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HYDERABAD NEPHROLOGY FORUM

HYDERABAD NEPHROLOGY FORUM

KIDNEY DIGEST

An official Newsletter of Hyderabad Nephrology Forum, Telangana, India

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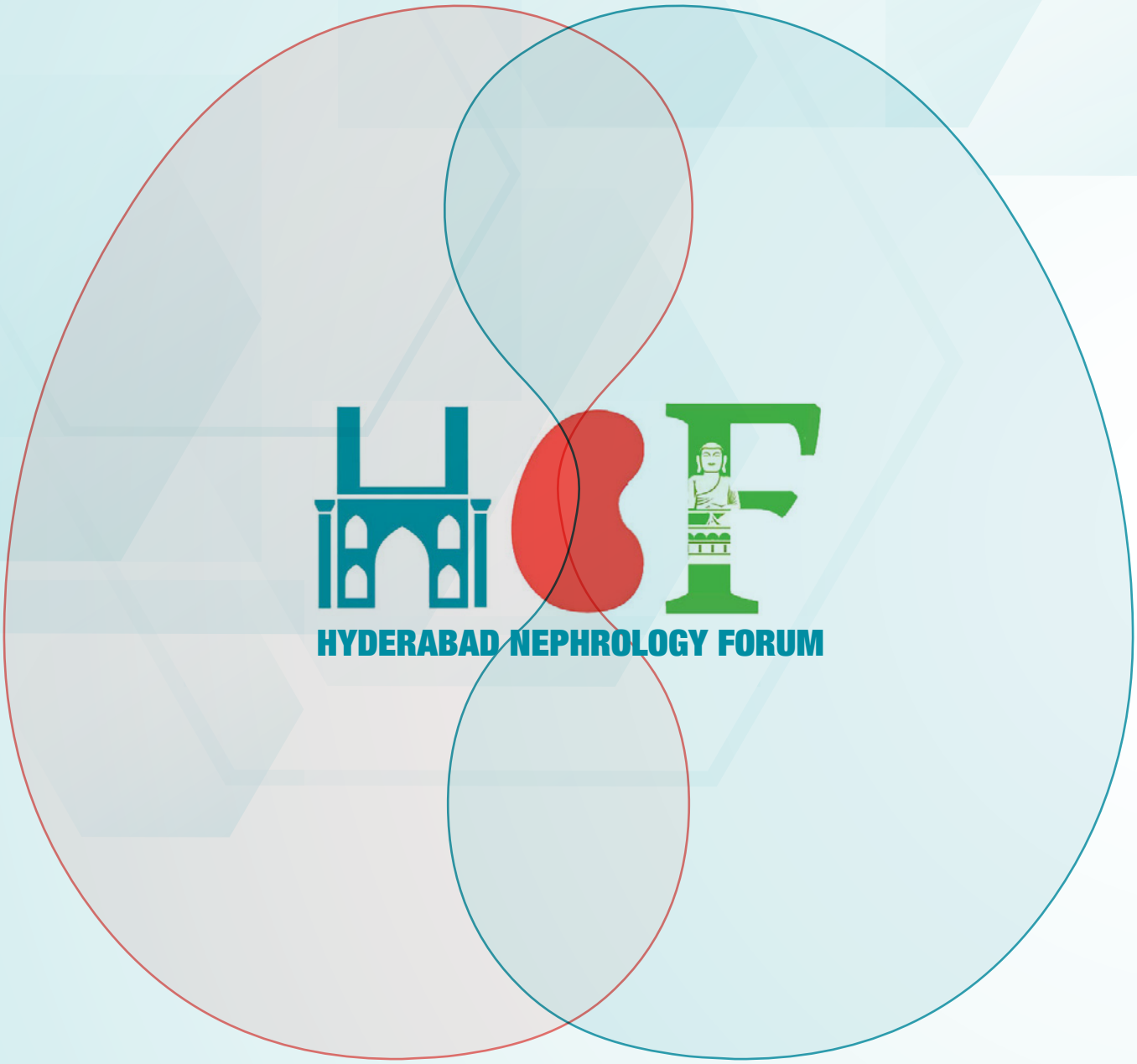

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EDITORIAL

Editor, Kidney Digest

Dr Praveen Kumar Etta

MD, DM (SGPGI)

Former Asst Prof (PIMS)

Editorial Fellow, IJOT

Executive Member, HNF

Senior Consultant Nephrologist

Hyderabad

Hyderabad Nephrology Forum (HNF)

Hyderabad Nephrology Forum (HNF) is a consortium of Nephrologists based at Hyderabad and Telangana. It has been active for over 25 years now. HNF is dedicated to advancing kidney health statewide through Education, Research and Advocacy. As you all know, it has been conducting various academic activities like monthly case based discussions involving the public institutions, private hospitals and from the nephrologists practicing in the districts; theme based sessions with invited National and International guest speakers; Mock Examination for final year residents; Twitter based educational Tweet chats; conducting Annual TSNCON and few non-academic career guided sessions. We are also working on to use other social media platforms like Facebook and Instagram apart from Twitter for educational activities. We are planning to restart physical meets soon, at least quarterly. We are in the process of forming a research committee to form guidelines for giving research grant to the post graduate students, which will help in performing research activities and thesis projects. We are also thinking to have non-academic clubs such as patient advocacy club, financial and career development club, and sports and fitness club. We are extremely happy to expand HNF to include the district hospitals and nephrologists from all over Telangana. We are planning to have district chapters of HNF and to elect executive members from the districts in council elections. The HNF website is completely renovated with all the updates on academic events, their youtube links, achievements, online membership registration as per the categories etc. Please follow us at our website, https://hyderabadnephrologyforum.com/ for the latest updates and to avail new membership.

The inaugural issue of HNF newsletter the “Kidney Digest” in June 2022 was a great success and it attracted interest of nephrologists of all over Telangana. We are now happy to bring the 2nd quarterly

issue of the HNF newsletter. It's been a wonderful platform to keep all the HNF members updated on the various activities, share achievements of HNF Members, and disseminate their publications in various scientific journals. This could play our part in bridging the knowledge gap in Nephrology especially for senior residents of both public and private sector hospitals. It is a wonderful platform to showcase the scientific work and to have networking among nephrologists of HNF.

It has various sections such as messages from pioneer Nephrologists, activities of HNF, journal scan, what's new in Nephrology, practice changing updates, resident's desk, must-read articles, academic and research activities, achievements, publications, patient education activities and advocacy and public awareness programs. Certain new sections would be included in upcoming newsletters; some of these include history in nephrology, clinical case studies, clinico-pathological conference, approach to a challenging case, nephro quiz, point of view, renal pathology pearls, drug update, nephrology image, crossword puzzle, focus on POCUS, make your diagnosis, teaching points, transplantation proceedings, landmark trials in nephrology, nuances in interventional nephrology, conference calendar, etc. We have also included few interesting topics and case reports from nephrologists outside Telangana in this newsletter.

I would like to thank all the editorial board members, senior faculty, and advisory board of HNF for all the efforts in brining the quarterly issues of Kidney Digest successfully. I thank the contributors of this newsletter Dr Swarnalata Gowrishankar, Dr Seera Pani Gopaluni, Dr Deepthi Ayanavelli, Dr Namrata Parikh, Dr Ramiz Panjwani, Dr S Anitha, Dr Purva Bavikar and Dr Lekha Pradhan. I'm eternally grateful to Dr Ravindra Prabhu, Dr T Saravanan and Dr G Gireesh Reddy who have contributed their bit from outside Telangana state and HNF. I wanted to express my deep gratitude to Dr Anuradha Raman, Dr Girish Narayen, Dr Pradeep Deshpande, Dr S Krishnan and Dr KV Dakshina Murthy for their continuous encouragement and advice. My special thanks to Dr Manisha Sahay, Dr Manjusha Yadla, Dr G Swarnalata, Dr Kiranmai, Dr PS Vali, Dr Raja Karthik, Dr G Srikanth and Dr Vikram for their constant motivation. Without their help, this success would not have been possible. I thank Dr Shaista Hussaini and Dr Vikranth Reddy for giving a message to the forum members. I once again request all the members of HNF to join hands to strengthen our forum and to make this newsletter more interesting and academic to the senior residents by contributing topics of interest which will be published with great honor.

Message from Prof. Dr. Girish Narayen

It gives me immense satisfaction and great pleasure to write this foreword for the forthcoming News letter from Hyderabad Nephrology Forum. The Forum has recently celebrated its silver jubilee which, despite the covid pandemic was a grand success with active participation of all the members. The young colleagues may not be aware of the history and the efforts made by members especially in early years to establish the Forum. It made its humble beginning in 1996 when the first meeting was held in the seminar room of Nephrology department of Osmania hospital. Initially 6-8 members were participating in discussions, but they had guidance from senior faculty members like Professor A. Gopal kishen and late Professor JCM Shastry. Gradually nephrologists from other hospitals of Hyderabad joined the monthly meeting. Later the forum meetings were held along with urologists and transplant team who participated with presentation of cases from respective units. The venue for the meeting by rotation was changed to various participating hospitals like Mediciti, NIMS, Satya kidney center, hotels, API hall and finally back to the present location in auditorium of Nizams Institute. The growth of Forum has been quite remarkable over the last quarter of a century. The academic activities improved, junior doctors and residents got a platform to present their cases and academic work. Guest lectures were arranged by inviting faculty in the field of urology, transplantation immunology, nuclear medicine, radiology, histopathology, microbiology, infectious diseases and some other allied specialities. Although so many members have contributed for the growth and development of the forum, I would be failing in my duties if I do not place on record the time spent and efforts made by Dr S Krishnan who has been the backbone of this forum and is like a “Permanent member of the security council”.

New developments in the field of genetics, immunology, diagnosis and therapeutics have revolutionised the evaluation and management of cases with various renal disorders. To learn about the advances made and to keep pace with them, need for a monthly magazine or newsletter was a long pending need for the benefit of all the members. I am very happy to note that this dream is now being fulfilled by the current younger colleagues and finally the news letter is going to be published at regular interval. I convey my best wishes to the editorial team and hope that the Hyderabad nephrology forum would fulfil the aspiration and requirement of the members of the forum and take it to new heights.

Prof. Dr. Girish Narayen

Former professor & HOD Nephrology
Osmania General Hospital

Message from Prof. Dr. K.V. Dakshinamurty

I heartily congratulate the office bearers of Hyderabad Nephrology Forum for conceptualizing and starting the News Letter of the Forum. It is a long awaited initiative. The News Letter provides a platform for the Nephrology community of Telangana State to project their work related to the academic achievements, nuances in patient care, events connected with community service. It helps in reaching out to the members of the Nephro-family and in networking among the stakeholders, resulting in spread of the knowledge of the new techniques, newer protocols of treatment modalities and sharing of difficult and rare cases in Nephrology. It also encourages the young Nephrologists in furthering their career ambitions.

I am very happy that the News Letter of Hyderabad Nephrology Forum has become a reality thanks to the hard work put in by the office bearers.

