), kidney transplantation (KT), post-transplant outcomes, pleiotropic effects.

THE VITAMIN D AXIS: IN HEALTH AND IN CHRONIC KIDNEY DISEASE

Vitamin D Metabolism in Healthy Subjects

Vitamin D (VD) and its metabolites are hormones and hormone precursors, synthesised predominantly (˜90%) endogenously in the skin. The ultraviolet rays from the sun transform 7-dehydrocortisol (provitamin D) to previtamin D, which isomerises to cholecalciferol (vitamin D3) under the influence of body temperature. Oral intake also contributes to VD levels (≤10%), in the form of ergocalciferol (vitamin D2) and vitamin D3.[1] Both substances have equivalent biological effectiveness. VD is activated by two-step hydroxylation, which occurs in the liver and kidneys. First, hydroxylation takes place in the liver, by the enzyme 25-hydroxylase (*CYP27A1*), and 25-hydroxyvitamin D (25VD) is synthesised. The final activation step occurs in renal tubules, where 25VD is hydroxylated to 1,25 dihydroxyvitamin D (1,25VD) by 1-α hydroxylase (*CYP27B1*). 1,25VD is the major active VD metabolite, as its binding capacity to the VD receptor (VDR) is almost 1,000-times higher than the other VD molecules.[2] *CYP27B1* is influenced by several factors. Serum calcium, phosphate, thyroid hormones, metabolic acidosis, fibroblast growth factor 23 (FGF-23), and 1,25VD suppress its activity, whereas prolactin, calcitonin, and somatotropin increase it.

25VD is the metabolite used to evaluate VD status due to its longer half-life (2–3 weeks). Apart from enzyme activity, sun exposure is a major factor influencing VD status, with the seasonal peak from July–September and the seasonal nadir from February–April.

VD generates its physiological effects via binding to the VDR. Thus, VD-reacting elements are activated, leading to the activation of genes, influencing calcium–phosphorus metabolism. As a result, intestinal calcium and phosphorus absorption is increased, bone remodelling occurs, parathyroid hormone (PTH) secretion is suppressed, and renal calcium and phosphate absorption is increased. These are the classical effects of VD.

VDR is detected in practically all human tissues. In addition, *CYP27B1* activity was detected in other organs: intestinal epithelial cells, prostate gland, pancreas, and the central nervous system. These factors explain the possible properties of VD beyond calcium-phosphorus metabolism: renal

protection, immunomodulation, and diabetes mellitus control. These non-classical effects are known as VD pleiotropy.[3] Figure 1 summarises VD metabolism and its classical and pleiotropic effects.

Vitamin D Metabolism in Chronic Kidney Disease

Abnormalities in VD metabolism are detected in the early stages of chronic kidney disease (CKD).[4] All components of the VD axis are affected: cholecalciferol, 25VD, 1,25VD, and the VDR. Table 1 summarises the VD abnormalities in kidney disease.

CKD-related abnormalities in VD are part of a wider CKD-related syndrome: CKD-related mineral bone disorder (CKD-MBD), which includes biochemical changes (abnormalities in serum calcium, phosphorus, PTH, alkaline phosphatase, FGF-23, and VD), bone pathology, and extraskeletal calcium deposits. CKD-MBD is associated with increased risk for bone fractures, higher incidence of cardiovascular events, and increased mortality in CKD patients. CKD-MBD changes become more expressed with the progression of kidney disease.[5]

Vitamin D Metabolism After Successful Kidney Transplantation

Significant changes in mineral metabolism occur after successful renal transplantation. Successful kidney transplantation (KT) leads to rapid reduction of FGF-23 level within the first 3 months after the procedure.[6] PTH levels rapidly decrease within the first 3 months, and remain stable and often elevated after the first post-transplant year.[5] Hypophosphataemia and hypercalcaemia are common in the early post-transplant period and tend to normalise after the third month of KT.

It takes ≤18 months for VD status to improve after renal transplantation. However, despite the presence of a functioning graft, VD status in kidney transplant recipients (KTRs) is usually suboptimal. VD sufficiency was <~18% in the spring-summer period and dropped further to 2.59% in the winter period in our transplant centre, indicating the persistent influence of sun exposure on VD status even after renal transplantation.[7,8] Similar rates were established in other transplant centres.[9] The reasons for poorer VD status after KT are multifactorial, but can be classified as CKD-related or transplantation-specific. Moderate or advanced CKD (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) is common after renal transplantation, reaching ≤70%.[10,11] CKD-related issues are outlined in Table 1.

Transplant-specific factors include limiting sun exposure in order to reduce the risk for skin malignancies, immunosuppressive treatment (steroids, calcineurin inhibitors [CNIs]), new onset diabetes after transplantation (NODAT), and a higher incidence of obesity after KT. Table 2 summarises the transplant-specific factors that have an impact on VD status.

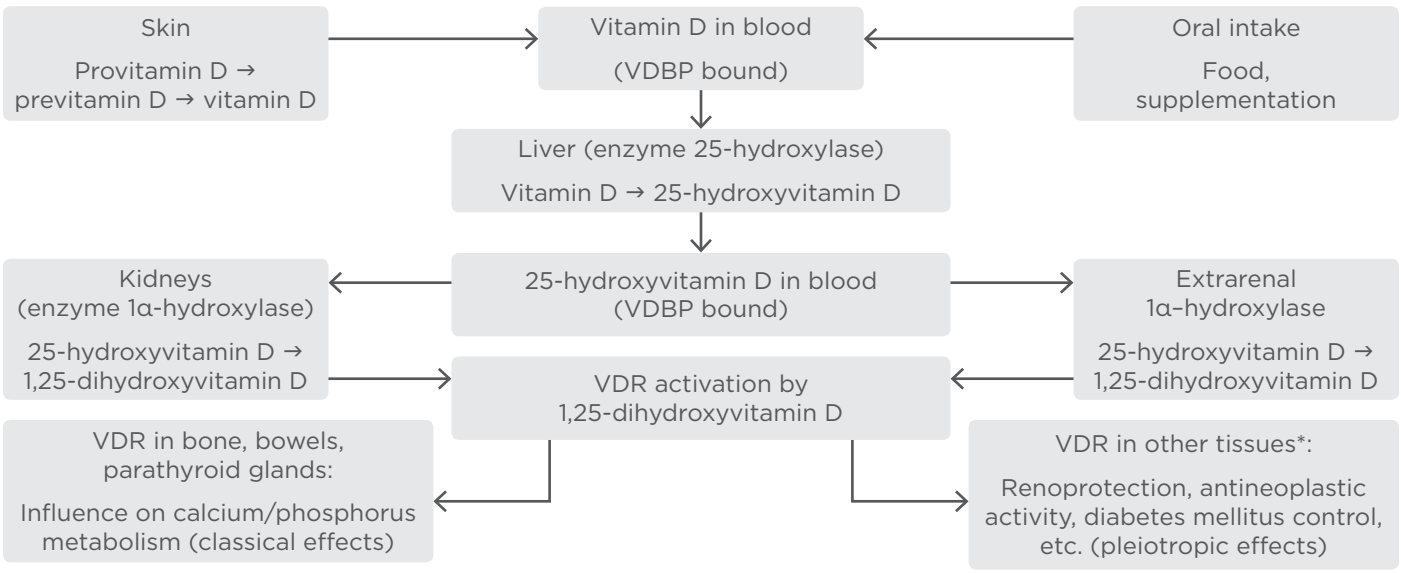

Figure 1: Metabolism and physiological effects of Vitamin D.
*Glomerular cells, immune cells, pancreatic islets cells, etc.
VDBP: vitamin D binding protein; VDR: vitamin D receptor.

Table 1: Vitamin D metabolism in chronic kidney disease: findings and pathogenesis.

Metabolite	Change in CKD	Pathogenesis
Cholecalciferol	Reduced level	Reduced synthesis in uraemic skin Reduced sun exposure Reduced oral protein intake
25VD	Reduced level	Reduced synthesis of its precursor Increased loss in nephrotic patients Higher incidence of obesity in CKD (sequestration of 25VD in adipose tissue)
1,25VD	Reduced level	Suppressed 1-α hydroxylase activity due to elevated FGF-23, hyperphosphataemia, and metabolic acidosis Reduced number of active renal tubules in the advanced stages of CKD Increased catabolism due to elevated FGF-23
VDR	Reduced expression; Impaired function	Downregulation of VDR expression due to low 1,25VD and hypocalcaemia Reduced VDR content in parathyroid hyperplasia Suppressed binding to VD-reacting elements

25VD: 25-hydroxyvitamin D; 1,25VD: 1,25-dihydroxyvitamin D; CKD: chronic kidney disease; FGF-23: fibroblast growth factor 23; VD: vitamin D; VDR: vitamin D receptor.

Table 2: Transplantation-associated factors influencing vitamin D status after kidney transplantation.

Factor	Mechanism of action
Reduced sun exposure	Reduced skin synthesis
Use of sun-protecting cosmetics	Reduced skin synthesis
Proteinuria	Increased urine loss
NODAT	Decreased intestinal resorption
Higher prevalence of obesity	Reduced bioavailability
Steroids	Increased catabolism
Calcineurin inhibitors	Suppressed liver synthesis

NODAT: new onset diabetes mellitus after transplantation.

Importance of Vitamin D in the Post-Transplant Period

The two major clinical issues concerning VD after KT are mineral-bone disease and VD pleiotropy.

Post-transplant mineral bone disease

Post-transplant mineral bone disease (PTr-MBD) consists of the same three components as CKD-related MBD (biochemical abnormalities, bone involvement, soft tissue calcification) and is similarly associated with increased fracture risk and death. Poor VD status is one of the factors for developing PTr-MBD, together with immunosuppressive therapy, persistent hyperparathyroidism, malnutrition, persistent CKD, duration of CKD Stage 5, hypogonadism, metastatic cancer disease, smoking, duration of dialysis and transplantation, obesity, and diabetes mellitus.

Biochemical abnormalities in post-transplant mineral bone disease

Biochemical findings are highly dependent on pre-transplant CKD-MBD, immunosuppressive treatment, post-transplant graft function, concomitant diseases, and medications. Apart from suboptimal levels of VD, all other factors in calcium-phosphorus metabolism can also be persistently dysregulated. PTH levels remain significantly increased ≤43% after the first year after KT.[7] Similar results were observed in our institution, with hyperparathyroidism reaching 33.69% in Bulgarian KTRs with a KT duration >12 months. Post-transplant PTH and FGF-23 abnormalities are associated

with higher incidence of hypophosphataemia and hypercalcaemia, though they tend to resolve after the first year.[12] An immunosuppressive regimen also indirectly influences mineral metabolism. Steroids suppress calcium intestinal absorption and increase VD catabolism. In addition, our findings suggest that CNIs are associated with lower 25VD levels, probably due to impaired liver synthesis.[8]

Mineral–bone indicators should be monitored closely immediately after KT. The frequency of testing for calcium, phosphorus, PTH, alkaline phosphatase, and 25VD should be determined according to graft function, duration of transplantation, magnitude of abnormalities, and when supplementation was initiated. An optional follow-up for CKD-MBD indicators was suggested by Kidney Disease: Improving Global Outcomes (KDIGO) for CKD patients and KTRs.[5] In our centre, a similar approach was adopted. However, 25VD levels are monitored at least twice annually, taking into consideration its seasonal variations. Thus, significant deterioration of VD status in the winter/fall was detected, allowing adequate supplementation to be initiated.

Post-transplant bone disease

A rapid reduction in bone density is widely reported, with faster bone loss during the first months after successful KT, though reduced bone density loss was reported years after the operation. A major complication is increased fracture risk, associated with increased morbidity and mortality. The factors contributing to post-transplant bone disease have already been listed. Pre-transplant bone health is crucial for post-transplant outcomes. A key factor in deteriorating bone health prior to kidney transplantation are excessive VD doses, which are associated with increased incidence of adynamic bone disease before KT. Therefore, adequate treatment of CKD-related MBD should be performed in the pre and post-transplant period.

Vascular calcification

Assessing the development of soft-tissue calcification is difficult due to the high prevalence of vascular calcification in advanced CKD. Only one study demonstrated possible slowing of the calcification process after KT.[13] Established risk factors for vascular calcifications were statin use, low 25VD levels, male sex, older age, and higher phosphate levels.[14] In addition, immunosuppressive treatment has multifaceted influence on vascular health. Mycophenolate mofetil proved to have protective effects against calcification, especially compared to steroids and CNIs.[15] The mTOR-inhibitor rapamycin was found to inhibit smooth muscle cell proliferation, thus reducing the risk for vascular calcification. Everolimus impaired the vasoactive and antithrombotic function of the endothelium.[16] Therefore, due to the contradictory reports, relatively scarce scientific data dealing with this problem, and difficulties in quantification of vascular calcification, this topic remains open for further discussion.

Vitamin D pleiothrophy after kidney transplantation

Short-term graft survival has improved significantly over the years, peaking at 98% survival for the first 12 months after KT. However, long-term graft survival is lagging behind: 10-year survival ranges between 60% and 70%. The reason for these poorer results are NODAT, interstitial fibrosis/tubular atrophy, and patient death due to cardiovascular disease (CVD) or neoplasia.

Due to the wider distribution of the VDR, VD is associated with several pleiotropic effects: renal protection, improving blood pressure, improved glycaemic control, antineoplastic effect, suppression of the renin-angiotensin-aldosterone system (RAAS), and immunomodulatory properties. Thus, we can expect that VD may solve the above-mentioned problems and improve post-transplant outcomes. These findings, however, were detected in the general population or CKD patients. The data for KTRs are relatively scarce and are limited to single-centre reports and retrospective studies.

Vitamin D and renal protection after transplantation

Lower 25VD levels were associated with poorer graft function and faster GFR decline.[17,18] Poorer VD status was associated with worse kidney function in the long run too.[19] A possible explanation for poorer graft survival in lower 25VD is increased rejection rate.[20] In addition, proteinuria is associated with faster decline of the graft function. Similarly to studies in the non-transplant population, we demonstrated that poorer VD status was associated with higher proteinuria after KT.[21] The possible antiproteinuric mechanisms of VD are RAAS suppression, nuclear factor κB inactivation, Wnt/β-catenin pathway suppression, and upregulation of slit-diaphragm proteins.

In animal models, treatment with the VDR activator paricalcitol reduced cyclosporine toxicity.[22] Data

from interventional studies in humans are still scarce and controversial. Cholecalciferol supplementation was not effective in modifying proteinuria and interstitial fibrosis/tubular atrophy after KT. Similarly, the single-centre randomised controlled trial (RCT) Vita-D failed to demonstrate renoprotective and immunomodulatory effects in KTRs supplemented with cholecalciferol.[23,24] Contrary to cholecalciferol supplementation, paricalcitol significantly reduced proteinuria in KTRs.[25]

Vitamin D and new onset diabetes after transplantation

The association between poorer VD status and diabetes mellitus has been reported in the general population.[26] In KTRs the evidence for VD–NODAT association is still uncertain. NODAT is associated with higher morbidity and mortality after transplantation, and is linked to the use of steroids and CNIs. However, a report demonstrated a link between its prevalence and VDR genetic polymorphism.[27] Observational data did not demonstrate better glycaemic control in diabetic DM in our transplant centre. Unfortunately, no interventional studies were reported that assessed the VD-NODAT relationship.[28]

Vitamin D and cardiovascular disease after transplantation

The risk for CVD is increased after transplantation compared to the general population, due to the persistent CKD-associated vascular and cardiac abnormalities, especially vascular calcifications. Poor VD status was associated with arteriosclerosis and endothelial dysfunction in end-stage renal disease patients. In addition, it was related to increased CVD incidence in poor VD status. An alternative explanation for CVD incidence in low VD levels is that VDR activation in cardiomyocytes suppresses their proliferation. However, the studies after solid organ transplantation are insufficient and inconclusive. As already mentioned, low 25VD is an established risk factor for vascular calcifications after KT.[13] Other reports did not demonstrate an association between CVD and VD insufficiency in KTRs.[29] Furthermore, higher doses of VD may be associated with increased risk for vascular calcifications.[30]

Vitamin D and rejection

VDR is expressed in all immune cells, including those of the innate immune dendritic cells and macrophages. Therefore, significant influence of VD on the immune system can be expected. Calcitriol was found to suppress T and B-lymphocyte proliferation; it inhibits dendritic cells and macrophages, suppresses interleukin and immunoglobulin G production, and downregulates major histocompatibility complex class II expression. Apart from experimental studies, there are a small number of studies in KTRs. A recent study indicated that better VD status is associated with lower incidence of acute rejection.[18] Horwedel et al.[31] detected a trend for lower acute cellular rejection incidence after high dose VD supplementation was applied, without reaching statistical significance.[31] An observational study also supported the protective effect of VD against acute rejection.[20] However, initial data from the Vita-D study do not reveal any positive effects from cholecalciferol supplementation.[24] In addition, a recent single-centre study also failed to establish a link between rejection and VD status in Canadian transplant recipients.[32] Evidently, there are conflicting results concerning this issue and larger RCTs are needed to evaluate the VD–rejection relationship.

Vitamin D and infection

Infection represents a major cause of patient death and graft loss after successful kidney transplantation. VD was established to upregulate the synthesis of the lysosome protein cathelicidin and the anti-microbial protein β-defensin. Several RCTs in the general population indicated that better VD status was associated with lower incidence of viral, bacterial, and fungal infections.[33,34]

The reports in patients with solid organ transplantation are controversial. Poorer VD status was associated with higher incidence of opportunistic pulmonary infections in KTRs and lung transplant patients.[35,36] Contrary to these findings, cholecalciferol supplementation did not improve the infection rate after renal transplantation in the Vita-D study.[24] VD status had no influence on bacterial urinary tract infection rate in Bulgarian KTRs followed up in our centre.[37] However, Kwon et al.[38] determined VD status as an independent risk factor for urinary tract infections after transplantation. Currently, RCTs evaluating the association between infection risk and VD status after KT are lacking.

Vitamin D and malignancy

Neoplasia is one of the most common causes for patient and graft loss in KTRs. VD was found to suppress cellular proliferation and angiogenesis,

and stimulates cell differentiation and apoptosis. In addition, VD reduces the metastatic potential of neoplasia via improving intercellular adherence. Several human studies indicate that better VD status is associated with lower incidence of colorectal cancer, breast cancer, and non-Hodgkin lymphoma.[39-41] However, in certain carcinomas both higher and lower serum 25VD levels are linked to increased incidence, e.g. prostate and pancreatic cancer.[42,43]

There have been several conflicting reports concerning the antineoplastic property of VD after KT. Poorer pre-transplant VD status was related to higher post-transplant cancer incidence; supplementation with active VD also reduced the malignancy risk in KTRs.[29,44] Contrary to these findings, another study did not find associations between neoplasia and VD status.[45] In order to fully understand the association between neoplasia and VD status, interventional studies are of crucial importance, as other pro-neoplastic factors exist after KT.

Vitamin D and mortality

All-cause mortality is increased in KTRs, due to persistent CKD, persistent cardio-vascular disease, post-transplant mineral bone disease, and increased neoplastic incidence and infection rate. Sub-optimal VD was associated with higher all-cause mortality in non-CKD and CKD patients.[46,47] Similar findings were established for KTRs: VD deficient recipients (VD <25 nmol/L) had increased mortality.[48] Again, prospective RCTs after KT are needed.

Vitamin D Treatment in Kidney Transplant Recipients

These are the main indications for VD treatment: native VD (cholecalciferol/ergocalciferol), active VD metabolite, or VDR agonists. Treatment should be tailored to the initial VD status after KT, as well as the post-transplant calcium–phosphorus metabolism, due to the increased incidence of hypercalcaemia and hypophosphataemia after successful KT. The therapy should follow the trends in the mineral-bone metabolism; therefore, the values for calcium, phosphorus, alkaline phosphatase, and PTH should be evaluated regularly. The frequency of laboratory testing should be based on graft function, degree of biochemical abnormalities, and supplementation initiated. Generally, the recommendations suggested by KDIGO are similar to those for non-transplant CKD patients and can be changed if stricter control is warranted.[5] Currently, data are present for the treatment of post-transplant MBD-related biochemical indicators during the first 12 months. There are no sufficient data for the influence of supplementation on fracture risk and VD pleiotropy in KTRs.

Cholecalciferol/ergocalciferol supplementation

Native VD effectively reduced PTH levels after KT.[49] The influence of VD supplementation on bone density is controversial. Sahin et al.[50] reported reduced bone loss in patients supplemented with cholecalciferol and calcium, whereas these findings were not confirmed by Wissing et al.[51] Therefore VD status should be assessed in all KTRs and supplementation is recommended with doses similar to those for the general population.[5] However, cholecalciferol/ergocalciferol treatment increases the risk for hypercalcaemia. In addition, we are waiting for the results from two large prospective trials with native VD supplementation in KTRs: VITALE and CANDLE-KIT, which will assess the effect of supplementation on graft function, NODAT incidence, rates of acute rejection, cancer incidence, and mortality rates.[52,53]

Treatment with calcitriol/VDR activators

Calcitriol was found to effectively suppress PTH levels and improve bone density after KT.[54] Paricalcitol significantly reduced PTH and proteinuria and improved bone density in KTRs.[25,55] Furthermore, paricalcitol treatment was not associated with increased risk for hypercalcaemia. More RCTs are needed to elucidate the effect of active VD or VDR activators on bone density and their pleiotropic effects.

CONCLUSION

Significant changes occur in the VD axis in CKD and after kidney transplantation. The importance of these changes spans beyond calcium-phosphorus metabolism and may have a direct impact on graft and patient survival. Larger prospective and interventional RCTs are needed to fully assess the influence of VD on post-transplant outcomes.

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INTRA-ABDOMINAL CANDIDIASIS

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ABSTRACT

Intra-abdominal candidiasis (IAC) is the second most common form of invasive candidiasis after candidaemia. IAC is a broad term and can be classified on the basis of anatomical site (*Candida* peritonitis, pancreatic candidiasis, biliary tract candidiasis, gastrointestinal candidiasis, and hepatosplenic candidiasis) as well as clinical setting (community acquired versus nosocomial). The risk factors linked with IAC are *candida* colonisation, anastomotic leak, multiple instrumentation, long-term broad spectrum antibiotic use, total parenteral nutrition, and immunocompromised state. Clinically, IAC is not different from intra-abdominal bacterial infection. Patients generally present with signs and symptoms of intra-abdominal sepsis after not responding to antibiotic therapy and with a background history of multiple surgical interventions or history of delayed source control. Radiological investigations, like ultrasonography and computed tomography scan, not only aid in diagnosis but also assist in differentiating medical from surgical cases. Microbiological diagnosis requires isolation of *candida* from an intra-abdominal specimen. Differentiation between colonisation and infection is difficult. Generally, progressive and persistent colonisation is associated with high risk of infection. Blood cultures have poor sensitivity for IAC. Non-culture based techniques used for diagnosis are mannan/anti-mannan assay, beta-D glucan assay, and validated polymerase chain reaction. Four types of antifungal strategies described in the literature are prophylaxis (risk factor driven), pre-emptive (colonisation or biomarker driven), empirical (fever driven), and targeted therapy (microbiology driven). Over recent years, global epidemiology has shown a shift from *Candida albicans* to non-albicans. Local epidemiology plays an important role in selection of the appropriate empirical therapy. The purpose of this review is to discuss different types of IAC based on their classification, risk factors, and management.

Keywords: Invasive candidiasis, intra-abdominal infections, epidemiology.

INTRODUCTION

Infections due to *candida* (candidiasis) can be classified as i) superficial candidiasis, which includes infection of skin and the mucous membrane; ii) locally invasive candidiasis (IC), which includes oesophageal candidiasis, *Candida* cystitis, etc.; and iii) IC comprising candidaemia and deep-seated candidiasis.[1] IC remains a perplexing problem for physicians. Characteristically, it targets the compromised host, remains clinically undifferentiated from bacterial co-pathogens, takes significant time to grow in blood cultures, is rapidly fatal if not treated appropriately, and increases morbidity along with cost of care even if treated appropriately.[2,3]

IC in patients with intra-abdominal infections can present as isolated intra-abdominal candidiasis

(IAC), isolated candidaemia, or IAC with concomitant candidaemia. Global epidemiology remains unclear. One of the largest point prevalence studies (EPIC II) conducted across 75 countries reported *candida* as the fourth most common isolate responsible for causing infection in intensive care unit (ICU) patients. In the study population, abdominal sepsis was the second most common site of infection after respiratory tract.[4]

Most epidemiological national surveillance and multicentre data originate from the USA and Europe. The rate of IAC has been reported as 4.7 per 1,000 admissions in one study. The largest study to date in this field, with the most robust data, was done by Bassetti et al.[5] They studied 481 IAC patients from 13 countries, admitted from 2011–2013. The inclusion criteria was, as according to the guidelines, given by a multidisciplinary expert panel. However, the true incidence of IAC remains elusive due to the following reasons.

Firstly, blood cultures have poor sensitivity, as *candida* is rapidly cleared from the blood. Many cases of IAC remain undiagnosed because blood cultures do not detect all cases of candidaemia and tissue cultures are not always possible in patients with suspected deep-seated infection.[6] Secondly, most studies either report IAC or isolated candidaemia in patients with intra-abdominal infections. There are very few studies that have reported the complete spectrum of IC in intra-abdominal infections.

Thirdly, IAC is a broad term, and it includes multiple conditions with different aetiologies (Figure 1). Currently, appropriate classification and nomenclature is lacking in the literature, resulting in scarce data in this field. Recently, in a consensus statement given by multinational experts, various agendas regarding IAC were addressed.[7]

Fourthly, *candida* is a normal flora of the gastrointestinal tract. Similar to *enterococci*, it has remained unclear whether its presence in an intra-abdominal specimen is relevant for therapy or outcome. Unlike candidaemia, isolation of *candida* in an intra-abdominal specimen is not synonymous with the need for antifungal therapy.

Treatment strategies for IAC have been classified as prophylactic, pre-emptive, empirical, and targeted. Prophylactic therapy is given to a subgroup of patients that have ≥1 risk factors for IAC. Pre-emptive therapy is based on colonisation density or biomarkers such as beta-D glucan. In this strategy, patients undergo regular surveillance of *candida* colonisation or biomarker serum levels. Once a predefined threshold is crossed, a patient becomes a candidate for antifungal therapy. A recently conducted randomised controlled trial (INTENSE) involving 241 patients undergoing gastrointestinal surgery for intra-abdominal infections from 53 centres across 17 countries failed to show benefit of pre-emptive antifungal therapy over placebo.[8] However, the study did show that patients with a positive beta-D glucan result had a higher risk of confirmed IAC (odds ratio [OR]: 3.66; 95% confidence interval [CI]: 1.01–13.29) as compared to those with negative results.