Prof. Dr. K.V. Dakshinamurty

Former professor & HOD Nephrology
NIMS Hospital

Message from Dr Shaista Hussaini

The Nephrology Forum is a gateway for learning, using the vast experience of the senior nephrologists, it opens the dimensions of collateral thinking and differential prospects for the budding nephrologists. The discussion of difficult and tough cases leads to better patient care. Additionally, review of literature in the Forum comes as a boon for busy professionals. With more involvement of Nephrologists from the surrounding districts of Telangana, the forum is taking excellent initiative for spreading mutual benefits. I applaud the Nephrology Forum's committee members for their immense painstaking efforts to raise this forum's standards. I wish the Forum the very best for future.

Dr Shaista Hussaini

Senior Consultant Nephrologist
Care Hospitals, Hyderabad

Message from Dr. Manjusha Yadla

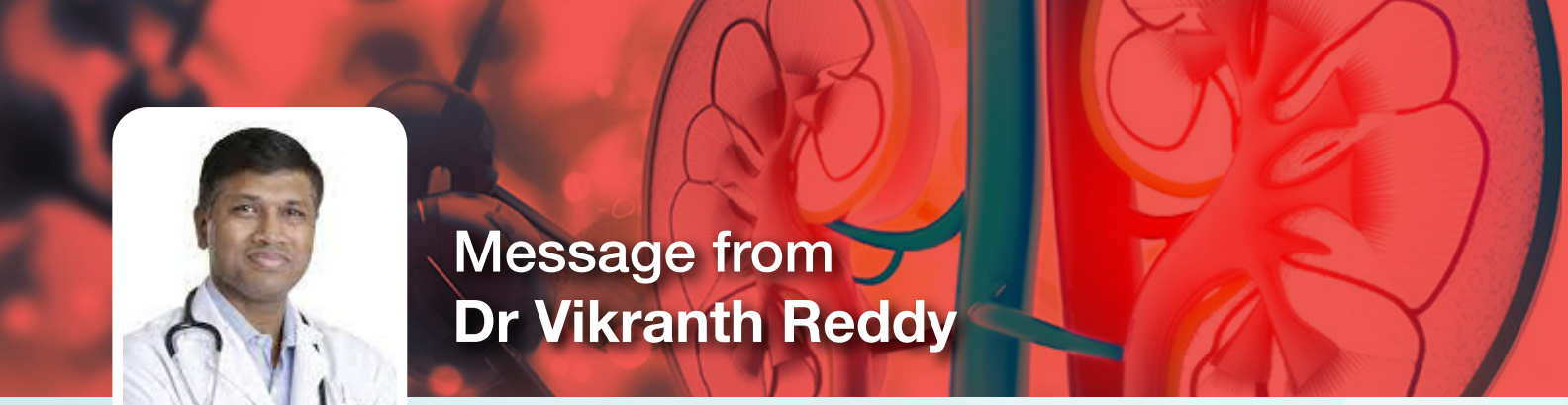
Its my proud privilege to write a message for HNF Newsletter. I had a long incredible and exciting association with Hyderabad Nephrology Forum. My first interaction with Forum was in my DM training period when I presented a case series of Atypical Mycobacterium peritonitis in CAPD patients, for which late Prof JCM Shastry Sir also attended. First compliment for my first presentation in Forum by Prof JCM Shastry is my sweet memory. In 2012, when I was Assistant Professor at Gandhi hospital, I took (forced to take) the responsibility of Forum meetings. With the help of senior teachers guidance and the support from senior faculty, we were able to take the Forum through many milsestones. Forum meeting in early 2000s used to be in Marriott Hotel and subsequently changed to API building ,few Hotels and then to NIMS, Auditorium. With the improvement in number of seats and the expansion of fraternity in Hyderabad and erstwhile Andhra Pradesh, we had regular conduct of meetings with guest lectures from Dr. Raghu Kalluri (Harvard university), faculty from other departments and the like. We had our first annual family meet in 2014 in Leonia resorts which was attended by many from twin telugu states. After the formation of Telangana State, We started our monthly meetings last Friday of every month and the agenda was made more student centric with inclusion of case presentations, discussions, vignettes etc. In the best interest of students, we started our annual mock exams (NEPHROMOCKS) with the guidance of Drs Anuradha Raman, Girish Narayan, Manisha sahay and Pradeep Deshpande. NEPHROMOCKS was conducted for both the telugu states with trainees attending from Vizag Medical College, Narayana medical College etc. We had external examiners from various states interacting with students and teaching them in best possible way.

We also conducted weekly training sessions for the benefit of final year exam going students with the help of Drs Manisha Shay, Kiranmai Ismal, Sree Bhushan Raju and Gangadhar in NIMS premises. We started Telangana state annual Chapters in 2019 -TSNCON with guest faculties from Vizag and the like. TSNCON was started with aim to provide a platform for students to show case their research. TSNCON 2020 was inaugurated by Honourable Governor Smt. Dr. Tamilisai Soundarrajan and we had guest faculty from Texas (USA) and Tamilnadu. With the COVID pandemic, we switched to zoom meetings , which were conducted regularly on every last Friday. 3rd annual chapter of TSNCON was a virtual conference with guest faculty from UK and 4th chapter was attended by many international members with guest faculty from USA. We had expert international faculty speaking to us in monthly meets too. Dr.S.Krishnan was an immense support in successful transformation of HNF.

We had celebrated our Silver jubilee in September 2021 appreciating the efforts of everyone who has contributed for the growth of Forum. Holding the forum for ten long years as Organising secretary, I am now elected as Vice -President of the HNF. I am sure the executive committee with inclusion of young faculty with diversity of thoughts and amalgamation of ideas would move forward in a more prosperous way. All the very best to the new Executive Team.

Dr. Manjusha Yadla

Professor and HOD Nephrology
Gandhi Hospital



Message from Dr Vikranth Reddy

Hyderabad Nephrology Forum (HNF) is an embodiment of science and intellect. It brings in every kidney specialist of the region onto a common platform. The forum focuses on bringing out interesting case scenarios with their clinical presentation, treatment perspectives, and the discussions happen unhindered. This helps in bringing out the latest management strategies which in turn helps all the members of the forum to be up-to-date. The senior faculty of the forum has a strong intellectual heartbeat. The Forum helps in nurturing the young and budding kidney specialists, encourages them in presenting the cases. The Forum also conducts Annual meet to encourage the students pursing Nephrology courses and gives a chance to every student to present their research work. The Forum also conducts guest lectures periodically which includes both national and international faculty. HNF is a boon to the kidney specialists of this region.

Dr Vikranth Reddy

Senior Consultant Nephrologist
Care Hospitals, Hyderabad

Hyderabad Nephrology Forum: An Eternal Journey

Learning is a continuous Journey; little steps of Hyderabad Nephrology Forum began 25 years ago by few seniors Nephrologists and now have expanded to including many young Nephrologists from all over Telangana.

The kidney health has been the focus of the forum through various academic programs. The world has witness novel path during COVID pandemic in the journey of learning process through **Social Media platforms.** We are happy to take academic learning forward by young Nephrologists on tweet chat, facebook and instagram. All the activities are being updated in the renovated & dynamic web portal **"hyderbadnephrologyforum.com."** We urge everyone to please follow HNF in social media and the website Hyderabadnephrologyforum.com

The real Voyage of discovery consists not in seeking new landscape but in having new eyes. Hyderabad nephrology forum is extremely happy to have new eyes:

1. **Patients Advocacy Club -** For educating the patients, care givers and the general public in kidney care and preventive measures
2. **Finance and Career Development Club –** For guiding the youngsters for better career opportunities and have more stable personal life
3. **Sports and Fitness Club -** Being healthy care provider, it's very important for us to be healthy and to be a real inspiration for the patients and to the society. HNF would plan various activities for physical and mental health of not only the kidney patients but also the nephrologists and paramedics.

No education institution is complete without research, HNF take pride to announce the initiative of **awarding research grants** to trainees and young faculty to improve the quality of research in the field of nephrology. The research committee consisting of senior Nephrologists with experience in research and publications would oversee, awarding the research grants to the trainees. We request all the trainees and young faculty to utilize the opportunity and come out with innovative research proposals.

We also welcome the nephrologists practicing in various districts of Telangana be active in academic and nonacademic activities though the **District Chapters.** And also encourage Nephrologists across the country to become member of HNF and avail the benefits of HNF which is rich in academic contents.

I am extremely thankful to all the seniors and congratulate council members for adding the new dimensions in Journey and making it more informative, exciting and joyful.

We hope to have wonderful journey ahead together with better kidney care.

Dr Swarnalatha Guditi

Prof & Unit Head

Dept of Nephrology, NIMS

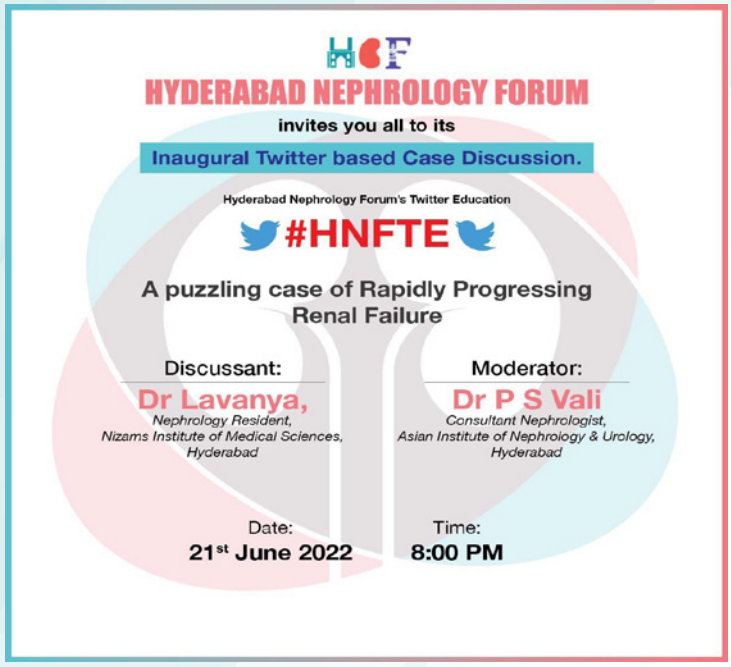
I/C Jeevandan Program

Deceased Donor Transplantation Program of Government of Telangana

General Secretary, HNF

Past and Upcoming Events

Last Friday of every month, we are conducting Forum meets and we have discussed many interesting cases and their diagnosis and management. We have invited few of the eminent National and International faculty to give guest lectures in Forum meets. Postgraduate students got the extensive benefit by these meets by knowledge sharing and applying it in clinical practice. In the June month, we have conducted a CME on a non-academic topic i.e., Financial management for Nephrologist and had a farewell to Dr Urmila Anandh; In the same month, we had an inaugural Twitter Chat on a case of RPRF. In July, we have conducted a theme based CME on Peritoneal Dialysis. In August, we had an expert talk by Dr Vinay Sakhuja along with case discussions.