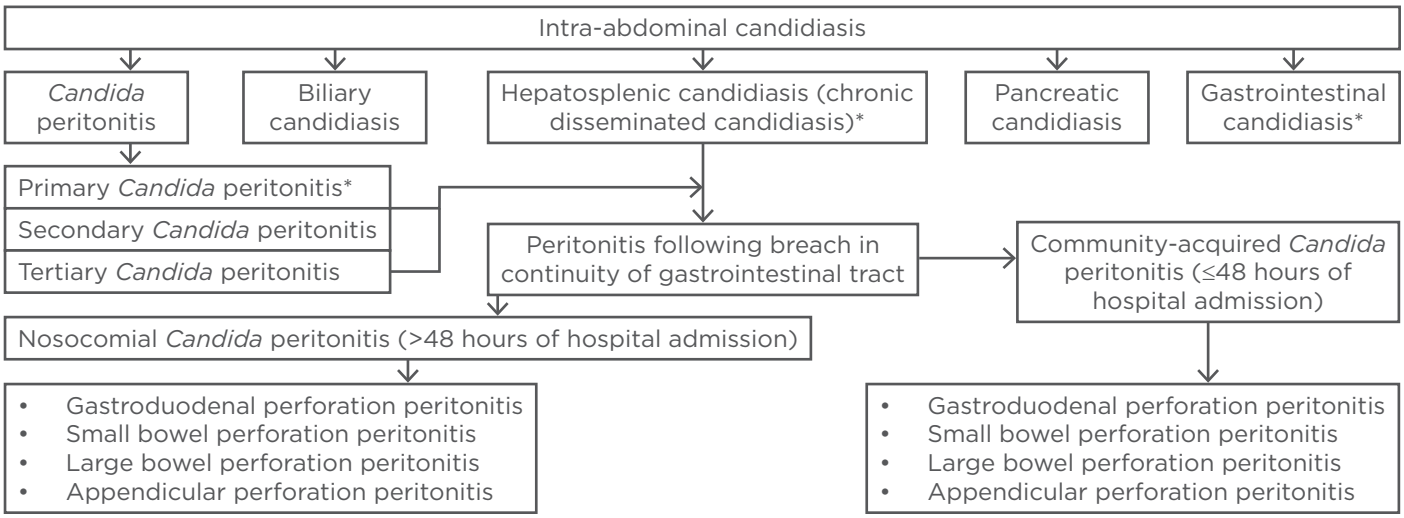

Figure 1: Classification of intra-abdominal candidiasis.
*Not discussed in the article.

Table 1: Studies showing *Candida* peritonitis studies from 2001 onwards.

Author Year	Type of study	No. of *Candida* peritonitis/ total patients with peritonitis	Inclusion criteria	Concomitant candidaemia	Mortality in *Candida* peritonitis patients (%)	Type of peritonitis (No. of patients with *Candida* peritonitis / total number)	Species distribution of candida (%)					
							Candida albicans	*Candida glabrata*	*Candida tropicalis*	*Candida parapsilosis*	*Candida krusei*	Others
Li et al.[14] 2015	Retrospective observational single-centre study	133 cases of CP	Community-acquired perforation peritonitis with growth of *candida* from ascites specimen	0	12%	Community-acquired peptic ulcer perforation peritonitis	NA	NA	NA	NA	NA	NA
Jindal et al.[15] 2015	Prospective observational single-centre study	68/140 (48.5%)	All patients with gastrointestinal perforation	NA	14	Gastroduodenal (48/68) Small intestinal (18/55) Large bowel (2/8) Appendix (0/9)	76.5	2.4	3.2	-	6.5	12
Montravers et al.[16] 2011	Prospective observational multicentre study	93 cases of CP	All patients with CP	28%	38	Nosocomial CP (73/93) Community-acquired CP (20/93)	58	20	3	3	8	8
de Ruiter et al.[17] 2009	Prospective observational single-centre study	44/221 (20%)	All patients with abdominal sepsis and organ failure admitted to ICU	NA	NA	Gastroduodenal* 41% Small intestine 34.1% Colorectal perforation 11.8% Appendicular perforation 0%	*C. albicans* most common isolate	-	-	-	-	-
Shan et al.[18] 2003	Observational single-centre study	63/145 (50%)	All patients with peptic ulcer perforation	NA	33	Peptic ulcer perforation peritonitis	*C. albicans* most common isolate	-	-	-	-	-
Sandven et al.[13] 2002	Randomised controlled trial	33/109 (30%)	Patients with intra-abdominal perforation	NA	24	Gastroduodenal (14/22) Small intestine (8/15) Large bowel (9/38) Appendix (1/28) Other (1/6)	76	15	-	-	-	3
Lee et al.[19] 2002	Observational single-centre study	23/62 (37%)	All patients with peptic ulcer perforation	NA	21.7	Peptic ulcer perforation peritonitis	78	13	4	-	-	5

*Type of perforation is expressed as a percentage.

CP: *Candida* peritonitis; NA: not available; ICU: intensive care unit.

Empirical therapy is a fever-driven approach. Fever in patients with various risk factors for IAC is used as a trigger to start antifungal therapy. Targeted therapy is the term used when antifungal therapy is given to patients with microbiologically proven IAC. Antifungals commonly used for treatment of IAC are azoles, echinocandins, and polyenes. Azoles act by interfering in fungal ergosterol synthesis and thus cause fungal cell membrane abnormalities. Polyenes (amphotericin B and its various lipid formulations) cause multiple pore formation in the fungal cell membrane while echinocandins interfere with fungal cell wall synthesis. Among the three groups, echinocandins are associated with the fewest side effects as their target site of action (i.e. the cell wall) is absent in human cells.

The current article is an attempt to describe various forms of IAC including their classification, risk factors, diagnosis, and management.

LITERATURE SEARCH

A literature search using keywords including "intra-abdominal candidiasis", "pancreatic candidiasis", "*candida* peritonitis", and "biliary candidiasis", from 2000–2017 was completed on PubMed, MEDLINE, EMBASE, and Google Scholar. References from relevant articles were also searched manually. Studies dealing with IAC were included in the review.

CANDIDA PERITONITIS

Definition and Classification

Peritonitis is defined as inflammation of peritoneal lining of the abdominal cavity, mostly caused by ≥1 infecting pathogen. Peritonitis occurring in patients without an obvious breach in continuity of the gastrointestinal epithelium is known as primary peritonitis.[9,10] Secondary peritonitis occurs in patients with disruption of gastrointestinal continuity leading to soiling of the abdominal cavity with gastrointestinal contents. Tertiary peritonitis is a term used to describe those cases in which initial definitive treatment fails to control the peritonitis. Such patients may require multiple surgical interventions.[11]

Anatomical site and subtypes

Candida peritonitis can be divided into subtypes on the basis of anatomical site of perforation. Most studies show increased incidence of *Candida* peritonitis in patients with gastro-duodenal perforations. Appendicular perforation rarely leads to *Candida* peritonitis.[12] In a study by Sandven et al.,[13] *candida* was isolated from intra-abdominal specimens in 33 (30%) out of 109 patients. When patients with an appendicular perforation were removed, the percentage increased to 39.5% (32 out of 81). Another method of classification is community-acquired peritonitis and nosocomial peritonitis.[14]

Epidemiology and risk factors

The rate of *Candida* peritonitis in patients with gastrointestinal perforation varies between 30% and 48%.[15-19] Studies dealing with *Candida* peritonitis have been summarised in Table 1. Due to the lack of a clear demarcation between *candida* colonisation and *candida* infection of peritoneal cavity, robust literature is lacking in this field.[20]

Species distribution

Over the past two decades there has been a shift from albicans to nonalbicans species in immunosuppressed and ICU patients.[21] A species like *Candida glabrate*, which is the second most commonly isolated species, is less susceptible, while *Candida krusei* is inherently resistant to fluconazole.[22] Knowledge of local epidemiology and resistance pattern can correctly guide the initial empirical antifungal therapy.[23]

Montravers et al.[16] described different case fatality ratios for different *candida* species in a study including 93 patients of *Candida* peritonitis. The case fatality ratio was higher for *Candida kefyr* (4/5, 80%) as compared to *Candida albicans* (22/63; 35%). Case fatality ratios were 7/22 (32%), 3/9 (33%), and 1/3 (33%), for *Candida glabrata*, *Candida krusei*, and *Candida tropicalis*, respectively.

Candida as a risk factor for mortality

Despite the ongoing controversy between the pathogenic and non-pathogenic nature of *candida*, its isolation has been linked with increased risk of death in certain subgroups. Montravers et al.,[24] in a case control study involving 91 cases and 168 controls of secondary and tertiary peritonitis, demonstrated isolation of *candida* as an independent predictor of mortality in patients with nosocomial peritonitis (infection >48 hours after admission) but not in community-acquired peritonitis (48% versus 28%). Upper gastrointestinal perforation was associated with increased risk of death (OR: 4.9; 95% CI: 1.6–14.8) in nosocomial peritonitis patients. Sandven et al.[13] showed that detection of yeast in intraoperative, intra-abdominal

specimen was associated with higher risk of death (OR: 11.5; p=0.03).

In a study by Dupont et al.,[25] upper gastrointestinal origin for peritonitis was found to be an independent risk factor for yeast isolation in severe intra-abdominal infections. Upper gastrointestinal perforation was identified as an independent risk factor for mortality in another study by the same author involving 83 *Candida* peritonitis patients.[26] Mortality in *Candida* peritonitis ranges between 12% and 38% in various studies.[14-19]

Pathogenesis

Its natural history involves progressive colonisation followed by invasion. In patients with peritonitis, other factors include extent and speed of debridement, adequacy of source control, number of re-operations, etc.

Calandra et al.,[27] in their landmark paper, studied 49 surgical patients in whom *candida* was isolated from ≥1 intra-abdominal specimen. Patients were divided into Group A (19 patients), in whom *candida* was considered pathogenic, and Group B (30 patients), in whom *candida* was considered non-pathogenic. *Candida* was regarded as pathogenic when isolated from intra-abdominal abscess or with postoperative peritonitis. In cases of mixed bacterial and fungal peritonitis, *candida* was regarded as pathogenic when associated with concomitant candidaemia or non-resolving clinical condition despite appropriate surgical management and antibiotic therapy. Group A patients had significantly higher mortality as compared to Group B patients. They were also subjected to multiple reoperations due to recurrent gastrointestinal perforations as compared to Group B patients, who mostly recovered after single surgical intervention. Authors highlighted that initial heavy growth of *candida* or a serial rise in the amount of *candida* growth should be considered highly predictive of infection.

Peritoneal contamination converts to invasive disease in the background of inadequate or delayed source control in a patient on broad spectrum antibiotic therapy.[28] The most important determinant of the course of illness in patients with intra-abdominal sepsis is 'source control'.[29] The adequacy of source control has not been properly addressed in most of the studies on IAC.

Diagnosis

Diagnosing fungal peritonitis is a challenge. Blood culture has low sensitivity (50%) for IC. In order to differentiate between *candida* colonisation and infection, an expert panel recommended systemic antifungal therapy to be considered only when the microbiological sample was obtained surgically or within 24 hours of external drainage. Positive cultures from the drains placed for >24 hours should not be treated.[10]

Newer diagnostic methods based on non-culture-based techniques are being employed to differentiate *candida* colonisation from infection.[30] Beta-D glucan acts as a serum marker for early detection of invasive fungal infection.[31] A recently published meta-analysis reported the sensitivity of this test as 76.8% and specificity as 85.3%.[31] León et al.,[33] in a study on 176 non-neutropenic patients of severe abdominal conditions, showed that beta-D glucan with a positive test for *Candida albicans* germ tube antibody accurately differentiated *candida* colonisation from IC.[33]

Management

Antifungal therapy in *Candida* peritonitis is still controversial. Antifungal prophylaxis is recommended in patients with recurrent perforation and anastomotic leaks by Canadian and European guidelines.[34,35] According to Infectious Diseases Society of America (IDSA) guidelines, patients with recent abdominal surgery, an astomotic leaks, or necrotising pancreatitis should be considered for empirical antifungal therapy.[36] Fluconazole achieves peritoneal concentration almost equal to that of serum after intravenous administration. Peritoneal concentrations of amphotericin B have been found to be variable. In one study, it was lower than serum level even during continuous infusion.[37] Weiler et al.[38] reported that though lipid formulations of amphotericin B achieve higher concentration in ascitic fluid, the concentrations were still low and may lead to treatment failure. Micafungin has been shown to have moderate penetration inside the peritoneum. Therapeutic levels were achieved for *Candida parapsilosis* (0.125–0.25 mg/L) and *Candida albicans* (minimal inhibitory concentration: 0.008–0.016) in a study including 10 patients of nosocomial peritonitis.[39] Caution is required in species with lower sensitivity.

PANCREATIC CANDIDIASIS

Definition and Classification

Pancreatic candidiasis is the term used when there is microbiological isolation of *candida* from

pancreatic tissue. Infection occurs characteristically in the middle and late phase of severe acute pancreatitis.[40] The risk of infective complications increases proportionally with the extent of pancreatic necrosis. Pancreatic *candida* infection is termed primary when positive culture is obtained during initial intervention (radiological/endoscopical/surgical). It is termed secondary when it occurs after prior intervention. The term 'tertiary infection' is used for patients with persistent inflammation and super-infection after surgery.

Epidemiology

The incidence of pancreatic candidiasis ranges between 5% and 68% in patients with severe pancreatitis, depending upon the patient population studied.[41] Due to lack of standard definition and variation in diagnostic criteria, there is a wealth of data which is invalid for inter-institution comparison. Schmidt et al.[42] evaluated microbial flora in a retrospective study of 78 patients with pancreatitis who underwent endoscopic transmural drainage and necrosectomy for infected walled off pancreatic necrosis. Fifty-five patients (78%) had culture proven infected necrosis, while 23 had sterile necrosis. *Enterococci* were the most common pathogen, responsible for 45% of the infections followed by *Enterobacteriaceae* (42%). *Candida* (22%) was the third most common pathogen. *Candida* was common in the antibiotic treated group (20% versus 4%, respectively). Fungi isolation at the time of index endoscopy was associated with increased risk of mortality.

According to the author's experience, IC occurred in 8 (27%) out of 30 consecutively studied severe acute pancreatitis (SAP) patients.[43] Among these eight patients, two had isolated, deep-seated infection (necrosum/drain fluid positive), three had isolated candidaemia, while three had both candidaemia and a deep seated infection. Multispecies candidiasis (>2 species) was found in two patients. Though mortality was not different between IC and the non-candidiasis group, patients with IC had increased durations of mechanical ventilation, shock, and days of ICU stay.

Hall et al.[44] conducted a single-centre retrospective observational study of 101 SAP patients admitted to ICU, out of which 18 (17.8%) developed IC. Mortality in patients with invasive *candida* infection was significantly higher as compared to SAP patients without invasive *candida* infection (55.6% versus 24.1%; p=0.02). Various studies dealing with fungal infections in SAP are listed in Table 2.[42-53]

Fungal Versus Bacterial Infection in Severe Acute Pancreatitis

Vege et al.[45] compared the outcome of fungal versus bacterial infection in a retrospective study involving 207 patients with SAP. Fifty-two percent of patients developed bacterial infections, while 30 (15%) also had concomitant *candida* infection. *Candida* infection was primary in 7 patients and secondary in the remaining 23 patients. Mortality rates were not different in bacterial infection and *candida* infection groups (20% versus 17%; p>0.41), but patients with *candida* infection had higher rates of organ failure and longer ICU and hospital stay.