Crossword Puzzle on Trials in Diabetic Nephropathy

Across

4. Non steroidal MRA study with salutary effects on cardiorenal outcomes with T2DM and CKD
6. Recent study on endothelin antagonist with renal benefits but fluid retention and anaemia were seen.
7. GLP 1 agonists study in high risk patients - reduce the risk of serious adverse cardiovascular and renal events among persons with type 2 diabetes and either a history of cardiovascular disease or current kidney disease.
8. Longest and largest multicenter trial- strict glycemic control (HbA1c 7.0%) reduced type 2 diabetic complications.
10. Study revealed that Telmisartan conferred comparable renoprotection to Enalapril and was associated with a low incidence of mortality

Down

1. Anti inflammatory pathway targeting drug study that showed increase in eGFR but FDA didn't

approve the drug yet.

2. 1st trial that showed ACEI (captopril) was effective in slowing renal function deterioration
3. Study discontinued as intensive HbA1c (6%) control increases mortality
5. Thanks to this study, SGLT2 inhibitors along with ACEI or ARBs yield favorable cardiorenal effects in patients with or without T2DM
9. Largest study, intensive HbA1C control showed 45% reduction in microalbuminuria in T1DM patients at 18 years

Drug Update

Selective Non-steroidal MRAs for Diabetic CKD - Finerenone (Kerendia) - Ready To Accept New Treatment Concept?

The management of type 2 diabetes and chronic kidney disease has undergone a fundamental transformation in the past 3 years. While since the last 3 decades RAAS blockade, blood pressure and glucose control were the main backbones of treatment for slowing kidney disease progression. SGLT2 inhibitors are now recommended for diabetic and non-diabetic albuminuric CKD, after promising results of CREDENCE and DAPA-CKD trials. Most recently FIDELIO-DKD and FIGARO-DKD trials demonstrated that Finerenone slows the progression of CKD and prevent cardiovascular mortality in people with type 2 diabetes and albuminuric CKD.

Finerenone is a non-steroidal selective mineralocorticoid receptor (MR) antagonist with no significant affinity or activity at androgen, progesterone, estrogen, and glucocorticoid receptors. It selectively blocks mineralocorticoid receptor-mediated sodium reabsorption and overactivation in both epithelial (eg. kidney) and non-epithelial (blood vessels and heart) tissues reducing fibrosis and inflammation. Comparison with steroidal non-selective MRAs is shown below.

Dosing in adults:

In chronic kidney disease associated with type 2 DM-

Initial -

- eGFR > 60 ml/minute/1.73 m2 – 20 mg once daily.
- eGFR < 60 ml/min/1.73 m2 - 10 mg once daily.
- eGFR < 25 ml/min/1.73 m2 - use not recommended.

Maintenance -

- Determine by serum potassium measured 4 weeks after initiation.

Dosing in hepatic impairment -

- Child-Pugh A or B - no dosage adjustment
- Severe - avoid use

It was FDA approved in July 2021 and recently launched in India.

Use: Chronic kidney disease associated with type 2 diabetes- To reduce the risk of sustained eGFR decline, ESRD, cardiovascular death, nonfatal MI, and hospitalization for heart failure in adult patients with chronic kidney disease associated with type 2 diabetes.

Adverse reactions:

>10%-Endocrine and metabolic- Hyperkalaemia.

1-10%- Cardiovascular hypotension (5%).

Hyponatremia (1%)

Evidence:

The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease trial published in NEJM 2020 (FIDELIO-DKD)

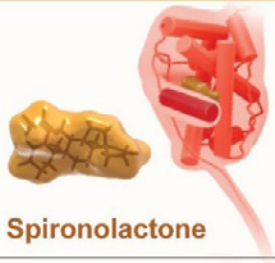
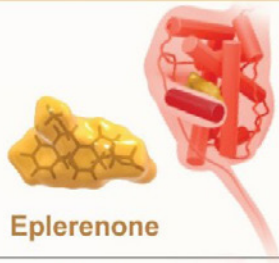
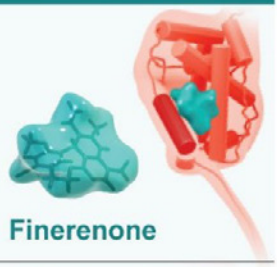
The incidence of the primary composite outcome of kidney failure was significantly lower in the finerenone

group than in the placebo group, (17.8%) vs (21.1%). Finerenone was associated with a 31% greater reduction in the urinary albumin-to-creatinine ratio from baseline to month 4 than placebo. Acute kidney injury–related adverse events and serious adverse events were balanced between the two groups. Overall hyperkalemia-related adverse events were twice as frequent with finerenone as with placebo (18.3% and 9.0%, respectively) and the frequency of hyperkalemia leading to discontinuation of the trial regimen was also higher with finerenone (2.3% and 0.9%). No fatal hyperkalemia adverse events were reported. These results suggest that in patients with CKD and type 2 diabetes finerenone may be an effective treatment for kidney and cardiovascular protection. In a patient population with multiple coexisting conditions and advanced CKD (almost 55% of the patients had a baseline eGFR of <45 ml per minute per 1.73 m2) who were at high risk for kidney and cardiovascular events, the benefits of finerenone were observed after 12 months for the kidney outcome and as early as 1 month for the cardiovascular outcome, and these benefits persisted throughout the trial.

Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes published in NEJM 2021 (FIGARO-DKD trial)

This trial evaluated whether treatment with finerenone would lead to lower risks of cardiovascular events and death from cardiovascular causes among patients with type 2 diabetes who had stage 2 to 4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria. The incidence of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure (the primary composite outcome) was significantly lower in the finerenone group than in the placebo group [12.4%] vs [14.2%]; Finerenone therapy improved cardiovascular outcomes, as compared with placebo, in patients with type 2 diabetes who had stage 2 to 4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria.

Dr. Ramiz Panjwani
Consultant Nephrologist
Omni Hospital, Hyderabad

	Steroidal MRAs		Finerenone
	 Spironolactone	 Eplerenone	 Finerenone
Structural properties	Flat (steroidal)	Flat (steroidal)	Bulky (nonsteroidal)
Potency to MR	+++	+	+++
Selectivity to MR	+	++	+++
CNS penetration	+	+	-
Sexual side effects	++	(+)	-
Half-life	> 20 hours	4-6 hours	2-3 hours
Active metabolites	++	-	-
Effect on BP	+++	++	+

Make your diagnosis:
A case of deposit Glomerulopathy

A 71-year-old woman was admitted with the chief complaints of edema with occasional gross hematuria. Her laboratory values indicated a creatinine (Cr) level of 1.72 mg/dl and massive proteinuria of 5.1 g/g Cr. There was no fever, and her white blood cells were within the normal range. Further examination revealed a high myeloperoxidase (MPO)-ANCA level (125 U/ml, normal<3.5), no monoclonal proteins, and normal complement protein levels. A renal biopsy was performed; it showed mesangial proliferation in all 13 glomeruli and crescent formation in 5 glomeruli. Immunofluorescence staining showed positivity for immunoglobulin G (IgG), C3, and C1q. Additional staining showed negativity for Congo red, and there was no kappa/lambda (κ/λ) imbalance. Electron microscopy showed the presence of electron-dense deposits in the glomerular mesangium and capillary walls. Higher magnification revealed deposits as random arrangement of nonbranching fibrils. The evaluation for diagnosis of nonamyloid fibrillary deposition disease has become simple with the availability of a sensitive as well as specific marker i.e., immunohistochemical staining for DNA-J heat shock protein family member B9 (DNAJB9). Hence evaluation with IHC for DNAJB9 was performed and was positive as shown in Figure below confirming the diagnosis of fibrillary glomerulonephritis.

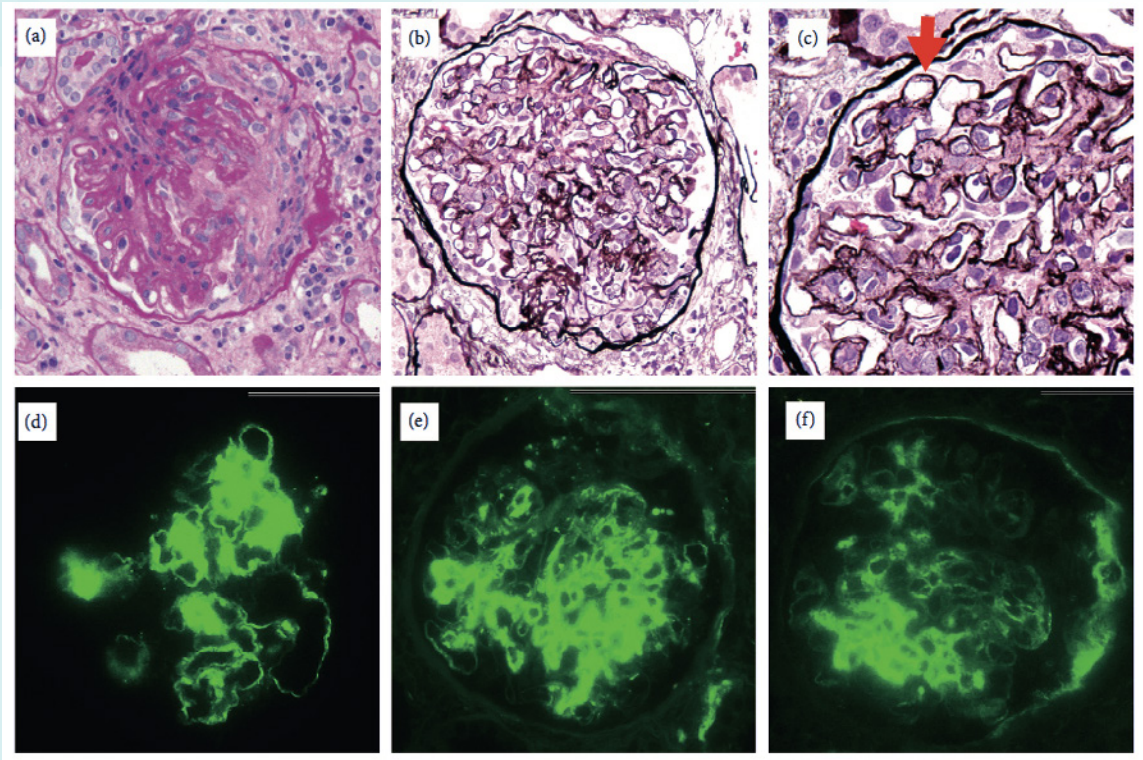


Figure 1: Light microscopic appearance. Periodic acidschiff (PAS) staining showed crescents formation (a) (x200). Periodic acid methenamine silver (PAM) staining showed mesangium expansion (b) (x200) and segmented duplication of glomerular basement membrane (c) (x200 arrow). Positive immunofluorescent staining of IgG (d), C3 (e), and c1q (f). IgM and IgA were negative.

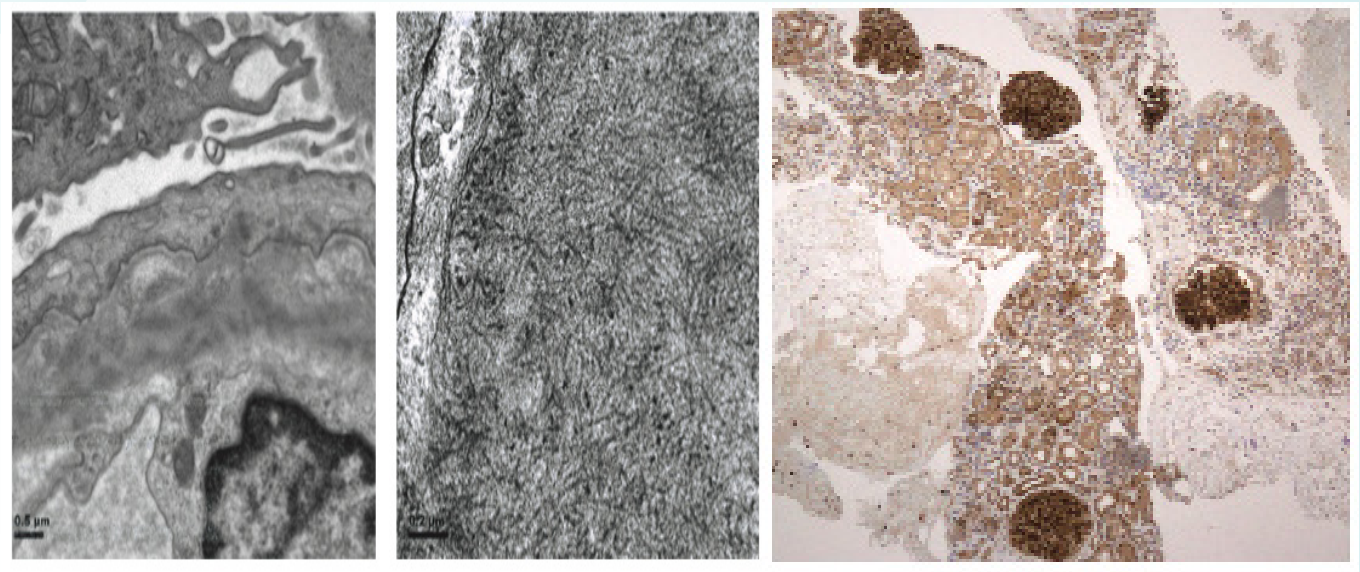


Figure 2: Electron microscopic image showed presence of electron-dense deposits in the glomerular mesangium and capillary walls (x7000) (a). Higher magnification revealed deposits as random arrangement of nonbranching fibrils (x20000) (b). Immunohistochemistry of DNAJB9 with strongly stained glomeruli (c).

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Nasr SH, Vrana JA, Dasari S, et al. DNAJB9 Is a Specific Immunohistochemical Marker for Fibrillary Glomerulonephritis. Kidney Int Rep 2017 Aug 8;3(1):56-64.

Dr. Anitha S

MD, DM (AIIMS, New Delhi)

Consultant Nephrologist

ESIC Medical College and Super Speciality Hospital

Hyderabad

Teaching Point
Graft hydronephrosis - a red herring

A 28 year old male, with native kidney disease of IgA nephropathy (biopsy proven) had undergone cadaveric renal transplant in 2018, treated with triple immunosuppression (tacrolimus, mycophenolate, and steroids) has maintained normal graft function (creatinine <1 mg/dl) until September 2020. Patient had immediate postoperative acute T-cell mediated rejection in the past and it was reversed with iv steroids. He developed graft dysfunction in September 2020 without any obvious signs of sepsis or calcineurin inhibitor toxicity. He denied any drug defaulting episodes during the period. His ultrasound revealed hydronephrosis. Evaluation showed BK virus positivity status and routine work up showed COVID PCR positive status and underwent treatment for the same. Bk Virus Nephropathy (BKVAN) treatment was given in the form of reduction of immunosuppressants and iv immunoglobulins. Hydronephrosis was also confirmed with CT abdomen and DTPA Renogram showed delayed clearance of the tracer. So a possibility of BKVAN associated ureteric stricture was considered and ureteric reimplantation with neocystoureterostomy was performed. In view of progressive graft dysfunction, intraoperative open graft biopsy was performed and it showed acute antibody mediated rejection (ABMR). Since it was cadaveric transplant, assessment of donor specific antibody (DSA) was not possible. ABMR was treated with 5 sessions of plasmapheresis and rituximab injection and other routine antirejection therapy but he progressed to graft failure and he became dialysis dependent. Graft nephrectomy was performed in view of graft reconstitution syndrome.

Teaching point: A finding of hydronephrosis in post-kidney transplantation status with graft dysfunction can delay a diagnosis of potentially treatable antibody mediated rejection. An early graft biopsy may be helpful in pointing out correct diagnosis and treatment due to clinico-radiological-histological discordance.

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Dr. T. Saravanan
Nephrologist
Abirami Kidney Care, Erode, Tamilnadu

Renal Pathology Pearls

Anti-nephrin autoantibodies: the new kid in the block

We presently diagnose minimal change disease in a renal biopsy done for nephrotic syndrome when the renal biopsy is normal on light microscopy, there are no significant immune deposits on immunofluorescence study and podocytopathic changes including diffuse foot process effacement are demonstrable on ultrastructure. Dysfunction of podocytes or podocytopathies is an important cause for nephrotic syndrome, especially in children. The genetic forms are caused by mutations in the podocyte genes. The etiology of acute-onset nephrotic syndrome has however been elusive. Recently auto-antibodies to nephrin, an important protein of the slit diaphragm, has been identified as an etiologic cause in a subset of patients, adults and children with non-congenital nephrotic syndrome. It is believed that the autoantibody causes redistribution of nephrin and a disturbance of the junctional adhesion complex, an action akin to anti-desmoglein antibodies in pemphigus in the skin.

The discovery of anti-nephrin autoantibodies in minimal change disease

The study comprised two cohorts of patients with minimal change disease, one from the NEPTUNE (Nephrotic syndrome Study Network) group and one of active cases from four institutes. 18 of 62 cases from the Neptune Cohort had elevated serum levels of anti-nephrin antibodies, as compared to the levels in an asymptomatic normal cohort and that in patients of membranous nephropathy. In 12 of these 18 patients who had a complete or partial remission of proteinuria, there was a complete absence or significant reduction of the serum anti-nephrin antibodies respectively. GBM-associated, scattered, subtle, punctate fine granular deposits of IgG had been observed earlier and were believed to represent anti-podocyte antigens. Further study of these biopsies revealed a co-localisation of IgG with the slit-diaphragm protein nephrin by confocal and Super-resolution Structured illumination microscopy (SR-SIM). The latter method, recently developed, achieves a higher spatial resolution. The IgG did not co-localise with other podocyte proteins, namely synaptopodin, podocin and WTI. Serum evaluation in 9 of these patients with the above IgG pattern of staining revealed high titres of anti-nephrin antibodies and negative anti-PLA2R titres. In the post-transplant setting, one child who had MCD progressing to ESRD and with a massive proteinuria recurrence post-tranplant was found to have elevated titres of anti-nephrin antibodies in the pre-transplant and post-transplant sera obtained and had a sustained remission with rituximab and plasmapheresis.

Implications of this study in our routine practice

The above findings if validated in further studies with larger numbers would have the following implications. IgG stains would have to be analysed very carefully to detect the fine dust like positivity around the GBM. Figure 1 illustrates one such case in our routine practice. EM study in these cases would not add more value. Serum anti-nephrin antibodies may be soon commercially available for routine assay and would be indicated in these cases and in other cases with a

diagnosis of MCD. Like anti-PLA2R serology, serum autoantibody levels could be used to monitor and manage the disease. In patients progressing to end-stage renal disease, autoantibody levels will help detect early recurrence and management.

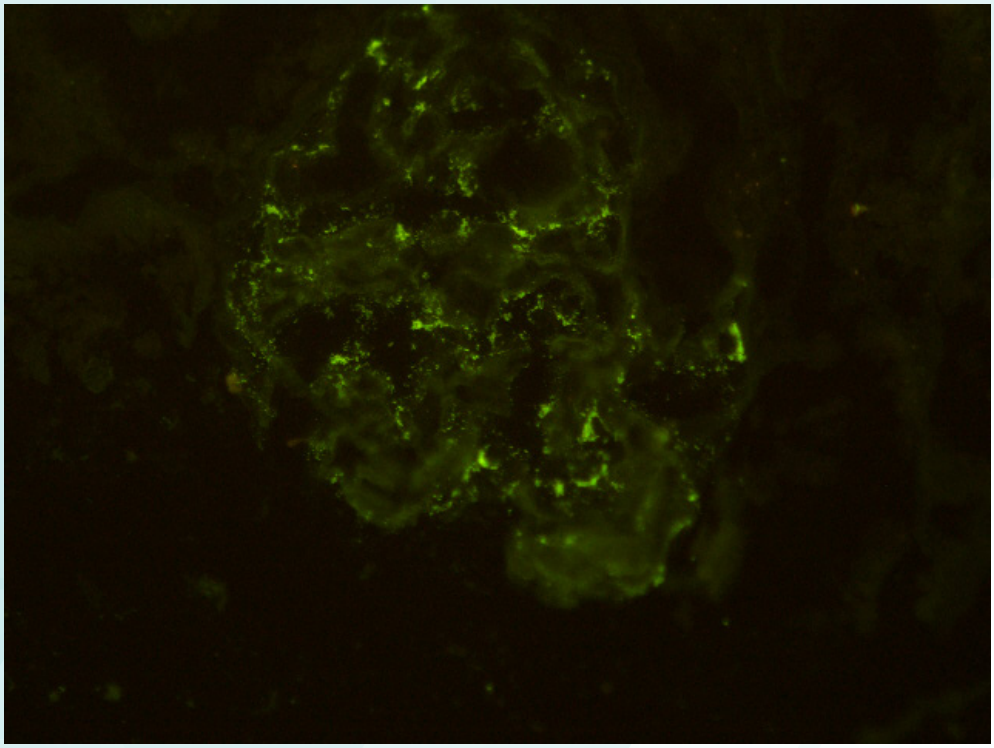


Figure 1: IgG by direct immunofluorescence showing fine, punctate, discontinuous peripheral subtle, dust-like positivity

References:

Watts AJB, Keller KH, Lerner G, et al. Discovery of Autoantibodies Targeting Nephrin in Minimal Change Disease Supports a Novel Autoimmune Etiology. J Am Soc Nephrol. 2022 Jan;33(1):238-252.

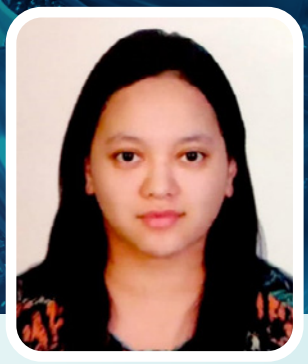
Ye Q, Chen A, Lai EY, Mao J. Autoimmune Podocytopathies: A Novel Sub-Group of Diseases from Childhood Idiopathic Nephrotic Syndrome. J Am Soc Nephrol. 2022 Mar;33(3):653-654.