Risk Factors

Prolonged broad spectrum antibiotic use is considered a risk factor for pancreatic fungal infection but evidence is inconclusive. Total parenteral nutrition, breach in mucosal and skin barrier due to percutaneous drainage tubes, and central venous catheters are other risk factors for IC. *Candida* colonisation was found to be an independent risk factor for IC in 101 SAP patients admitted to the ICU in a single-centre observational study.[44]

Diagnosis

The spectrum of the disease can vary from low grade infection to fulminant sepsis with multiple organ failure which remains unresponsive to antibiotic therapy. Once the diagnosis of infected pancreatic necrosis is made, necrotic material for culture and sensitivity can be obtained either through computed tomography (CT)-guided needle aspiration or during endoscopic or open necrosectomy. Blood cultures have poor sensitivity, as *candida* is rapidly cleared from the blood. Non-culture based techniques (beta-D glucan, mannan, and anti-mannan antibodies, polymerase chain reaction [PCR]-based assays) are increasingly being used for early and rapid diagnosis of these infections.

Management

Treatment of *candida* infection of acute necrotising pancreatitis involves source control as well as systemic antifungal therapy. Echinocandins are the drugs of choice for targeted as well as empirical therapy in haemodynamically unstable patients, with the exception of infection with *Candida parapsilosis*.

Table 2: Studies on invasive candidiasis in acute/severe acute pancreatitis from 2001 onwards.

Author Year	Type of study	No. of SAP pts with IC/ total No. of SAP pts	Inclusion criteria	Concomitant candidaemia	Mortality in SAP with IC (%)	Species distribution (%)					
						Candida albicans	*Candida glabrata*	*Candida tropicalis*	*Candida parapsilosis*	*Candida krusei*	Others
Baronia et al.[43*] 2017	Prospective observational study	8/30	Severe acute pancreatitis admitted to ICU	3: isolated candidaemia 2: deep-seated candidiasis 3: both candidaemia and deep-seated candidiasis	62	25	12.5	25	25	0	12.5
Schmidt et al.[42] 2014	Retrospective observational study	30/78 (38%)	Patients with acute pancreatitis who underwent endoscopic transmural drainage and necrosectomy for wall off necrosis	NA	NA	80	16	3	0	0	0
Hall et al.[44] 2013	Retrospective observational study	18/101 (17%)	Severe acute pancreatitis admitted to ICU	5: candidaemia 10: IAC 3: Both	55.6	67	22	0	11	0	11
Vege et al.[45] 2009	Retrospective observational study	30/207 (14.5%)	Severe acute pancreatitis	Blood cultures not evaluated	20	93	0	0	0	6	0
Kochhar et al.[46] 2008	Prospective observational study	18/50 (36%)	Severe acute pancreatitis	8: candidaemia 8: IAC 2: both	55	56	6	32	0	0	0
Berzin et al.[47] 2007	Retrospective observational study	7/65 (11%)	Necrotising pancreatitis	NA	0	100	0	0	0	0	0
Chakrabarti et al.[48] 2007	Retrospective observational study	22/335 (6%)	Acute pancreatitis	NA	41	36	18	41	0	5	0
Farkas et al.[49] 2006	Observational study	46/220 (21%)	Infected pancreatic necrosis undergoing open surgical necrosectomy	NA	19	NA	-	-	-	-	-
King et al.[50] 2005	Retrospective observational study	5/30 (16.7%)	Acute pancreatitis undergoing open surgical necrosectomy	NA	60	100	-	-	-	-	-
de Waele et al.[51] 2003	Retrospective observational study	17/46 (37%)	Infected pancreatic necrosis	NA	35	88	0	6	0	6	0
Isenmann et al.[52] 2002	Retrospective observational study	22/92 (24%)	Infected pancreatic necrosis	NA	64	18	0	0	0	0	82
Gloor et al.[53] 2001	Prospective observational study	8/103 (7.8%)	Necrotising pancreatitis	NA	25	NA	-	-	-	-	-

*Species identification done only for candidaemia isolates in this study.

SAP: severe acute pancreatitis; IC: invasive candidiasis; ICU: intensive care unit; NA: not available; IAC: intra-abdominal candidiasis.

Fluconazole is the preferred agent in infection with *C. parapsilosis,* as well as haemodynamically stable patients with no history of azole exposure. Antifungal prophylaxis remains an unresolved issue.[54] There are limited reports on antifungal drug concentration in pancreatic tissue. Shrikhande et al.,[55] in a study including 15 patients undergoing pancreatic surgery, reported that mean fluconazole concentration in the pancreas was 96% of the corresponding serum concentration. Penetration of the drug in pancreatic pseudocyst is slow and lower than that in plasma.[56]

BILIARY CANDIDIASIS

Definition

'Biliary candidiasis' is used when *candida* is isolated during microbiological analysis of bile fluid. While making a diagnosis of biliary candidiasis, it is important to differentiate infection from colonisation and contamination.

Epidemiology

There is scarcity of literature in the field of biliary candidiasis. Reports from various authors show variable rates of *candida* isolation from bile depending upon the cohort studied (Negm et al. 10%,[57] Lenz et al. 44%[58]). Studies related to biliary candidiasis are listed in Table 3.[58-62]

Pathogenesis and Risk Factors

The pancreatobiliary system is a sterile environment. Sphincter dysfunction can play a role in translocation of *candida* from the gut into the relatively sterile environment of the pancreatobiliary system. In agreement with this concept, Lenz et al.[58] found previous endoscopic sphincterotomy (EST) to be an independent risk factor for biliary candidiasis in a multicentre study involving 127 patients. Other factors include repeated instrumentation, stasis, immunosuppression, prolonged broad spectrum antibiotic use, and surgery.

There are two observational studies on biliary candidiasis in primary sclerosing cholangitis (PSC) patients.[59,61] In one study,[63] 8 out of 67 PSC patients showed growth of *candida* in their bile samples. Patients with biliary *candida* had more severe cholangitis and higher CRP and serum bilirubin levels. In another study, 150 PSC patients admitted to a single centre from 2002–2012 were analysed.

Table 3: Studies on biliary tract candidiasis from 2001 onwards.

Author Year	Type of study	No. of cases/ total patients studied	Inclusion criteria	Concomitant candidaemia	Mortality	Species distribution (%)				
						Candida albican	*Candida glabrata*	*Candida tropicalis*	*Candida krusei*	Others
Lenz et al.[58] 2014	Prospective observational multicentre study	38/127 (29.9%)	Suspected cholangitis and biliary stricture of unknown origin	None	5%	61%	16%	11%	3%	9%
Rupp et al.[59] 2014	Retrospective observational single-centre study	30/150 (20%)	Primary sclerosing cholangitis	NA	60%	83%	10%	3%*	6%*	3%
Lenz et al.[60] 2009	Prospective observational single-centre study	54/123 (44%)	Patients undergoing ERCP for various indications	NA	NA	52%	31%	3%	2%	12%
Kulaksiz et al.[61] 2009	Prospective observational study	8/67 (12%)	Primary sclerosing cholangitis	NA	NA	62	12	12	0	12
Domagk et al.[62] 2006	Case series	7 cases	Biliary tract candidiasis	NA	NA	100**	14**	-	-	-

*In one patient *krusei* and *tropicalis* were concomitantly detected, **One patient showed growth of two species i.e. *Candida albicans* and *Candida glabrate*.
NA: not available; ERCP: endoscopic retrograde cholangiopancreatography.

Thirty patients were diagnosed as biliary candidiasis. They were sub-classified as transient biliary candidiasis (15 patients) and persistent biliary candidiasis (15 patients). Patients with persistent biliary candidiasis had reduced survival with a greater need for liver transplantation.

Diagnosis

Clear diagnostic criteria are lacking in literature. Domagk et al.[62] published a case series of seven patients with biliary tract candidiasis. In two patients, hypoechoic material was visible in trans-abdominal ultrasonography, while in six patients a diagnosis of biliary mycosis was made via endoscopic retrograde cholangiopancreatography, where they were able to extract obstructing fungal tissue from the biliary tract.

Lenz et al.[58] suggested an algorithm for diagnosis and management of biliary candidiasis based on a multicentre prospective observational study conducted at three tertiary care centres in Germany. Bile samples from 127 patients of suspected cholangitis and biliary stricture of unknown origin were studied. The algorithm included *candida* antigen serology, infection parameters, and histological evidence for correct selection of patients for therapy.

Management

Treatment of biliary candidiasis includes systemic antifungals as well as endoscopic interventions (drainage of obstructed system via stent placement, debridement of biliary system by balloon catheter, placement of naso-biliary tube for local delivery of antifungal suspensions). Hepatotoxicity of the antifungal drugs should be considered when selecting an agent. Fluconazole and echinocandins are associated with lower risk of hepatic injury. Among the echinocandins, anidulafungin showed the lowest risk of elevated liver enzymes. Pooled risk estimates from randomised controlled trials showed elevation of liver enzymes (but not requiring stopping of treatment) was highest for voriconazole (19.7%), followed by itraconazole (17.4%) and amphotericin B formulations (14.1%).

CONCLUSION

IAC may include *Candida* peritonitis, pancreatic candidiasis, biliary candidiasis, hepatosplenic (chronic disseminated), and gastrointestinal candidiasis. True differentiation between colonisation, contamination, and infection is difficult in IAC. Patients with progressive persistent colonisation, surgery, multiple instrumentation, immunosuppression, prolonged broad spectrum antibiotic use, and multiple organ failure are at increased risk of IAC. Current data in this field are heterogeneous due to lack of uniformity in diagnostic criteria. Further research in the field can be streamlined by conducting studies as per the recommendations given by a multidisciplinary expert panel.

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ACUTE KIDNEY INJURY IN THE CRITICALLY ILL STILL REMAINS A CHALLENGE

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ABSTRACT

Acute kidney injury (AKI) is a common complication of critical illness and is associated with high morbidity and mortality. The epidemiology and pathogenesis of AKI and changes in renal function and preventive strategies are areas of interest. Although the aetiology of AKI is often multifactorial, sepsis has been consistently found to be a leading contributing factor in AKI during critical illness. Despite revised guidelines and better haemodynamic management, the outcome of AKI is still a reason for concern. Critically ill patients with AKI have significantly improved short-time prognosis with current treatment standards but are more prone to develop increased morbidity in the near future.

Keywords: Acute kidney injury (AKI), Acute Kidney Injury Network (AKIN), Kidney Disease: Improving Global Outcomes (KDIGO), Risk, Injury, Failure, Loss of kidney function and End-stage renal disease (RIFLE), sepsis.

INTRODUCTION

Acute kidney injury (AKI) is a common complication of critical illness and is associated with high morbidity and mortality.[1] The epidemiology and pathogenesis of AKI, assessment of baseline and changes in renal function, and preventive strategies are particular areas of research interest. AKI is a syndrome that is characterised by a rapid decline in renal function and urine output, resulting in retention of waste products such as urea, nitrogen, and serum creatinine. Life-threatening consequences include volume overload, hyperkalaemia, and metabolic acidosis.[2-4]

The incidence of AKI in intensive care unit (ICU) patients is rising due to the population age increasing, more comorbidities, and a higher prevalence of risk factors. Improved ICU management has, however, significantly diminished morbidity and the mortality of patients who develop AKI. Despite an increase in the number and severity of comorbidities, in-hospital mortality has declined, but the incidence of AKI and AKI requiring renal replacement therapy (RRT) has increased over time.[5] In a retrospective cohort study, Hsu et al.[6] recently identified diagnoses or procedures that may be a driver for the risk in dialysis-requiring AKI. Results showed that the temporal trend in acute or chronic diagnoses: septicaemia, hypertension, respiratory failure, coagulation/haemorrhagic disorders, shock, and liver disease accounted for the progressive trend in dialysis-requiring AKI. In contrast, temporal trends in surgeries (e.g. cardiovascular surgery, non-kidney solid organ transplantation) or procedures (e.g. respiratory intubation/mechanical ventilation) commonly associated with dialysis-requiring AKI did not account for the increasing dialysis-requiring AKI trend.[6]

Although these results are interesting, they should be interpreted with caution. Some diagnoses or procedures can be influenced by multiple factors (such as comorbidity, difference in critical care, prevention of nephrotoxic injury, and use of AKI definitions), which can differ between hospitals. Heart failure, age-related structural changes, and functional changes in the kidney can increase the risk for AKI; however, the extent to which these increases reflect changes in underlying patient characteristics, provider practices, or increased availability of RRT over time is not yet known.[7]

Utilisation of RRT to support ICU patients with AKI is growing.[8] A more liberal application of dialytic support could explain the increasing incidence of

AKI requiring RRT. Other possibilities include the increasing availability of RRT and earlier or lower thresholds for initiation; however, to date there is no consensus about an early start or 'wait and see' approach.[7] Furthermore, recent practice surveys suggest that nephrologists are more likely to initiate RRT based on more imminent indications, such as hypervolaemia, acidosis, or electrolyte disturbances, rather than the degree of azotaemia alone, particularly as the severity of illness increases.[7,9]

EARLY RECOGNITION OF ACUTE KIDNEY INJURY IN THE CRITICALLY ILL

In 2004, the Acute Dialysis Quality Initiative (ADQI) group, which represents nephrology and critical care specialists, proposed the Risk, Injury, Failure, Loss of kidney function and End-stage renal disease (RIFLE) criteria to define AKI.[2] RIFLE includes two separate criteria for renal failure: changes in serum creatinine (SCreat), changes in urine output (UO), or both. RIFLE defines three levels of increasing severity of AKI (i.e. Risk, Injury, and Failure) and two outcome classes (i.e. Loss and End-stage renal disease).

In 2007, the Acute Kidney Injury Network (AKIN) refined this approach and proposed some small modifications to the RIFLE criteria. Briefly, relatively minor changes in SCreat occurring within a 48-hour window were associated with significant risk of adverse outcome. According to the new definition, the RIFLE-R category was broadened (increase in SCreat of ≥0.3 mg/dL even if a 50% threshold was not attained) and patients were categorised as 'failure' when they received RRT, regardless of SCreat values or UO at initiation. The AKIN also proposed the use of Stages 1, 2, and 3 instead of the categories R, I, and F.[10-12]

The Kidney Disease: Improving Global Outcomes (KDIGO) working group recently combined the RIFLE and AKIN classifications to establish one internationally accepted AKI classification for clinical, research, and public health use. KDIGO takes changes in creatinine within 48 hours, or a decline in the glomerular filtration rate (GFR) over 7 days, into account. AKI is defined as an increase in sCreat ≥0.3 mg/dL within 48 hours, or an increase in sCreat ≥1.5-times baseline, which is known or presumed to have occurred within the prior 7 days, or a UO of <0.5 mL/kg/h for 6 hours.[13]

However, despite improvements of definition, renal function should be measured and monitored in real time so that a decline in renal function and the occurrence of AKI is visible as soon as possible. However, the diagnosis of AKI is based on SCreat rise and/or fall in UO, two markers which are not renal specific and have important limitations.[14]

The reported incidence of AKI in the literature varies substantially with the population evaluated and the definition used and the importance of the oligo-anuria component is thoroughly covered. Koeze et al.[15] assessed which of the AKI definitions, with or without UO criteria, recognised AKI most rapidly and frequently. They concluded that AKIN and KDIGO criteria detect more patients with AKI compared to RIFLE criteria. The addition of UO criteria helps to detect patients with AKI 11 hours earlier than SCreat criteria and may double AKI incidences in the critically ill.[15] It was concluded by Leedahl et al.[16] that 3–5 hours of consecutive oliguria in patients with septic shock may provide a valuable measure of AKI risk. Although this trial is a retrospective analysis, it did show that duration of oliguria is of high importance in the development of septic AKI.[16]

TYPES OF ACUTE KIDNEY INJURY

There is still some dispute over the characterisation of the different types of AKI. Classically there are three types of AKI: pre-renal, intrinsic renal, and post-renal failure. These are characterised as decreased renal blood flow (in 40–70% of the patients), direct (intrinsic) renal parenchymal damage (in 10–50% of the patients), and obstruction of urine flow, which is less common in the ICU (10%), respectively.[3,17]

According to this classification, pre-renal AKI represents a separate entity characterised by a rapidly reversible increase in SCreat and urea concentration altering glomerular filtration, without primary parenchymal disease. This can be seen as adapted renal responses to a variety of negative stimuli. Pre-renal AKI and acute tubular necrosis (ATN) can exist simultaneously in the same patient. It is possible that some regions of the kidney can have severe morphologic and functional ATN, whereas other parts may be structurally intact, requiring only reperfusion to resume normal filtration. Therefore, AKI should be seen as a continuum between pre-renal, without structural injury, AKI, and AKI with renal injury, such as ATN, and in this instance the term transient AKI can be used. The aetiology and prognosis of transient AKI

is arbitrarily defined as AKI of ≤3 days duration. A kidney biopsy can be helpful in excluding rapidly progressive glomerulonephritis, vasculitis, and interstitial nephritis.[18]

In the absence of pathophysiological findings of a renal biopsy, pre-renal disease can be distinguished from ischaemic or nephrotoxic ATN by examination of the urine. The kidney varies the rate of sodium excretion to maintain effective circulating volume. This response is mediated by a variety of factors including the renin-angiotensin-aldosterone system and possibly atrial natriuretic peptide. The urine sodium concentration can be used as a measure of volume status. A urine sodium concentration below 20 meq/L is indicative of hypovolaemia or a pre-renal origin of AKI. In ATN, the urine sodium concentration usually exceeds 40 meq/L because of tubular damage, not reaching maximum sodium reabsorption. Determination of fractional excretion of sodium (FeNa) and urine osmolality also help to differentiate between pre-renal and intrinsic renal AKI.

A low urine sodium concentration points to hypovolaemia, whereas a high value suggests ATN. However, a urinary sodium concentration of 20–40 meq/L can be seen with either disorder. This overlap can be differentiated by calculating FeNa. Sodium reabsorption is enhanced in hypvolaemic states leading to a FeNa <1% (99% of the filtered sodium has been reabsorbed), whereas tubular damage produces a FeNa >2%.[19]

The use of FeNa as a marker of tubular injury may be questioned. At the onset of sepsis and endotoxaemia, arterial vasodilatation is associated with stimulation of the renin-angiotensin system, arginine vasopressin release, and activation of the sympathetic nervous system. The resulting renal vasoconstriction is associated with an early increase in tubular sodium reabsorption leading to a decrease in urinary sodium concentration and FeNa.

FeNa values vary with respect to timing of measurement from onset of sepsis-induced tubular necrosis. This may explain why FeNa measurements range from very low to high in the more 'controlled' animal setting.[20] Moreover, prolonged renal vasoconstriction during endotoxaemia will cause tubular dysfunction that is associated with increased cytokine, chemokine, and oxidant induced injury. This tubular damage converts a decreased FeNa into an increased FeNa which is dependent on the severity of sepsis and endotoxaemia. Thus, depending on the negative stimuli, FeNa may increase from <1% to >1%.[21]

Although urinary biochemistry could be an opportunity to explore the underlying diagnosis, the use of urinary examination is controversial and has not yet been validated. Many factors may lead to variable FeNa values during the day, which calls into question the usefulness of urinary biochemistry in daily practice. As a result, most studies were not able to find a consistent role for measurement of FeNa and/or fractional excretion of urea (FeUr).[22] Vanmassenhove et al.[23] have shown that in septic patients a low FeNa and FeUr is highly prevalent in the first hours of sepsis. A combination of a high FeNa and a low FeUr is associated with intrinsic AKI, whereas a combined high FeNa and FeUr is strongly predictive of transient AKI.[23]

BIOMARKERS

Currently, the standard diagnostic tools for AKI detection are monitoring of SCreat and UO, both of which are markers of renal function but not of kidney injury. SCreat is a delayed and insensitive biomarker of changes in kidney function and does not differentiate structural kidney damage and functional haemodynamic triggers and can be altered by a variety of factors. In addition, patients with reduced muscle mass may not have a robust rise in SCreat despite a substantial kidney injury.[24] Biomarkers of AKI should have the ability to allow early detection of patients who are going to develop AKI. Furthermore, biomarkers should assist in the evaluation of the intensity of injury, differential diagnosis, and the impact of interventions on the recovery from kidney injury.

Within the past two decades, potential novel biomarkers measurable in urine or plasma of patients with AKI have been identified, including neutrophil gelatinase associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), interleukin 18 (IL-18), liver-type fatty acid-binding protein (L-FABP), tissue inhibitor of metalloproteinase 2 (TIMP-2), insulin-like growth factor binding protein 7 (IGFBP7), calprotectin, urine angiotensinogen (AGT), and urine microRNAs. However, the aforementioned biomarkers are not specific for AKI.[24]

Using a combination of two new markers, TIMP-2 and IGFBP7 (NephroCheck, Astute Medical Inc., San Diego, California, USA), appears to improve the identification of patients at risk of AKI at

12 hours compared with previous biomarkers.[24,25] *TIMP2*IGFBP7* measured early in the setting of critical illness may identify patients with AKI at increased risk for mortality or receipt of RRT over the subsequent 9 months.[26] However, the challenge for the usefulness of biomarkers remains. This is not only in the early detection of AKI but also in the question of whether biomarkers can improve the outcome of AKI.

The same questions arise for the use of automated electronic alerts (e-alerts). E-alerts configured from electronic medical records and clinical information systems to warn healthcare providers of early or impending AKI have been evaluated.[11] Recently, Lachance et al.[27] reviewed all literature regarding e-alerts for AKI and concluded that e-alerts are heterogeneous in design, variably implemented, and seldom include clear direction for decision support. E-alerts for AKI appear not to improve patient outcomes, lead to improved utilisation of health services, or reduce RRT utilisation.[27]

RISK FACTORS

Although global care of critically ill patients has improved, AKI still carries a mortality rate of 50–90%.[28-30] Depending on different clinical settings, such as post-cardiac surgery, contrast media exposure, severe heart failure with low output, and sepsis, pathophysiology and clinical features of AKI will differ and aetiology is multifactorial in most cases. It has been suggested that CKD is a risk factor for AKI because chronically impaired kidneys lose their ability to auto regulate, and therefore become susceptible to AKI whenever exposed to a sufficiently severe stimulus.[31-33] Bedford et al.[34] suggest that both AKI and CKD are not separate disease entities but are in fact components of a far more closely interconnected disease continuum. Considerable conceptual overlap may exist between these two separate conditions with regard to underlying pathology and pathophysiology, definitions, risk factors, and clinical outcomes. However, the true nature of this relationship is complex and poorly understood.[34] The pathophysiology of AKI represents a very complex interplay between the immune system, the accompanying inflammatory response, tubular injury and the extent of any associated vascular insult.[31,35]

Ischaemia, inflammation, and direct toxic injury to the kidney are all major areas that contribute to the pathogenesis of AKI with significant overlap. Furthermore, epidemiological studies in AKI patients have determined additional risk factors such as age, hypertension, diabetes mellitus, and heart failure.[32,36] Similar risk factors have also been identified for CKD. Prospective trials, such as the US-based ASSESS-AKI study, and the UK-based ARID study, are likely to shed new light on the relationships between AKI and CKD in the near future.[31]

Critically ill patients receive a myriad of medications. In the ICU, nephrotoxic drugs and antibiotics that reach toxic levels are responsible for 19–25% of AKI cases.[37] Comorbidities known to significantly enhance the risk for drug-induced nephrotoxicity are underlying AKI or CKD, sepsis, advanced cirrhosis, liver failure, acute or chronic left heart failure, and various malignancies. Drug-related renal injury may be caused by haemodynamic instability, altered drug pharmacokinetics, direct renal parenchymal injury, or a combination of these factors.[37] All phases of drug pharmacokinetics are disturbed in critically ill patients, including absorption, distribution, metabolism, and clearance. These changes often result from organ dysfunction, the acute-phase response of the underlying critical illness, multiple drug interactions, intravenous fluids, diagnostic procedures, and various medications.[37]

Although the aetiology of AKI in critically ill patients is often multifactorial, sepsis has been consistently found to be a leading contributing factor in AKI during critical illness.[4,38,39] Because of the complexity of sepsis and AKI, it should be noted that no single pathway can explain all the features of septic AKI. Each septic AKI patient moves along an individual disease trajectory; therefore, the therapeutic targets vary with the underlying pre-existing conditions, time course, disease trajectory of sepsis, and AKI.[33]

In contrast to AKI, sepsis has benefited from a consensus-driven standardised definition for over a decade. Recently, the definition of sepsis was updated and validated (Table 1).[40] Multicentre European studies found that AKI was attributable to sepsis and/or septic shock in 41.4–45.5% of critically ill patients.[41,42] Parmar et al.[43] proposed to define septic AKI as the simultaneous presence of both sepsis and AKI, in the absence of other clear and established, non-sepsis-related precipitants of AKI, for example, urinary tract obstruction, radiocontrast dye, and other nephro-toxins.[43] The discrimination between septic and non-septic AKI may have clinical relevance.

Table 1: Definition of sepsis and septic shock.[40]

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection.
Patients with suspected infection who are likely to have a prolonged intensive care unit stay or to die in the hospital can be identified with qSOFA, i.e. alteration in mental status, systolic blood pressure ≤100 mmHg, or respiratory rate ≥22/min.
Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.
Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mmHg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation.

MAP: mean arterial pressure; qSOFA: quick Sepsis Related Organ Failure Assessment.
Adapted from Singer et al.[40]

Septic AKI is characterised by distinct pathophysiology and has different clinical outcomes and responses to interventions compared with non-septic AKI. AKI has a negative impact on the long-term mortality of hospital-surviving septic patients.[4,44,45]

Observational data highlighted that septic AKI occurs more commonly among elderly and female patients compared to non-septic AKI. Septic AKI patients are also more likely to have a higher burden of pre-existing comorbidity compared with patients with non-septic AKI. In particular, septic AKI patients have a higher prevalence of congestive heart failure, chronic obstructive pulmonary disease, CKD, liver disease, diabetes mellitus, active malignancy, and immune system disorders and are more likely to be admitted for medical indications.[43]

The duration of hypotension before initiation of effective microbial therapy is a critical determinant of survival in human septic shock.[46] Despite this clear observation, the literature on the exact haemodynamic goals to be applied in a clinical setting is scarce. There are no randomised control studies on the effects of different blood pressure levels on outcome to date. However, limited data from small cohort studies suggest a slight consensus on the use of arterial blood pressure targets in sepsis, and the preferred target range of 65–75 mmHg.[47] Dünser et al.[48] investigated the association between the arterial blood pressure during the first 24 hours and mortality in sepsis and concluded that a mean arterial pressure (MAP) level ≥60 mmHg may be as safe as higher MAP levels during the first 24 hours in septic patients. The group also hypothesised that although a MAP of 60 mmHg does not influence mortality, a higher MAP may be required to maintain kidney function.[48] This hypothesis is confirmed by our study, which showed a significant influence of severe hypotension (<65 mmHg) on the evolution to failure.[49]

The FINNAKI study reported on the haemodynamic variables and progression of AKI in critically ill patients with severe sepsis.[50] This prospective, observational study investigated the progression of AKI within the first 5 days of ICU admission, defined as new onset or worsening of AKI, according to the KDIGO guidelines, for both the AKIN/RIFLE classifications. They concluded that patients with progression of AKI had significantly lower time-adjusted MAP, 74.4 mmHg (68.3–80.8), than those without progression, 78.6 mmHg (72.9–85.4), p<0.001. A cut-off value of 73 mmHg for time-adjusted MAP best predicted the progression of AKI. Moreover, only the duration of a MAP <60 mmHg had a highly significant poor effect on the progression of AKI.[50]