Dr. Swarnalata Gowrishankar

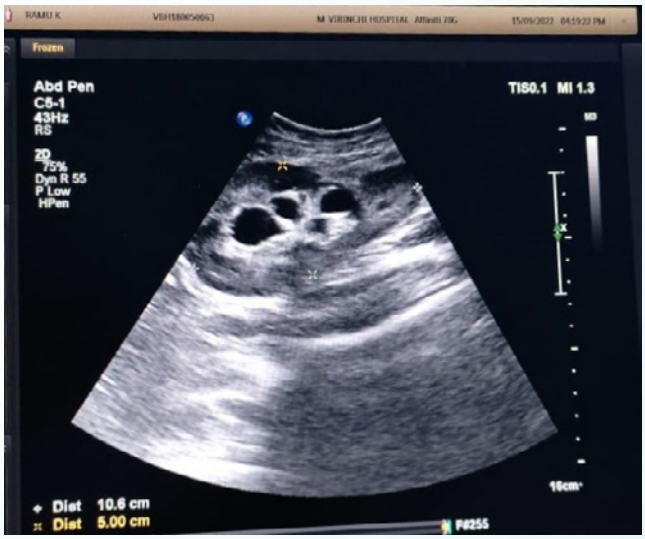
Senior Consultant Pathologist

Department of Histopathology, Apollo Hospitals, Hyderabad

Focus on POCUS



Point-of-care ultrasonography (POCUS) has evolved as a valuable adjunct to physical examination in the recent past in various medical specialties including Nephrology. Here, we present a case of graft hydronephrosis (HDN) identified by bedside ultrasonography when patient is being evaluated for graft dysfunction after admission. The cause of obstruction is due to encrusted DJ stent which was forgotten to remove at his transplant centre elsewhere (Figure 1).



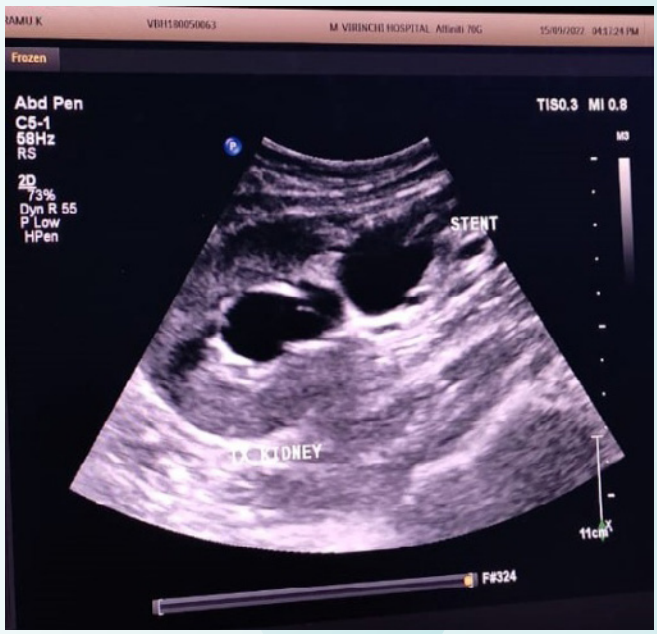


Figure 1. Hydronephrosis of renal allograft with visible DJ stent on ultrasonography

HDN of renal allograft can occur secondary to ureteral obstruction or vesicoureteral reflux (VUR). Other causes can include secondary megaureter of various etiologies, neurogenic bladder, loss of ureteral tonicity following denervation, and polyuric states which can present with non-obstructive non-refluxing transplant HDN. Rejection as a cause of non-obstructive non-refluxing HDN is a very rare entity. Infections including BK virus ureteritis can also cause HDN. Allograft HDN has been correlated with worsening renal function and increased incidence of pyelonephritis and rejection.

The incidence of transplant ureter complications including stenosis ranges from 3 to 10%. Early ureteral obstruction secondary to post-operative oedema, torsion or kink, extrinsic compression from hematoma or lymphocele, difficult or faulty ureteral implantation, or deficient blood supply leading to ischemia of the distal ureter can all lead to allograft HDN. Late ureteral stenosis, usually beyond the first month post-RT, could be related to ischemic fibrosis due to persistently deficient blood supply, decreased ureteral tone due to denervation, vasoconstriction due to calcineurin inhibitors, ureterolithiasis, and infection due to CMV and BK virus.

Late rejection occurring in association with non-obstructive non-refluxing transplant HDN has been described only in few studies (Table 1). The most likely explanation of HDN is that, in addition to the renal tubulointerstitial cells, rejection episodes can lead to oedema of the uroepithelial cells as well, leading to transient obstruction. This oedema along with the narrowing of the blood vessels due to thrombosis, mainly seen in vascular rejection, may also cause ischemic damage to the uroepithelial cells. With severe or repeated episodes of rejections, subsequent fibrotic reactions and loss of ureteral elasticity may occur leading to anatomic stenosis.

Study	HDN of renal transplant	Rejection	Treatment
Faenza et al.	27 out of 869 RT recipients; 2 months to 12 years post RT	15 (12 acute rejections, 3 chronic rejections)	Ureteral reimplantation, stent
Rigg et al.	126 episodes of HDN out of 1,016 RT recipients; up to 12 years post RT	38 rejection episodes	Anti-rejection treatment led to HDN resolution in some; some had urologic interventions
Maier et al.	2 RT recipients; 14–18 years post RT	Both had rejection 1 and 10 months prior; histology showed evidence of ureteral rejection	Resection of stenosis and ureteral reimplantation
Acharya et al.	2 RT recipients; 4 and 10 years post-RT	First case had several episodes of transplant pyelonephritis& ABMR , other had ABMR	treated for ABMR with pulse steroid, plasma exchange, intravenous immunoglobulin (IVIG), and rituximab

References:

Etta PK, Madhavi T, Gowrishankar S. Coexistent BK-virus-associated nephropathy and ureteric stenosis in a patient with acute cellular rejection after renal transplantation: A case report and review of literature. Indian J Transplant 2020;14:147-51.

Faenza A, Nardo B, Catena F, et al. Ureteral stenosis after kidney transplantation. A study on 869 consecutive transplants. Transpl Int. 1999;12(5):334–40.

Rigg KM, Proud G, Taylor RM. Urological complications following renal transplantation. A study of 1016 consecutive transplants from a single centre. Transpl Int. 1994;7(2):120–6.

Maier U, Madersbacher S, Banyai-Falger S, et al. Late ureteral obstruction after kidney transplantation. Fibrotic answer to previous rejection? Transpl Int. 1997;10(1):65–8.

Acharya R, Aly R, Upadhyay K. Renal Transplant Hydroureteronephrosis as a Manifestation of Rejection: An Under-Recognized Entity? Case Rep Nephrol Dial. 2021 Mar 15;11(1):87-94.

Dr Lekha Pradhan

Senior resident DNB

Virinchi Hospital

Hyderabad

Nuances in Interventional Nephrology

Reteplase, New kid in the block with a lot of promise

Vascular Access (VA) is an essential component of the life-sustaining therapy in end stage kidney disease patients relying on a sustained extracorporeal circulation for hemodialysis (HD) or haemodiafiltration (HDF). Indeed, Vascular Access is often referred to as the lifeline or Achilles heel for a dialysis-dependent patient. VA performance is a key factor to drive success or failure in all forms of extracorporeal renal replacement treatment. Furthermore, VA dysfunction or complication is the major cause of morbidity requiring interventional procedures. Exhausted central venous access is a potentially life-threatening situation for patients dependent on haemodialysis.

International guidelines and various study groups such as National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) 2006 Clinical Practice Guidelines, European Best Practice Guidelines, and Canadian Society of Nephrology recommend autogenous, native vessel AVFs over the central venous catheters (CVCs) for initiation of HD. Patients who receive dialysis with a functional AVF have lower complication rates and longer duration of event-free patency than with catheter access and arteriovenous grafts (AVGs). The ideal AVF should have early placement, easy accessibility, minimal primary failure rates, early maturation, long-term patency, and minimal complications. Despite a reported failure rate of 7 to 40% with an average of 15.3%, a well-made AVF lasts as long as 10 to 12 years when used carefully.

The order of preference - NKF-KDOQI guidelines suggest radiocephalic, brachiocephalic, and Brachiobasilic transposition fistulae and then prosthetic grafts as vascular access options. India's health-care delivery is at the cusp of change due to increasing economic growth. Maintenance hemodialysis was accessed by a privileged few in the past, but welfare structures focusing on the indigent population are ensuring that long-term hemodialysis is possible in this group of patients. Even though a very large number of Indian patients begin dialysis with temporary catheters, around 75% to 80% have functioning AVFs by 3 months. Increasingly, the use of TCs and their relative advantages is replacing rigid temporary catheters as an intermediate form of access. This is a welcome change, as patients receive increasingly better dialysis and often live long enough to require multiple accesses.

The use of routine access monitoring by angiography, with subsequent thrombectomy, angioplasty, and surgical venous grafting for access salvage is often prohibitively expensive; often, creation of a fresh fistula is a more feasible option. Indian nephrologists, vascular surgeons, and radiologists involved in vascular access care have adapted various modifications to provide patients with cost-effective alternatives, albeit with unknown outcomes. Several studies have shown that working native AVFs at HD initiation is associated with improved outcomes, and reduced cost of care. In a survey, the cost of AVFs is less than tunneled catheters and less than one-third of the cost of arteriovenous grafts. Poor maturation of AVFs in pre-dialysis patients,

need for recurrent operations and hospital admissions is a cause for starting HD without fistula, primarily in the elderly and the diabetic population, as shown in the DOPPS survey. The incident HD population in India is younger and primary maturation rates are higher. Encouragingly, the AVF utilization rates are higher in the prevalent population, though not close to those recommended by guidelines. Majority of the patients dropping out of the dialysis unit are because of Vascular Access dysfunction. Thrombosis of the Vascular Access itself is a major concern accounting for major morbidity and mortality in dialysis patients.

KFIGO recommends thrombolysis of the thrombosed Vascular Access to rescue the Vascular Access. In this setting, the role of thrombolytic drugs is very important. There are various thrombolytic drugs that are available for the thrombolysis of Vascular Access. They have been classified into three generations. First generation thrombolytics include streptokinase and Urokinase. Second generation thrombolytics include Alteplase. Third generation from thrombolytics include Reteplase and Tenecteplase. Streptokinase has not been considered in end-stage renal disease patients as the concerns of hypertension and severe allergic reactions have limited its use. Urokinase was commonly used thrombolytic in India for all Vascular problems in CKD population; in the past 1 year the availability was severely limited and this has forced the Nephrology community to evaluate other thrombolytics for the vascular issues. In this regard Reteplase turned out to be the best and most viable option.

Reteplase is a novel plasminogen activator, designed by protein engineering, that consists of the kringle 2 and protease domains of alteplase, and is not glycosylated at the consensus sequences because of its expression in Escherichia coli. When compared with alteplase, reteplase has been shown to achieve more rapid clot lysis. In an experimental dynamic clot lysis assay, the dose- response curves demonstrated superiority of reteplase over alteplase. These differences suggest that there may be differences in the mechanism of clot lysis between reteplase and alteplase. This may also explain the higher catheter clearance rates observed with reteplase at shorter dwell times compared with the other agents. Given the generally superior success rates of Reteplase over alteplase for hemodialysis catheter clearance, the comparative cost between the agents becomes a relatively more important issue that may influence drug product selection. When the acquisition costs of aliquotted reteplase are compared with alteplase, reteplase is approximately 750 Rs/ treatment episode vs alteplase approximately 2000 Rs/treatment episode (1250Rs/treatment episode less than tenecteplase).

Thrombolytic therapy is commonly used to treat dysfunctional hemodialysis catheters. Currently, no thrombolytic agent is specifically FDA approved to treat thrombosed hemodialysis catheters, but alteplase is available in a 2-mg/ml vial indicated for central venous catheter clearance. Of the 18 trials considered in a systematic review, most included data were observational or collected retrospectively. None of the trials compared one thrombolytic agent directly with another. The average catheter clearance success rates were generally similar for alteplase (81%) and reteplase (88%), whereas the success rate with tenecteplase was substantially lower (41%). The reasons for the lower success rate with tenecteplase are not known. None of the thrombolytics were associated with adverse effects, most likely because of limited systemic exposure to drug. Reteplase is currently used for hemodialysis catheter clearance by using an aliquot method requiring sterile preparation. The cost of delivering a dose of reteplase is lower per treatment episode than alteplase. This cost advantage may be of sufficient importance at dialysis centers to influence drug product selection.

A deep dive into literature has yielded lot of interesting facts about Reteplase. Apart from being third generation thrombolytic with very less side-effect profile, Reteplase has been shown to be more effective in the Vascular Access thrombosis. Among all the thrombolytics evaluated for dysfunction in Vascular Access Reteplase has shown most promising results with more than 96% patency achieved after treatment. Although there was ample data from the west there was

no Indian study to evaluate the efficacy of Reteplase in Indian end-stage renal disease population.

Results of recently initiated observational study at Institute of NephroUrology (INU) Bengaluru, are evaluating the efficacy of Reteplase in various kinds of vascular access issues. The vascular access issues being addressed are

1. Dysfunctional Tunneled haemodialysis catheters (17 cases)
2. Thrombosis of the AV Access (3 cases)
3. Thrombosis of the Central Vein after the insertion of Non-Tunneled Catheter (1 case)

The results were good and Reteplase was effective in achieving 100% patency in all the cases.

The dose used in Tunneled HD Catheter was 1 unit in total (0.5 units of Reteplase along with 5000 units of heparin) in each port of Tunnelled catheter. Dwell time of 120-180 minutes. The dose used in thrombosis of Vascular Access was 4 units with 10,000 units of heparin. The dose used in thrombosis of internal jugular vein following non-tunnelling catheter insertion and subsequent removal was 10 units along with 10,000 units of heparin (Dose requirements vary with size and volume of the thrombus). All the results were excellent in terms of restoration of flow and maintenance of the patency. Given that Reteplase is being manufactured by Indian pharma companies and being available at a very economical price comparable to other thrombolytics, Reteplase is offering lot of hope to the health care providers in Nephrology community to address the Vascular Access issues.

Dr G Gireesh Reddy

Fellow American Society of Diagnostic and Interventional Nephrology

Institute of Nephro Urology

Bengaluru

What's new in Nephrology?

Prescribing Nirmatrelvir/Ritonavir for COVID-19 in Advanced CKD

The COVID-19 pandemic which started in 2020 appears to have lost some of its steam now but continues to be a problem for the immunocompromised population, which includes patients with chronic kidney disease. Various drugs have been tried in the management of COVID-19 infected patients, with variable success. Nirmatrelvir/Ritonavir (Paxlovid) has emerged as a promising new drug in this field. However, due to presumed toxicity, this drug combination has so far not been tried in patients with advanced CKD. Hiremath et al have outlined a strategy for the use of Paxlovid in patient with kidney disease including those with eGFR <30 mL/min/1.73m2 and on dialysis. They propose that the safety profile of nirmatrelvir is favourable, with few serious adverse effects, and that the animal data are not indicative of dose-dependent toxicity. This drug is however subject to drug interactions and requires careful assessment of medication which these patients may already be taking and their adjustment, as required. In this article, they have described working guidelines for the use of Paxlovid in patients with advanced CKD.

Hiremath S, McGuinty M, Argyropoulos C, et al. Prescribing Nirmatrelvir/Ritonavir for COVID-19 in Advanced CKD. Clin J Am Soc Nephrol. 2022 Aug;17(8):1247-1250.

Association of Night-time Masked Uncontrolled Hypertension With Left Ventricular Hypertrophy and Kidney Function Among Patients with Chronic Kidney Disease Not Receiving Dialysis

Night-time hypertension is a subtype of masked hypertension that has been associated with adverse cardiovascular outcomes. However, the association between night-time hypertension and chronic kidney disease is unknown. Fu et al carried out a retrospective cohort study of non dialysis CKD patients (eGFR > 20 mL/min/1.73m2) and evaluated the office blood pressure readings and ambulatory blood pressure monitoring readings of 675 eligible patients. It was determined that about one-third of these patients had night-time masked hypertension. This was associated with left ventricular hypertrophy and adverse kidney outcomes (composite end point consisting of initiation of kidney replacement therapy and a reduction of eGFR by 50% or greater, whichever occurred first). Thus, it can be concluded that 24 hour ambulatory blood pressure monitoring is essential for management of chronic kidney disease patients.

Fu X, Ren H, Xie J, et al. Association of Nighttime Masked Uncontrolled Hypertension With Left Ventricular Hypertrophy and Kidney Function Among Patients with Chronic Kidney Disease Not Receiving Dialysis. JAMA Netw Open. 2022 May 2;5(5):e2214460.

Reduction of dietary sodium to less than 100 mmol in heart failure - SODIUM-HF trial

Restriction of dietary sodium is advocated as a part of management of heart failure. Ezekowitz et al carried out an international, open-label, randomised, controlled trial (SODIUM-HF) to test the utility of sodium restriction in heart failure patients. 806

patients were randomised to either usual care or a low sodium diet of less than 100 mmol (ie, <1500 mg/day). By 12 months, composite of cardiovascular-related admission to hospital, cardiovascular-related emergency department visit, or all-cause death had occurred in 60 (15%) of 397 patients in the low sodium diet group and 70 (17%) of 409 in the usual care group (p=0·53). All-cause death occurred in 22 (6%) patients in the low sodium diet group and 17 (4%) in the usual care group (p=0·32). Thus, it was concluded that dietary salt restriction had no influence on clinical events in patients with heart failure.

Ezekowitz JA, Colin-Ramirez E, Ross H, et al; SODIUM-HF Investigators. Reduction of dietary sodium to less than 100 mmol in heart failure (SODIUM-HF): an international, open-label, randomised, controlled trial. Lancet. 2022 Apr 9;399(10333):1391-1400.

Azithromycin use increases the risk of sudden cardiac death in patients with hemodialysis-dependent kidney failure

It is well known that hemodialysis patients are at high risk of various adverse cardiovascular events including sudden death. Unfortunately, this group of patients has been traditionally excluded from trials evaluating safety of drugs. Azithromycin is a macrolide antibiotic with known propensity to cause QTc prolongation and arrhythmia. It is alarming that in spite of the fact that not much safety data exists for the use of Azithromycin in dialysis patients, this drug continues to be used in such patients for various indications. Using data from the United States Renal Data System (2007-2017), Assimon et al conducted two cohort studies to examine the cardiac safety of azithromycin relative to amoxicillin-based antibiotics (amoxicillin, amoxicillin/clavulanic acid) and levofloxacin in the hemodialysis population. The primary outcome was five-day sudden cardiac death. Inverse probability of treatment weighted survival models were used for statistical analysis. It was found that Azithromycin vs. amoxicillin-based antibiotic treatment was associated with higher relative and absolute risks of sudden cardiac death, while Azithromycin vs. levofloxacin treatment was associated with lower relative and absolute risks of sudden cardiac death. Thus, it can be concluded that while selecting antibiotics for hemodialysis patients, caution should be exercised regarding cardiac safety and the risk of precipitating sudden cardiac death.

Assimon MM, Pun PH, Wang L, et al. Azithromycin use increases the risk of sudden cardiac death in patients with hemodialysis-dependent kidney failure. Kidney Int. 2022 Jun 23:S0085-2538(22)00461-6.

Sequential Stem Cell-Kidney Transplantation in Schimke Immuno-osseous Dysplasia

The use of immunosuppression in kidney transplantation while essential for maintaining graft survival and longevity, is associated with antecedent risks of infection and malignancy in addition to adverse effects related to the medications themselves. It has long been the dream of nephrologists to develop a strategy to ensure graft function without the use of immunosuppressive medications. Hematopoietic stem-cell transplantation (HSCT) may be the light at the end of the tunnel. Bertaina et al studied three patients with Schimke immuno-osseous dysplasia who had both T-cell immunodeficiency and renal failure. Each patient received sequential transplants of $\alpha\beta$ T-cell–depleted and CD19 B-cell–depleted haploidentical hematopoietic stem cells and a kidney from the same donor. This strategy has been defined as hematopoietic chimerism. At 22 to 34 months after transplantation, all 3 patients had normal kidney function, without immunosuppression. Further studies are required to study chimerism in recipients with normal immune systems but these findings certainly seem promising.

Bertaina A, Grimm PC, Weinberg K, et al. Sequential Stem Cell-Kidney Transplantation in Schimke Immuno-osseous Dysplasia. N Engl J Med. 2022 Jun 16;386(24):2295-2302.

Progress toward Pig-to-Human Xenotransplantation

A team at the university of Alabama at Birmingham did the world's first clinical grade pig to human kidney transplantation procedure whose results are published

in the American journal of transplantation. Humans do not express galactose-alpha-1,3-galactose ("alpha-gal"), which is made by an enzyme called alpha-1,3-galactosyltransferase. Since many microbial species express the alpha-gal epitope, circulating antibodies that recognize alpha-gal develop in humans and can cause hyperacute rejection of transplanted alpha-gal–positive organs. To avoid this, pigs have been bred with a knockout of the alpha-1,3-galactosyltransferase gene and with subcapsular autologous thymic tissue. Genetically modified kidney xenografts from pigs remained viable and functioning in brain-dead human recipients for 54 hours, without signs of hyperacute rejection. Genetically engineered pigs with 10 key gene edits were used. 4 pig genes (GGTA1, CMAH, β4GalNT2) and (GHR) were deleted and 6 human genes (DAF, CD46, TBM, EPCR, HO1, CD47) were added to these genetically engineered pigs prior to transplantation. The study recipient (Late Mr Jim Parson) had two genetically modified pig kidneys transplanted in his abdomen after his native kidneys were removed. The transplanted kidneys filtered blood, produced urine and, importantly, were not immediately rejected. The kidneys remained viable until the study was ended, 77 hours after transplant.

Porrett PM, Orandi BJ, Kumar V, et al. First clinical-grade porcine kidney xenotransplant using a human decedent model. Am J Transplant. 2022 Apr;22(4):1037-1053.