Patients with an increased risk of AKI require careful attention for their haemodynamic status. First, hypotension results in decreased renal perfusion and, if severe or sustained, may result in kidney injury. Second, the injured kidney loses autoregulation of blood flow, a mechanism that maintains relatively constant flow despite changes in pressure above a certain point (mean: ~65 mmHg).[51] Management of blood pressure and cardiac output require careful titration of fluids and vasoactive medication. Vasopressors can further reduce blood flow to the tissues if there is insufficient circulation of blood volume. However,

early fluid resuscitation in the management of hypotensive patients with septic shock has been a standard treatment paradigm for decades. It has not been made clear how much fluid to give, for how long, or what type of fluid therapy is optimal in the physiologic support of septic shock, except avoiding synthetic starches. It is recommended by the updated international guidelines for management of septic shock that, in the resuscitation from sepsis-induced hypo-perfusion, at least 30 mL/kg of intravenous crystalloid fluid be given within the first 3 hours (strong recommendation, low quality of evidence). Following initial fluid resuscitation, additional fluids should be guided by frequent reassessment of haemodynamic status.[52,53]

Conversely, patients with AKI are also at increased risk of fluid overload and continued fluid resuscitation, despite increased intravascular volume, can cause harm.[51,52] In resuscitated, critically ill patients, the distribution volume of SCreat is higher, which may lead to underestimating the severity of AKI. Fluid overload can be managed by diuretics, but the role of diuretics during septic shock is still controversial.[54] Therefore, the working group for critical care nephrology made some recommendations for clinical practice: i) controlled fluid resuscitation in true or suspected volume depletion, ii) MAP >60–65 mmHg, yet target pressure should be individualised whenever possible and particularly when pre-morbid blood pressure values are known, iii) correction of vasoplegic hypotension in sepsis requires the use of norepinephrine as first-line therapy with vasopressin as a second-line agent along with fluid resuscitation.[53]

Next to critical care nephrology and the management of sepsis, it is necessary to gain further advances in targeted therapies in sepsis-associated AKI (SA-AKI) to improve outcome. Today, there is no effective therapy that has been shown to alter the outcome of SA-AKI.[52] Human recombinant alkaline phosphatase (RecAP) is one of the limited pharmaceutical treatment options for SA-AKI currently being tested in a clinical trial setting. AP is a dephosphorylating, membrane-bound, endogenously occurring enzyme, exerting detoxifying effects through dephosphorylation of endotoxins, involved in sepsis pathogenesis. Although the mechanism of action is not completely understood, previous clinical trials in healthy volunteers and patients with sepsis, with or without AKI, have established the tolerability and potential efficacy of purified bovine intestinal AP (biAP). In patients with SA-AKI, biAP significantly improved renal function according to the combined endpoint of endogenous creatinine clearance, requirement for RRT, and duration of RRT.

Moreover, a range of markers of systemic inflammation, renal function, and renal damage in blood and urine demonstrated improvement, suggesting that a systemic anti-inflammatory effect induced by biAP prevented further renal injury. Following these encouraging results, a human recombinant AP (recAP) has been developed as a pharmaceutically acceptable replacement for bovine-derived AP. In line with preclinical and clinical studies using purified biAP, animal studies with recAP revealed potent anti-inflammatory activity preserving function and histological integrity of the affected kidneys (unpublished data) and no safety concerns were raised when administered to healthy volunteers. Therefore, a randomised, double-blind, placebo-controlled, four-arm, proof-of-concept, dose finding adaptive Phase IIa/IIb study was conducted and is still recruiting critically ill patients with SA-AKI.[55]

RECOVERY OF KIDNEY FUNCTION AND BEYOND

Recovery of kidney function is increasingly recognised as an important determinant of morbidity. Oppert et al.[42] found that patients with pre-existing non-dialysis dependent CKD had a lower mortality as compared with septic AKI patients without pre-existing CKD.

Evaluation of a database of >40,000 critically ill patients highlighted that patients with presumed sepsis, advanced age, and underlying renal dysfunction had an increased risk for AKI regardless of having another organ failure at the time of ICU admission. Although proper management of AKI will improve outcomes for both low-risk (i.e. no respiratory failure or circulatory shock) and high-risk patients, there may be additional benefit for low-risk patients because their short-term outcomes (30-day ICU and hospital mortality) are more significantly impacted by AKI. This also emphasises the need for care after ICU discharge in an attempt to improve the patients' outcomes and for assessment of potential recovery of renal function. Unfortunately, clinical follow-up of AKI survivors is low.[56]

Coca et al.[57] carried out a meta-analysis of long-term renal and non-renal outcomes in patients with AKI. The pooled incidence of CKD and end-stage renal disease (ESRD) were 25.8 per 100 person-years and 8.6 per 100 person-years, respectively. Patients with AKI had higher risks for developing CKD (pooled adjusted hazard ratio [HR]: 8.8; 95% confidence interval [CI]: 3.1–25.5), ESRD (pooled adjusted HR: 3.1; 95% CI: 1.9–5.0), and mortality (pooled adjusted HR: 2.0; 95% CI: 1.3–3.1) compared with patients without AKI. The relationship between AKI and CKD or ESRD was graded based on the severity of AKI, and the effect size was dampened by decreased baseline GFR. This review demonstrates an association between AKI and CKD, because AKI was identified as an independent risk factor for CKD, ESRD, death, and other important non-renal outcomes (e.g. risk for cardiovascular disease and congestive heart failure).[57] The long-term risk for cardiovascular events due to AKI was recently confirmed by a meta-analysis by Odutayo et al.[58] AKI was associated with an 86% increased risk of cardiovascular mortality and with a 15% increased risk of stroke.

Because of an increased cardiovascular risk, life expectancy in survivors of AKI and critical illness is compromised. However, according to a small follow-up trial of those who survived AKI and recovered from RRT it seems that these patients have a satisfactory quality of life. Regular follow-up examinations should therefore be recommended by the attending physicians at hospital discharge.[59]

Regarding RRT, two main issues remain: the timing and the dialysis modality. The optimal timing of RRT in critically ill patients with AKI remains uncertain.[60] Recently, two trials regarding initiating RRT with conflicting results have been published.[61,62]

In the ELAIN trial, Zarbock et al.[61] investigated whether early initiation of RRT in patients who are critically ill with AKI reduces 90-day all-cause mortality. In this randomised clinical trial, 231 critically ill patients with AKI KDIGO Stage 2 (≥2 times baseline or UO <0.5 mL/kg/h for ≥12 hours) and plasma neutrophil gelatinase-associated lipocalin level >150 ng/mL were enrolled. Patients were divided into three groups: early start of RRT (within 8 hours of diagnosis of KDIGO Stage 2), delayed start of RRT (within 12 hours of Stage 3 AKI), or no initiation of RRT.[61]

Ninety-day mortality was 39.3% for patients undergoing early initiation of RRT compared to 54.7% for patients with delayed initiation (HR: 0.66; 5% CI: 0.45-0.97); more patients (53.6%) in the early group recovered renal function by Day 90 versus 38.7% in the delayed group.[61]

Gaudry et al.[62] concluded in their randomised trial with AKI patients KDIGO Stage 3 divided into two groups: early strategy when RRT therapy was started immediately after randomisation or patients following the delayed strategy, when RRT was initiated if at least one of the following criteria was met: severe hyperkalaemia, metabolic acidosis, pulmonary oedema, blood urea nitrogen level >112 mg/dL, or oliguria for >72 hours after randomisation, that the mortality at Day 60 did not differ significantly between the early and delayed strategies, early-strategy group (48.5%; 95% CI: 42.6–53.8), and delayed-strategy group (49.7%; 95% CI: 43.8–55.0; p=0.79). The rate of catheter-related bloodstream infections was higher in the early-strategy group than in the delayed-strategy group (10% versus 5%; p=0.03). Moreover, diuresis (a marker of improved kidney function) occurred earlier in the delayed-strategy group (p<0.001).

Early RRT facilitates better fluid balance and electrolyte and acid base homeostasis and may remove circulating toxins and inflammatory cytokines during sepsis. Initiating RRT is not free of risks, which was agreed in the study of Gaudry et al.[62] Both trials included patients according to the KDIGO criteria for AKI; however, it should be noted that patients in Stage 1, 2, or 3 normally do not receive RRT. Initiating RRT was part of the trial, but in daily life starting RRT is a decision, which is based on patient's individual clinical status and dependent on more factors than only the KDIGO criteria; however, the trial of Gaudry et al.[62] may support the wait and see approach.

Finally, if the decision is made to start with RRT, different modalities are available to provide RRT in ICU, including intermittent RRT (haemodialysis), hybrid therapies (i.e. sustained low efficiency dialysis, extended daily dialysis, prolonged intermittent RRT, continuous RRT [CRRT], and peritoneal dialysis). CRRT and intermittent RRT are generally considered complementary therapies with no clear evidence that either modality has a survival advantage. Selecting the optimal RRT modality should consider both patient specific characteristics (i.e. multi-morbidity, acuity, multi-organ failure) and ICU-specific operational

characteristics (e.g. expertise to deliver prescribed therapy, resources). Intermittent RRT may be preferable when mobilisation and rehabilitation are a priority, provided metabolic fluctuations and fluid shifts can be tolerated.[63] CRRT may be the preferable initial therapy over intermittent RRT particularly in clinical circumstances, for example, haemodynamically instable patients and acute brain injury. However, whether CRRT or intermittent RRT improves outcome and renal recovery remains uncertain.[63] Anticoagulation strategy, choice of filter, and type of catheter are mainly subject of clinical judgement.

Next to the controversy in initiating RRT, the decision whether, or when, to stop RRT in a patient with AKI is still a subject of discussion.[64] Withdrawal or withholding of RRT needs reflection regarding improvement of sufficient kidney function in relation to demand, improvement of the disorder(s) that prompted kidney support, and futility.

CONCLUSIONS

The kidney is an organ that can tolerate exposure to several negative stimuli without suffering significant structural or functional change. For this reason, any acute change in kidney function often indicates severe systemic derangement and predicts a poor prognosis. Risk for AKI is increased by exposure to factors that cause AKI or the presence of factors that increase susceptibility to AKI. Despite revised guidelines and better haemodynamic management, the outcome of AKI is still a reason for concern. Critically ill patients with AKI have better short-time prognosis than before but are more prone to develop increased morbidity in the nearby future. Therefore, any strategy in the critically ill with AKI requires consideration of each individual patient's prospects on cure, care, and comfort.

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NEW THERAPIES TARGETING CYSTOGENESIS IN AUTOSOMAL POLYCYSTIC KIDNEY DISEASE

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ABSTRACT

Autosomal dominant polycystic kidney disease is the most common inherited kidney disease and results from mutations in the polycystin 1 gene (*PKD1*) or the polycystin 2 gene (*PKD2*). The disease is characterised by the progressive development of fluid-filled cysts derived from renal tubular epithelial cells that destroy the architecture of the renal parenchyma and lead to kidney failure. Until recently, the causes and the molecular pathways that lead to cystogenesis remained obscure. In the last decade, enormous progress has been made in understanding the pathogenesis of autosomal dominant polycystic kidney disease and developing new therapies. The purpose of this review is to provide an update on the promising therapies that are being developed and tested, based on knowledge of recent advances in molecular and cellular targets involved in cystogenesis.

Keywords: Adult autosomal polycystic kidney disease (ADPKD), cystogenesis, vasopressin 2 receptors, somatostatin analogues, mammalian target of rapamycin (mTOR) signalling.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) affects 1:400–1:1,000 of live births and is the most common monogenic inherited form of kidney disease across all ethnic types. ADPKD is characterised by cyst formation and enlargement in the kidney and other organs. It represents the fourth leading global cause for kidney failure, and end-stage renal disease (ESRD) usually occurs by late middle age, requiring renal replacement therapy in ~50% of patients by 70 years of age.[1,2]

In 85% of cases, ADPKD occurs as a result of germline mutation in the polycystin 1 gene (*PKD1*), while in 15% of cases it is due to a germline mutation in the polycystin 2 gene (*PKD2*).[3] Recently, a polycystic kidney and/or polycystic liver disease-3 (*PKD3*) caused by heterozygous mutation in the gene encoding for glucosidase II subunit-a (*GANAB*) has been described.[4] Polycystin-1 (PC1) and polycystin-2 (PC2) interact with each other through their C-terminal cytoplasmic domains and are known to form a complex that functions as a transient receptor potential channel involved in the regulation of intracellular calcium homeostasis.[5,6] Glucosidase II subunit-a is required for maturation and surface and ciliary localisation of PC1 and PC2.

Analysis of *GANAB*-null human renal cells resulted in absence of the mature N-terminal PC1 but full-length PC1 and PC2. Heterozygous-null *CANAB* renal cells had a 50% depletion of mature N-terminal PC1.[4] On average, patients with mutations in *PKD1* developed ESRD at younger ages.[7]

Cystogenesis follows a two-hit model. ADPKD is recessive at the cellular level and cysts develop clonally from a tubular cell only after the cell has acquired a second, somatic mutation to inactivate the remaining normal allele.[8] Although the exact mechanisms of cystogenesis remain to be elucidated, the pathological processes that facilitate cyst enlargement are probably a result of two specific abnormalities: i) increased fluid secretion into the cyst lumen, and ii) inappropriately

increased cell division by the epithelium lining the cyst.[9] The major signalling pathways implicated in these phenotypic changes include the intracellular deregulation of calcium homeostasis, cyclic adenosine monophosphate (cAMP) accumulation and activation of protein kinase A (PKA), activation of mitogen activated protein and mammalian target of rapamycin (mTOR) kinases, and other intracellular signalling mechanisms.[10-12]

Until recently, the treatment of ADPKD was aimed at the management of secondary conditions, particularly hypertension, to limit morbidity and mortality after the disease becomes symptomatic. Recent developments arising from a better mechanistic understanding of the molecular pathways involved in cyst growth have allowed targeting the disease pathogenesis, rather than the disease complications. The current review focusses on these novel therapeutic approaches that interfere with the molecular pathways of cystogenesis (Figure 1).