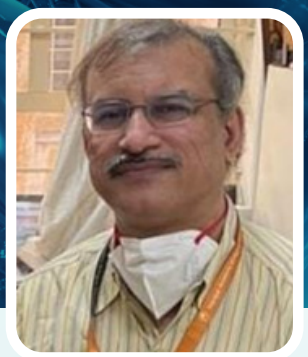
Dr Namrata Parikh

Transplant Fellow

Division of Nephrology

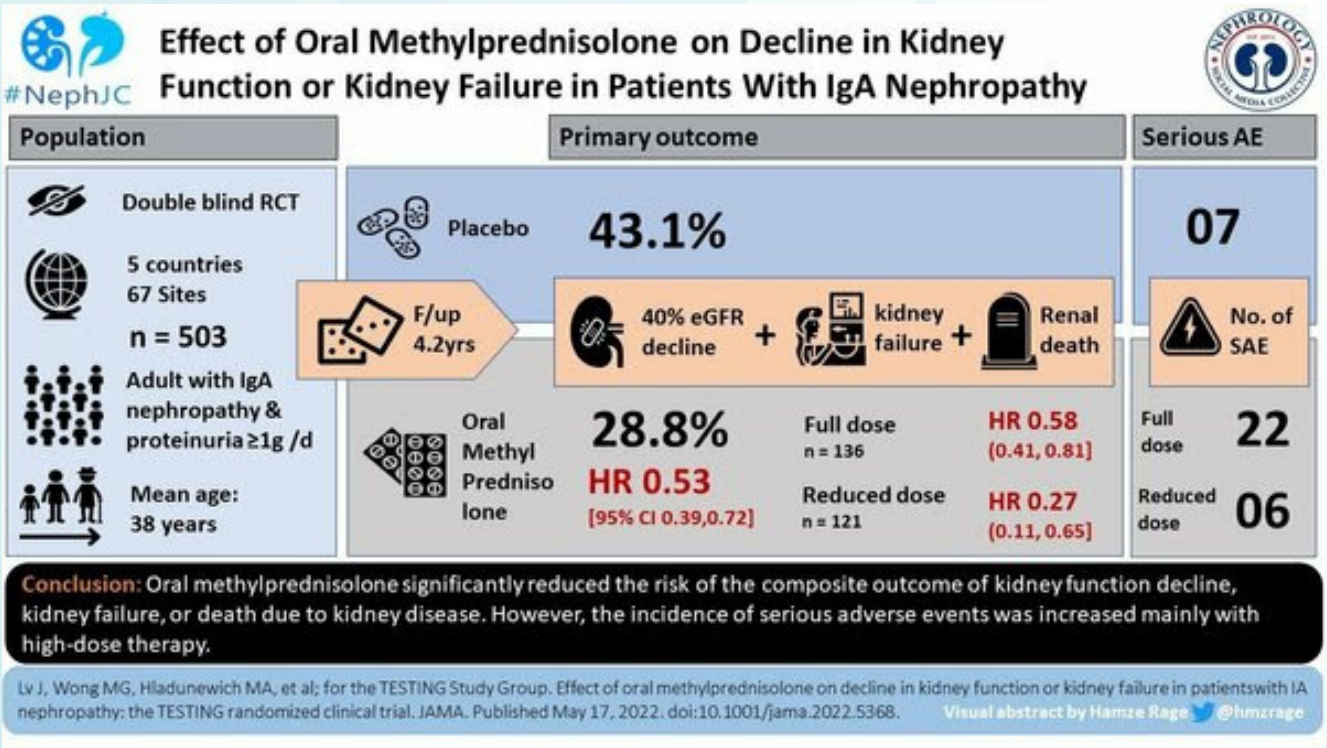
Ottawa Hospital, Canada

Journal Scan



Oral methylprednisolone in patients with IgA Nephropathy: The TESTING Randomized Clinical Trial

In patients with immunoglobulin A (IgA) nephropathy who are at high risk for progressive disease, the effect of glucocorticoids on clinical outcomes has been uncertain. The original TESTING study published in 2017 found that patients on methyl prednisolone had statistically better kidney outcomes than those not on it. However, it was noted that this study was terminated early due to increased risk of adverse events including death in the steroid arm. In what has been called the RETESTING study or Testing 2.0, the study was repeated in a larger cohort (503 vs 262 in TESTING 1.0) with a lower dose of methyl prednisolone. The current trial includes the original TESTING cohort in which participants were randomized to receive oral methylprednisolone (initially 0.6-0.8 mg/kg/d) or placebo. After the findings of TESTING 1.0, the dose of methyl prednisolone was reduced to 0.4 mg/kg/d. Antibiotic prophylaxis for pneumocystis pneumonia was added for subsequent participants. At a mean follow up of 4.2 years, 40% eGFR reduction, kidney failure, or death due to kidney disease - occurred in 28.8% patients in the methylprednisolone group compared to 43.1% patients in the placebo group (p <0.001), over a mean follow-up of 4.2 years. Thus, it was concluded that treatment with oral methylprednisolone for 6 to 9 months reduces the risk of adverse kidney outcomes. However, it may increase the risk of serious adverse events, especially at high doses.



Lv J, Wong MG, Hladunewich MA, et al; TESTING Study Group. Effect of Oral Methylprednisolone on Decline in Kidney Function or Kidney Failure in Patients With IgA Nephropathy: The TESTING Randomized Clinical Trial. JAMA. 2022 May 17;327(19):1888-1898.

Restriction of Intravenous Fluids in ICU Patients with Septic Shock - The CLASSIC trial

Fluid management in ICU patients is one of the grey areas of critical care nephrology with no clear consensus. It can become quite challenging to ensure adequate volume status while at the same time avoiding complications of fluid therapy. The CLASSIC trial was designed to evaluate the effects of fluid restriction in ICU patients with septic shock. This is against one of the fundamental principles of the Surviving Sepsis guidelines which state that patients with septic shock should receive fluids at an initial rate of 30 mL/kg body weight. CLASSIC was an international, stratified, parallel-group, open-label, randomized clinical trial. 1554 patients in 31 ICUs were randomized to receive either restrictive intravenous fluid therapy or standard intravenous fluid therapy. At 90 days, death had occurred in 42.3% patients in the restrictive-fluid group and 42.1% in the standard-fluid group (P=0.96). In the ICU, serious adverse events occurred at least once in 29.4% patients in the restrictive-fluid group and in 30.8% patients in the standard-fluid group. Thus, intravenous fluid restriction did not result in fewer deaths than standard intravenous fluid therapy in ICU patients with septic shock at 90 days.

Meyhoff TS, Hjortrup PB, Wetterslev J, et al; CLASSIC Trial Group. Restriction of Intravenous Fluid in ICU Patients with Septic Shock. N Engl J Med. 2022 Jun 30;386(26):2459-2470.

Efficacy and safety of tirzepatide in people with obesity

In a recently concluded SURMOUNT-1 trial published in NEJM Jastreboff et al. demonstrated that once a week Tirzepatide in different doses targets nutrient stimulated hormones with agonist activity for glucagon-like peptide-1 (GLP-1) receptor and Glucose-dependent insulinotropic polypeptide (GIP) and was effective in reducing weight by 10 to 20 % and 33.9% mean reduction in total body fat. This was higher than Semaglutide and had other effects like decrease in waist circumference and lowered blood pressure, lipids, fasting insulin, and glycated hemoglobin; Adverse effects limited to GI such as nausea, diarrhea. Also the effect approached that of Gastric bypass and gives another option for treatment of obesity apart from six other FDA approved therapies namely orlistat, phentermine, phentermine–topiramate, bupropion, liraglutide, and Semaglutide. This moves obesity further into the realm of a disease requiring separate treatment rather than just a variation from normal.

Jastreboff AM, Aronne LJ, Ahmad NN, et al; SURMOUNT-1 Investigators. Tirzepatide Once Weekly for the Treatment of Obesity. N Engl J Med. 2022 Jul 21;387(3):205-216.

Acetazolamide in Acute Decompensated Heart Failure with Volume Overload - ADVOR Study

Whether acetazolamide, a carbonic anhydrase inhibitor that reduces proximal tubular sodium reabsorption, can improve the efficiency of loop diuretics, potentially leading to more and faster decongestion in patients with acute decompensated heart failure with volume overload, is unclear. ADVOR study, a multicenter, parallel-group, double-blind, randomized, placebo-controlled trial assigned patients with acute decompensated heart failure to receive either intravenous acetazolamide (500 mg once daily) or placebo added to standardized intravenous loop diuretics. Acetazolamide treatment was associated with higher cumulative urine output and natriuresis, findings consistent with better diuretic efficiency. The incidence of worsening kidney function, hypokalemia, hypotension, and adverse events was similar in the two groups.

Mullens W, Dauw J, Martens P, et al; ADVOR Study Group. Acetazolamide in Acute Decompensated Heart Failure with Volume Overload. N Engl J Med. 2022 Aug 27.

Leflunomide for maintenance therapy of lupus nephritis

Leflunomide is an immunosuppressant widely used in the treatment of rheumatoid arthritis. A recent study compared the efficacy and safety of leflunomide versus azathioprine as maintenance therapy for LN. 270 adult patients with biopsy-confirmed active LN from 7 Chinese Rheumatology Centres were enrolled. All patients received induction therapy with 6-9 months of intravenous cyclophosphamide plus glucocorticoids. Patients who achieved complete response (CR) or partial response (PR) were randomized to receive prednisone in combination with leflunomide or azathioprine as maintenance therapy for 36 months. The primary efficacy endpoint was the time to kidney flare. Secondary outcomes included clinical parameters, extrarenal flare and adverse effects. A total of 215 patients were randomly allocated to the leflunomide group (n=108) and azathioprine group (n=107). Kidney flares were observed in 17 (15.7%) leflunomide-treated patients and 19 (17.8%) azathioprine-treated patients. Time to kidney flare did not statistically differ (leflunomide: 16 months vs azathioprine: 14 months, p=0.676). 24-hour proteinuria, serum creatinine, serum albumin, serum C3 and serum C4 improved similarly. Extrarenal flare occurred in two patients from the azathioprine group and one patient from the leflunomide group. The incidence of adverse events was similar in the 2 groups: leflunomide 56.5% and azathioprine 58.9%. The study concluded that the efficacy and safety profile of leflunomide are non-inferior to azathioprine for maintenance therapy of LN. Leflunomide may provide a new candidate for maintenance therapy in patients with LN.

Fu Q, Wu C, Dai M, et al. Leflunomide versus azathioprine for maintenance therapy of lupus nephritis: a prospective, multicentre, randomised trial and long-term follow-up. Ann Rheum Dis. 2022 Jul 4:annrheumdis-2022-222486.

CHIP in CKD progression

Clonal hematopoiesis of indeterminate potential (CHIP) is an inflammatory premalignant disorder resulting from acquired genetic mutations in hematopoietic stem cells and is a proposed novel cardiovascular risk factor. This condition is common in aging populations and associated with cardiovascular morbidity and overall mortality. Its Pathogenetic role in CKD progression is emerging. Increased kidney fibrosis and glomerulosclerosis were described in mouse models of CHIP. In individuals with preexisting CKD, CHIP was associated with higher baseline Kidney Failure Risk Equation scores, greater progression of CKD, and anemia.

Vlasschaert C, McNaughton AJM, Chong M, et al. Association of Clonal Hematopoiesis of Indeterminate Potential with Worse Kidney Function and Anemia in Two Cohorts of Patients with Advanced Chronic Kidney Disease. J Am Soc Nephrol. 2022 May;33(5):985-995.