DRUGS TARGETING cAMP-DEPENDENT CYSTIC EXPANSION

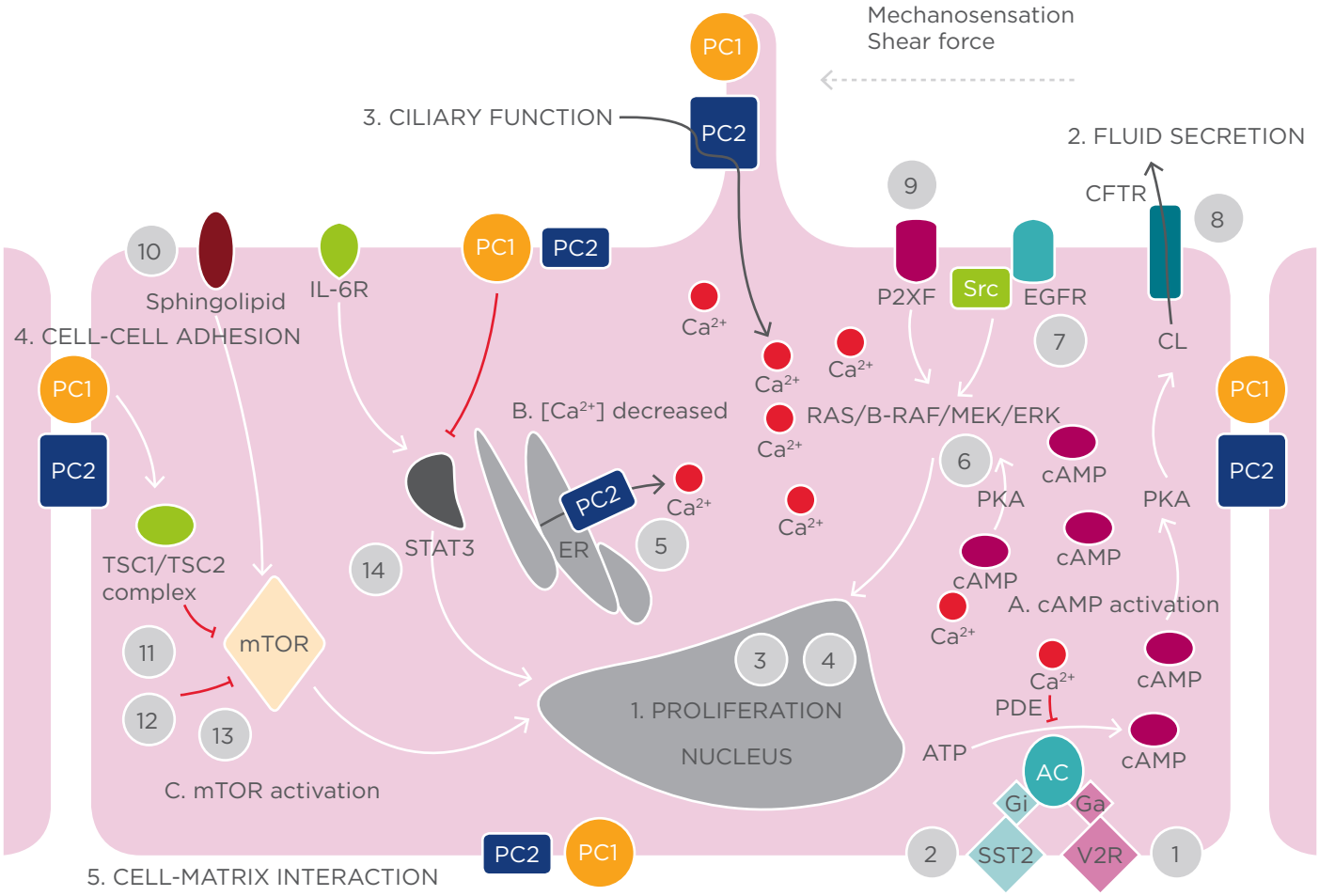
Role of cAMP in Cystogenesis

In ADPKD, disruption of intracellular Ca^{2+} homeostasis due to mutations in the *PKD* gene leads to low intracellular calcium and consequently increased levels of intracellular cAMP. Normally, the levels of cAMP are controlled by a balanced activity of membrane-bound and soluble isoforms of adenylate cyclase (AC) (which catalyses the formation of cAMP from ATP) and phosphodiesterases (which degrades cAMP to AMP). Decreased intracellular calcium inhibits the activity of phosphodiesterases and activates ACs, thus producing a net increase in cAMP concentration.[10] cAMP exerts its effects via PKA, which phosphorylates a number of metabolic enzymes and promotes transepithelial fluid secretion. Chloride secretion drives sodium into the cystic cavity through paracellular mechanisms; this causes movement of water through aquaporins and cyst expansion.[13] In addition, in ADPKD, cAMP promotes cyst enlargement by stimulating epithelial cell proliferation, primarily through the activation of the B-Raf/MEK/ERK pathway.[14,15]

Vasopressin 2 Receptor Antagonists

Normally, vasopressin (AVP) is secreted into the circulation by the posterior pituitary gland, in response to an increase in serum osmolality or a decrease in effective circulating volume. In the kidney, AVP binds to the V2 AVP receptor in the basolateral membranes of collecting-duct cells. The V2 receptor is a typical member of the large superfamily of G protein–coupled receptors. Thus, occupancy of this receptor results in mediated activation of AC and the formation of cAMP with subsequent activation of PKA, which promotes the fusion of cytoplasmic vesicles containing aquaporin-2 water-channel proteins with the apical membrane. As a result, this normally water-tight membrane becomes water-permeable. Driven by the osmotic gradient of sodium, water is then transcellularly reabsorbed, entering the cells through aquaporin-2 in the apical membrane and leaving the cells for the interstitial space through aquaporin-3 and aquaporin-4, which reside in the basolateral membrane.[16] In patients with ADPKD, there is a pathologically hyperactive AVP/V2 receptor system. Serum concentrations of AVP correlate positively with both serum osmolality, as well as with total kidney size and negatively with glomerular filtration rate (GFR).[17-20] The central role of cAMP in cystogenesis and the pathologically hyperactive AVP/V2 receptor system have made the blocking of V2R particularly appealing in the treatment of ADPKD.

In preclinical trials, a non-peptide AVP antagonist mozavaptan (OPC-31260), administered in murine cystic models orthologous to human disease, including the *Pkd*$^{2WS25/-}$ mouse (ADPKD), PCK rat (ARPKD), and pcy mouse (nephronophthisis Type 3), reduced renal cAMP and inhibited disease progression, as measured by the reduction in kidney volume, the cystic area, the number of mitotic and apoptotic cells, and the blood urea nitrogen.[21-23] Additional studies were conducted to examine the effects of tolvaptan (OPC-4106), a more potent and highly selective human V2R antagonist, in comparison with mozavaptan.[24] Tolvaptan showed similar results on renal cAMP and *PKD* progression in the PCK rat model using the lowest dose. Reif et al.[25] in an *in vitro* study examined the effect of tolvaptan on intracellular cAMP, ERK activity, cell proliferation, and transcellular chloride anion secretion using human ADPKD cyst epithelial cells. Tolvaptan caused inhibition of cAMP AVP-induced production, ERK signalling AVP-induced, cell proliferation, and chloride anion secretion. These effects significantly contributed to decreased *in vitro* cyst growth.



1. V2R antagonist
2. Somatostatin analogues
3. Roscovitine
4. HDAC inhibitors
5. Triptolide
6. Raf inhibitors
7. Src inhibitors
8. CFTR inhibitors
9. P2X7 inhibitors
10. GloCer synthase inhibitors
11. mTOR inhibitors
12. Metformin
13. Curcumin
14. Pyrimethamine

Figure 1: Illustration of the key mechanisms of adult autosomal polycystic kidney disease pathogenesis and targets of potential treatments.

Polycystin-1 and polycystin-2 expressed in different subcellular locations and regulate 1) proliferation, 2) fluid secretion, 3) ciliary function, 4) cell-cell adhesion, and 5) cell-matrix interaction of renal epithelial cells. Dysfunction of polycystin-1 or polycystin-2 results to aberrant signalling pathways including: A) activation of cAMP, B) decreased intracellular calcium concentrations, and C) activation of mTOR. The targets of candidate drugs are depicted as grey circles.

CFTR: cystic fibrosis transmembrane regulator; ER: endoplasmic reticulum; ERK: extracellular-signal regulated kinase; GlcCer: glucosylceramide; HDAC: histone deacetylase; IL-6R: interleukin-6 receptor; MEK: mitogen activated protein kinase; mTOR: mammalian target of rapamycin; PC: polycystin; PDE: phosphodiesterase; PKA: protein kinase A; SR: somatostatin receptor; TSC: tuberous sclerosis; V2R: vasopressin V2 receptor; EGFR: estimated glomerular filtration rate; cAMP: cyclic adenosine monophosphate.

The large randomised, double-blind, placebo-controlled, multinational, Phase III TEMPO 3:4 trial[26] confirmed the aforementioned experimental studies. This trial enrolled 1,445 patients aged 18–50 years with ADPKD, rapidly progressive kidney growth (total kidney volume [TKV] ≥750 mL) as measured by magnetic resonance imaging (MRI) and chronic kidney disease (CKD) Stages 1–3. Tolvaptan reduced the rate of TKV growth (primary endpoint) by 49% and the rate of estimated GFR (eGFR) loss on treatment (secondary endpoint) by 26% per year during the median observation period of 3 years. The effect on TKV appeared greater during the first year of treatment than

during the second or third years. Beneficial effects on renal function have been observed in all patient subgroups, especially in patients aged ≥35 years and in patients with hypertension or a TKV of ≥1,500 mL. Another important secondary endpoint was the reduction in kidney pain occurring early and throughout treatment. The results of the TEMPO 3:4 trial suggested that tolvaptan had no effect compared with placebo on albuminuria. Conversely, in a post hoc exploratory analysis, tolvaptan decreased albuminuria compared with placebo independently of blood pressure. In addition, the treatment efficacy of tolvaptan on changes in TKV and eGFR was more readily detected in patients with higher albuminuria.[27]

Based on the results of the TEMPO 3:4 trial, tolvaptan has been approved to delay the progression of ADPKD in patients with a rapid increase of TKV in Japan, Canada, the European Union (EU), the UK, and South Korea. The European Renal Association-European Dialysis and Transplant Association (ERA-EDTA)[28] has issued detailed guidance on this topic. ERA-EDTA suggests that tolvaptan can be prescribed to adult ADPKD patients aged <50 years with CKD Stages 1–3a (eGFR >45 mL/min/1.73 m^2) who have demonstrated, or who are likely to have, rapidly progressing disease. ERA-EDTA recommends not starting tolvaptan in patients aged 30–40 years with CKD Stage 1 (eGFR >90 mL/min/1.73 m^2) or patients aged 40–50 years with CKD Stages 1 or 2 (eGFR >60 mL/min/1.73 m^2). The organisation recommends that rapid disease progression be defined as a confirmed annual eGFR decline of ≥5 mL/min/1.73 m^2 in 1 year, and/or ≥2.5 mL/min/1.73 m^2 per year over a period of 5 years. It can also be defined as a >5% increase in TKV per year by repeated measurements (preferably ≥3, each at least 6 months apart and by MRI). With regard to dosing, ERA-EDTA suggests that tolvaptan be started with a dose of 45 mg in the morning and 15 mg in the evening, uptitrating the dose to 50/30 and 90/30 when tolerated, and discontinuing tolvaptan when patients approach ESRD.

Tolvaptan has significant adverse effects including aquaretic effects (polyuria, nocturia, and polydipsia) and elevation of aminotransferase enzyme concentrations with the potential for acute liver failure.[26,29,30] Although the incidence of hepatic enzyme elevation was low, three patients treated with tolvaptan in the TEMPO 3:4 trial met criteria for Hy's law (elevation of aminotransferase enzymes >3-times the upper limit of normal, plus elevation of total bilirubin >2-times the upper limit of normal, without other explanatory mechanisms), which have a fatality rate of ~10% from liver injury. Therefore, the Cardiovascular and Renal Drugs Advisory Committee of the US Food and Drug Administration (FDA) declined to approve tolvaptan for ADPKD, as they were worried that liver damage might progress with long use treatment.[31] Appropriate patient selection is critical to optimise long-term benefits and minimise adverse effects and hepatotoxic risk factors.

Studies to further assess the efficacy and tolerability of tolvaptan in patients with ADPKD are ongoing or just completed. TEMPO 4:4 is a 2-year, open-label extension of TEMPO 3:4 and was completed in March 2016. This study aimed to evaluate the long-term efficacy and safety of tolvaptan in patients with ADPKD; the findings are soon to be published. In addition, the long-term safety of titrated tolvaptan in patients with ADPKD is currently being assessed in a Phase III open label trial,[32] while the ongoing Phase IIIb REPRISE trial aims to extend the understanding of the efficacy and safety of tolvaptan in patients with late Stage 2–early Stage 4 CKD.[33]

Somatostatin Analogues

Somatostatin (SST) is an endogenous hormone primarily secreted by the pancreatic islet δ-cells. SST has anti-secretory and anti-proliferative effects mediated by the interaction with five subtypes of G protein–coupled receptors (SSTR1-5).[34] SST receptors are expressed by renal tubular epithelial cells and by cholangiocytes. SST selectively inhibits cAMP synthesis in the epithelial cells of the distal tubules and collecting ducts both *in vitro* and *in vivo*[35,36] and exerts similar effects to cholangiocytes.[37] As plasma half-life of the native SST is very short (1–3 minutes), the synthetic analogues octreotide, lanreotide, and pasireotide were developed for use in clinical practice.

In particular, octreotide and lanreotide have a half-life of 2 hours and present a high affinity for SSTR2 and SSTR3 and moderate affinity for SSTR5. By comparison, pasireotide has high affinity for all the receptors of SST, except SSTR4, and its plasma half-life is about 12 hours.[38] Currently, formulations of octreotide and lanreotide with long-acting release (LAR), which allows the administration every 28 days intramuscularly or intradermally, have been introduced into clinical practice. Ruggenenti et al.[39] have evaluated for the first time the

effectiveness of octreotide-LAR by performing a randomised, crossover, placebo-controlled trial in 14 ADPKD patients, which demonstrated the potential efficacy in slowing the growth of TKV and the relative safety of the treatment. Van Keimpema et al.[40] compared the effects of 6 months of treatment with lanreotide or placebo in 54 patients with polycystic liver disease (PLD), including 32 with ADPKD and the remaining with isolated PLD. The average volume of the liver decreased in patients treated with lanreotide while it increased in the placebo group. Moreover, in patients with ADPKD, TKV was reduced after treatment with lanreotide, while it was increased in the placebo group. In a subsequent open label extension study[41] patients who participated in the initial trial were re-enrolled to complete a treatment period of 12 months with lanreotide. Liver volume decreased after 12 months of treatment with lanreotide, with the greatest effect seen during the first 6 months. In the 25 patients with ADPKD, TKV remained stable at the end of 12 months. In another 12-month study, 42 patients with PLD, including 34 with ADPKD, were randomised to receive treatment with octreotide-LAR or placebo.[42] The total volume of the liver was reduced in the treatment arm with octreotide-LAR but increased in the placebo group. In patients with ADPKD, the TKV remained unchanged in the octreotide-LAR group but increased in the placebo group. In addition, renal function had a slower reduction in patients treated with octreotide-LAR, although the difference did not reach statistical significance. More recently in the ALADIN multicentre study conducted in Italy, 79 patients with ADPKD and eGFR >40 mL/min/1.73 m^2 were randomised to a 3-year treatment with octreotide-LAR or placebo.[43] After the first year, the average increase in TKV was significantly lower in patients treated with octreotide-LAR compared to those receiving placebo. In the third year, the average increase in TKV in the treatment arm was lower than the placebo group without reaching statistical significance. During the entire study period, the annual reduction in GFR was lower in the octreotide-LAR group than in the placebo group, although the difference did not reach statistical significance. A more recent open label clinical study evaluated the efficacy of 6 months of treatment with lanreotide in 43 patients with symptomatic PLD and ADPKD (eGFR >30 mL/min/1.73 m^2).[44] Compared to baseline, the median liver volume decreased significantly, as well as that of the kidney. In addition, renal function remained stable until the end of the study. A recent meta-analysis confirmed the efficacy of SST analogues in reducing the progressive increase of TKV on average, with a reduction of 9% compared to the growth observed in patients treated with placebo or conventional therapies. However, treatment with SST analogues did not demonstrate significant effects on the eGFR.[45]

Based on these studies, in August 2015 the European Medicines Agency (EMA) has attributed to lanreotide the 'orphan drug' designation for the treatment of ADPKD. Designated orphan medicinal products are products that are still under investigation and are considered for orphan designation on the basis of potential activity. Opinions on orphan medicinal product designations are based on the following three criteria: i) the seriousness of the condition; ii) the existence of alternative methods of diagnosis, prevention, or treatment; and iii) either the rarity of the condition (affecting no more than 5 in 10,000 people in the EU) or insufficient returns on investment.

In the studies mentioned above, treatment with SST analogues was generally well tolerated with no particular problems, diarrhoea being the most common adverse event. However, recently, the authors of a randomised, controlled trail documented an increased risk for hepatic cyst infection during lanreotide treatment. A literature review also suggested an increased risk for hepatic cyst infection during the use of SST analogues.[46]

Additional clinical trials of SST analogues for ADPKD and/or PLD are currently ongoing.[47-50]

DRUGS TARGETING THE mTOR SIGNALLING PATHWAY

Role of the mTOR Signalling Pathway in Cystogenesis

Serine/threonine-protein kinase mTOR is an enzyme that plays a critical role in proliferation and cell growth.[51] The first suggestion of a prominent role of the mTOR pathway in the pathogenesis of ADPKD comes from studies in patients with severe infantile-onset of ADPKD due to a large deletion of chromosome 16 involving the *PKD1* gene [16p13.3] and the adjacent tuberous sclerosis 2 (*TSC2*) genes [16p13.3].[52] *TSC1* and *TSC2* encode for hamartin and tuberin, respectively. These two proteins together with TBC1 domain family member 7 (TBC1D7) form the TSC protein complex that acts as a critical negative regulator of mTOR

complex 1 (mTORC1).[53] PC1 has also an important function in the regulation of the mTOR pathway, as the C-terminal cytoplasmic tail of PC1 interacts with tuberin. In ADPKD this interaction is impaired, and the mTOR pathway is inappropriately activated in cyst-lining epithelial cells of human ADPKD patients and mouse models.[54] Based on these data, a possible therapeutic role for mTOR inhibitors in ADPKD has been suggested.

mTOR Inhibitors

Sirolimus and its derivative everolimus, used in maintenance immunosuppression in patients undergoing kidney transplantation, have been proposed as potential new drugs to slow the growth of cysts and the progression of ADPKD in ESRD. The effects of treatment with mTOR inhibitors have been assessed in different experimental models of ADPKD.[55-58] The first published randomised double-blind study compared the effects of 2 years of treatment with everolimus (5 mg/day) or placebo in 433 patients with ADPKD and GFR >30 mL/min/1.73 m^2.[59] During the first year of study, the increase of TKV was significantly lower in the treatment arm with everolimus compared to placebo. This effect was not confirmed at the end of the second year. In addition, the initial effectiveness of everolimus in slowing TKV did not translate into improvement of renal function.

The SUISSE study compared the effects of treatment for 18 months with sirolimus (2 mg/day) or conventional therapy in 100 patients with ADPKD and GFR ≥70 mL/min/1.73 m^2.[60] The median increase in TKV was comparable between the two groups as well as the eGFR throughout the entire study period. The randomised trial SIRENA compared the effects of treatment with sirolimus or with conventional therapy alone for 6 months in 21 patients with ADPKD and GFR ≥40 mL/min/1.73 m^2.[61] The treatment with sirolimus was associated with a minor increase of the TKV compared to conventional therapy. In a subsequent open label study (RAPYD), 55 patients with ADPKD and mild-to-moderate renal impairment were randomised to 24 months of treatment with ramipril (control group), ramipril in combination with high doses of sirolimus (target blood levels: 6–8 ng/mL) or ramipril in combination with low-dose sirolimus (target blood levels: 2–4 ng/mL).[62] Compared to baseline, total cyst volume decreased significantly in both treatment arms with sirolimus, while increasing in the control group. In a more recent study, 30 patients with ADPKD and measured GFR ≥25 mL/min/1.73 m^2 were randomised to receive low-dose sirolimus (target blood levels 2–5 ng/mL), standard doses of sirolimus (target blood levels >5–8 ng/mL) or conventional therapy for 12 months.[63] TKV did not change significantly in the two treatment groups with sirolimus as in the group assigned to conventional therapy. In addition, the renal function improved (GFR measured by plasma clearance of iothalamate) with low-dose sirolimus but not with the standard dose of the drug. Currently, there are two ongoing trials that are testing mTOR inhibitors in ADPKD.[64,65]

OTHER THERAPEUTIC TARGETS IN PRECLINICAL STUDIES AND IN EARLY CLINICAL TRIALS

In addition, other agents targeting different molecules or pathways involved in cystogenesis have been used in preclinical studies and some of them are ongoing in early clinical trials in humans.[66] All these agents are summarised in Table 1.

Bosutinib (SKI-606) is a Src/Abl tyrosine kinase inhibitor effective in inhibiting epithelial cell proliferation and reducing extracellular matrix adhesion. In the BPK and PCK rodent models of ADPKD, bosutinib was found to suppress kidney cyst formation by inhibiting epidermal growth factor receptor activation and downregulating B-RAF/ERK signalling.[67] Based on this evidence, a Phase II, multicentre, randomised, double-blind, placebo-controlled clinical trial with bosutinib[68] has been conducted and completed, and we currently are expecting publication of the study results. Tesevatinib, a new tyrosine kinase inhibitor, is being currently evaluated in two ongoing trials.[69,70]

Triptolide, by acting as a PC2 agonist to restore cytosolic Ca^{2+} release, has been effective in arresting cellular proliferation and attenuating overall cyst formation in $Pkd1^{-/-}$ murine kidney epithelial cells.[71] A clinical trial conducted in China has been terminated due to a high rate of drop-outs[72] and another trial is underway.[73]

In an experimental model, sorafenib, a non-selective RAF inhibitor, reduced the basal activity of ERK, inhibited cAMP-dependent activation of B-RAF and MEK/ERK signalling, and caused a concentration dependent inhibition of cell proliferation induced by cAMP and EGF. In addition, it completely blocked *in vitro* cyst growth of human ADPKD cystic cells.[74] A different Raf inhibitor (PLX5568) has been evaluated in the Han:SPRD rat model.[75]

Table 1: New agents in preclinical models or in early clinical trials in humans.

Therapeutic target	Agents	Preclinical models	Human trials
Tyrosine kinase inhibitors[67]	Bosutinib (SKI-606) Tesevatinib	Mice	NCT01233869[68] NCT02616055[69] NCT01559363[70]
Polycystin-2-mediated Ca^{2+} release[71]	Triptolide	Mice	NCT02115659[73]
Raf kinase inhibitors[74,75]	Sorafenib PLX5568	Mice Rats	NA NA
Cyclin dependent kinase inhibitors[76,77]	R-roscovitine S-CR8	Mice Mice	NA NA
Histone deacetylases inhibitors[78,79]	Trichostatin A Valproic acid Niacinamide EX-527	Fish Mice Mice Mice	NA NA NCT02140814[80] NCT02558595[81] NA
CFTR inhibitors[82]	Thiazolidinones Glycine and Malonic acid hydrazides PPQs	Mice Mice Mice	NA NA NA
Activation of AMP-activated protein kinase[83,84]	Metformin	Mice	NCT02656017[85]
Agonists of peroxisome proliferator-activated receptor gamma[86,88]	Pioglitazone Rosiglitazone	Rats Rats	NCT02697617[89]

CFTR: cystic fibrosis transmembrane conductance regulator; PPQs: pyrimido-pyrrolo-quinoxalinediones; AMP: adenosine monophosphate.

In this study, cyst enlargement attenuated without an improvement in kidney function. Furthermore, the authors reported increased renal and liver fibrosis.

A preclinical study with the CDK inhibitor (R)-Roscovitine in juvenile cystic kidney and congenital polycystic kidney mouse models of *PKD* effectively attenuated cystogenesis by inhibiting cell cycle progression, proliferation, and apoptosis.[76] In addition, a more potent second-generation analogue of roscovitine (S-CR8) showed effective inhibition of both renal and hepatic cystogenesis in an orthologous mouse model of ADPKD with inactivated *PKD1* gene.[77]

Altered expression of histone deacetylases (HDCAs) causes abnormal transcription of key genes controlling principal cellular functions such as cell proliferation, cell-cycle regulation, and apoptosis.[78] A pan-HDAC inhibitor called trichostatin A (TSA) has been evaluated in a *PKD2* zebrafish model showing the ability to suppress pronephric cyst formation.[79] The same results have been obtained after administration of valproic acid (VPA), a Class I HDAC inhibitor.[79] The NIAC-*PKD1* trial[80] has just been completed, and we are currently awaiting publication of the results. In addition, another trial, NIAC-*PKD2*,[81] is currently recruiting participants.

Each of the three chemical classes of cystic fibrosis transmembrane conductance regulator (CFTR) inhibitors has been tested in *PKD* models: i) thiazolidinones, ii) glycine and malonic acid hydrazides, and iii) pyrimido-pyrrolo-quinoxalinediones. The best thiazolidinone, tetrazolo-CFTRinh-172, and the best glycine hydrazide, Ph-GlyH-101, were found to inhibit cyst formation and enlargement in Madin–Darby canine kidney cyst models and in *PKD1* mice.[82]

AMP-activated protein kinase regulates cell growth via suppression of the mTORC1 pathway, by direct phosphorylation of the tumour suppressor *TSC2* and Raptor (regulatory associated protein of mTOR).[83] Recently, Takiar et al.[84] showed in a *PKD1* mice model, that metformin inhibited renal cystogenesis and caused a significant decrease in the cystic index by activating AMP-activated protein kinase and suppressing mTOR and CFTR. Currently, the TAME trial[85] is recruiting ADPKD patients to see if metformin is safe and well tolerated.

Agonists of peroxisome proliferator-activated receptor gamma (PPAR-γ) have been shown to have anti-cystogenic properties in *PKD* animal models. Pioglitazone has been shown to inhibit the growth

of renal and hepatic cysts in PCK rats by inhibiting the CFTR-mediated ionic current and the secretion of fluid.[86] In another study, pioglitazone also reduced cellular proliferation, highlighted by a reduction in the number of cells positive for Ki67 (a proliferation marker) in the dilated tubules and in cysts from treated rats.[87] Another powerful agonist of PPAR-γ, rosiglitazone, has been used to treat Han:SPRD rats. Rosiglitazone delayed the onset of renal failure but was associated with cardiac enlargement due to excessive renal sodium reabsorption.[88] Based on these preclinical data, the PIOPKD trial[89] is currently recruiting participants.

CONCLUSION AND FUTURE DIRECTIONS

Multiple signalling pathways are involved in cyst formation and progression, and studies of these signalling pathways have led to potential treatments for ADPKD. In this review, we have covered the successes obtained in recent years in understanding the pathogenesis of ADPKD and presented novel therapeutic strategies targeting molecular pathways of cystogenesis. V2R antagonists and SST analogues have been shown to safely slow kidney growth and protect renal function in patients with ADPKD, and represent the most well-characterised and promising candidate therapies to date. According to the results of the TEMPO3/4 study and registration by the EMA, tolvaptan seems to be the first choice drug. Some medical interventions successful in experimental models failed in clinical practice and others still need to be evaluated in clinical trials. It is possible that monotherapy may not be sufficient and that targeting multiple molecular pathways will be required to retard cyst growth and disease progression in the feature. Combination therapy is then the right direction of further clinical trials in order to find effective treatment. To date no association of drugs inhibiting cystogenesis has proven to be effective: further research is needed. The association of tolvaptan and angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), and statins are reported as effective associations in a recent study.[90]

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