Effect of Perioperative Dexmedetomidine on Delayed Graft Function

Delayed graft function (DGF) is a risk factor for acute rejection and graft failure after kidney transplant. Previous studies have suggested that dexmedetomidine may be renoprotective, but whether the use of dexmedetomidine would improve kidney allograft function is unknown. Patients who were randomized to the dexmedetomidine group received a 24-hour perioperative dexmedetomidine intravenous infusion (0.4 µg/kg/h intraoperatively and 0.1 µg/kg/h postoperatively). This randomized clinical trial found that 24-hour perioperative dexmedetomidine decreased the incidence of DGF after DCD kidney transplant. The findings support the use of dexmedetomidine in kidney transplants.

Shan XS, Hu LK, Wang Y, et al. Effect of Perioperative Dexmedetomidine on Delayed Graft Function Following a Donation-After-Cardiac-Death Kidney Transplant: A Randomized Clinical Trial. JAMA Netw Open. 2022 Jun 1;5(6):e2215217.

Physical Exercise on the Risk for Hospitalization and Death in Dialysis Patients – EXCITE study

In the EXerCise Introduction to Enhance Performance in Dialysis (EXCITE) trial, a simple, personalized 6-month walking exercise program at home during the day off of dialysis improved the functional status and the risk for hospitalization in patients with kidney failure. In the post-trial observational study, authors found that a simple, personalized, home-based, low-intensity exercise program was associated with a lower risk of hospitalization.

Mallamaci F, D'Arrigo G, Tripepi G, et al. Long-Term Effect of Physical Exercise on the Risk for Hospitalization and Death in Dialysis Patients: A Post-Trial Long-Term Observational Study. Clin J Am Soc Nephrol. 2022 Jul 25:CJN.03160322.

Netrin G1 is a Novel Target Antigen in Primary Membranous Nephropathy

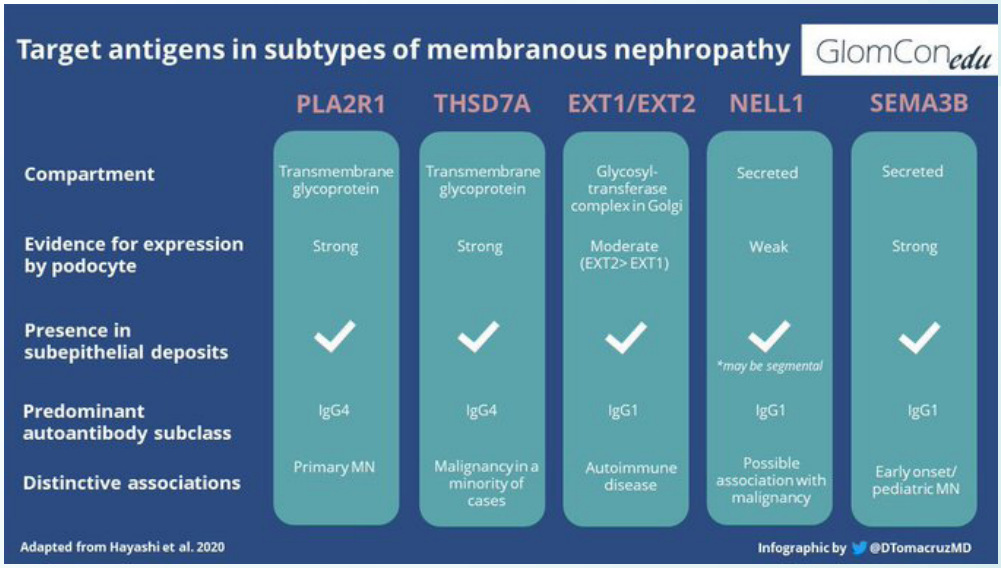
Primary membranous nephropathy (MN) is caused by circulating autoantibodies (ab) binding to antigens on the podocyte surface. PLA2R1 is the main target antigen in 70-80% of cases, but the pathogenesis is unresolved in 10-15% of patients. Netrin G1 (NTNG1) was identified as a novel target antigen in MN in a recent study published in JASN. It is a membrane protein expressed in healthy podocytes. Immunohistochemistry confirmed granular NTNG1 in subepithelial glomerular immune deposits. In prospective and retrospective MN cohorts, authors identified three patients with NTNG1-associated MN, who showed IgG4-dominant circulating NTNG1-ab, enhanced NTNG1 expression in the kidney, and glomerular IgG4 deposits. No NTNG1-ab were identified in 561 PLA2R1-ab positive patients, 27 THSD7A-ab positive patients, and 77 patients with other glomerular diseases. NTNG1 expands the repertoire of target antigens in patients with MN (shown below).

Reinhard L, Machalitza M, Wiech T, et al. Netrin G1 is a Novel Target Antigen in Primary Membranous Nephropathy. J Am Soc Nephrol. 2022 Aug 19:ASN.2022050608.

Dr Ravindra Prabhu

Professor of Nephrology

Kasturba Medical College, Manipal



Practice changing updates

Oral tacrolimus versus intravenous cyclophosphamide for lupus nephritis

Calcineurin inhibitors (CNIs) in combination with mycophenolate (MMF) have been used for initial therapy for lupus nephritis (LN) as an alternative to cyclophosphamide, but the efficacy of CNIs without MMF remains unclear. In a trial that randomly assigned over 300 patients with LN to oral tacrolimus or iv cyclophosphamide for 24 weeks, the rate of complete response was higher in the tacrolimus group (50 versus 36 percent). Rates of serious treatment-emergent adverse events were lower in the tacrolimus group; however, patients receiving tacrolimus had an increase in serum creatinine that was sustained for the duration of the trial. In this study, oral tacrolimus appeared noninferior to iv cyclophosphamide for initial therapy of active LN, with a more favorable safety profile. Tacrolimus may be an alternative to iv cyclophosphamide as initial therapy for LN.

Zheng Z, Zhang H, Peng X, et al. Effect of Tacrolimus vs Intravenous Cyclophosphamide on Complete or Partial Response in Patients With Lupus Nephritis: A Randomized Clinical Trial. JAMA Netw Open. 2022 Mar 1;5(3):e224492.

Removal of small, asymptomatic kidney stones and risk of relapse

In patients undergoing surgical removal of kidney or ureteral stones, the benefits of simultaneously removing small, asymptomatic stones are uncertain. In a trial that randomly assigned 73 adults scheduled for endoscopic stone removal surgery and with small (<6 mm) asymptomatic (secondary) stones on preoperative computed tomography to removal of both primary and secondary stones (treatment group) or primary stones alone (control group), rates of stone relapse were lower in the treatment group after a median of four years. Removing secondary stones added a median of 25 minutes to overall surgery time, and rates of adverse events were similar between the groups. These findings support the approach of routinely removing ipsilateral asymptomatic stones when removing an obstructing or symptomatic stone by endoscopic methods.

Sorensen MD, Harper JD, Borofsky MS, et al. Removal of Small, Asymptomatic Kidney Stones and Incidence of Relapse. N Engl J Med. 2022 Aug 11;387(6):506-513.

Five-year graft survival for recipients of HCV-RNA-positive donor kidneys

Transplantation of hepatitis C virus (HCV) ribonucleic acid (RNA)-positive donor kidneys into HCV RNA-negative recipients, combined with direct-acting antiviral (DAA) therapy, has been shown to be safe and efficacious, but data on long-term patient and graft outcomes have been lacking. An analysis of nearly 76,000 adult deceased-donor kidney transplant recipients from 2016 to 2021 found that five-year graft survival was similar between recipients of HCV RNA-positive versus HCV RNA-negative donor kidneys (72

versus 69 percent). These findings add to the growing evidence that transplantation of HCV RNA-positive kidneys into HCV RNA-negative recipients in the era of DAA therapy can provide well-functioning allografts and increase organ supply.

Schaubel DE, Tran AH, Abt PL, et al. Five-Year Allograft Survival for Recipients of Kidney Transplants From Hepatitis C Virus Infected vs Uninfected Deceased Donors in the Direct-Acting Antiviral Therapy Era. JAMA. 2022 Aug 22:e2212868.

Dr Purva Bavikar

Consultant Nephrologist

Virinchi Hospital

Hyderabad

Transplantation Proceedings

Virtual crossmatching and its virtues in Indian setting!

Crossmatching is an integral part of assessing the immunological risk before proceeding to transplantation between a donor and a recipient. Human leukocyte antigens (HLA) or major histocompatibility complex (MHC) genes located on the short arm of chromosome 6 determine the HLA proteins expressed on the surface of all nucleated cells. HLA glycoproteins are surface markers that inform the immune system of self and non-self antigens, thus determining allo-immunity.

Crossmatching is a process where the presence of pre-formed antibodies against donor HLA (anti-HLA antibodies) in the recipient's serum is determined. Donor's lymphocytes are mixed with recipient's serum in the presence of complement. The test is considered positive, if there are complement binding antibodies against the donor lymphocytes leading to cell lysis. In such cases, the transplantation cannot proceed due to risk of hyperacute rejection. Existence of low-level donor specific antibodies and complement non-binding antibodies, which may be missed on CDC crossmatching can be determined by a much sensitive "flow-crossmatching" technique. In this assay fluorochrome tagged anti-IgG antibody is added in place of complement and the assay is run on a flow-cytometer. These assays are labour and resource intense and can be logistically challenging.

Introduction of solid phase assays in the field of transplantation has paved the way for virtual crossmatching. Two independent tests done on the recipient and donor separately would help to establish the immunological risk of a transplant. Initially the anti-HLA antibody status of the recipient is established by using single antigen bead (SAB) assay. Then this result is compared against the donor's HLA phenotype to understand if there are any "unacceptable antigens" that are likely to cause a positive crossmatch.

What is single antigen bead (SAB) assay?

SAB testing is a solid phase assay. Microspheres or beads displaying unique HLA allelic antigens can be uniquely identified by a combination of two different fluorochromes. A bead set (containing prevalent HLA antigens in the population) is incubated with the serum of a recipient along with an anti-IgG fluorochrome. Using the combination of three fluorochromes, the presence of an anti-HLA antibody against a specific HLA antigen (for e.g., anti-HLA-A2:02) is determined. The output is expressed as mean fluorescence index which is an arbitrary value and is specific to each laboratory.

What is HLA phenotyping?

Depending on the structure, the HLA molecules are classified into class I and class II. Class I HLA molecules (categorized as HLA-A, HLA-B and HLA-C) are expressed on all nucleated cells whilst class II HLA molecules (HLA-DP, HLA-DQ, HLA-DR) are expressed on antigen presenting cells (dendritic cells, macrophages, and B cells). Each HLA gene has two alleles, one from mother and one from father, thus in total there are 12 alleles in total determining the HLA phenotype of any individual.

Historically, the HLA phenotype of an individual was determined by mixing the lymphocytes with sera containing well defined HLA antibody specificities. Next generation sequencing or polymerase chain reactions are used now to determine the phenotype. HLA allele name is a unique combination of 4 different fields typically separated by a colon. Low resolution

sequencing will only help to understand the serological variant, whilst high resolution would reveal the DNA sequence of the antigen binding site (up to field 2).

What are donor specific antibodies?

The antibodies present in a recipient which can recognise donor HLA antigens are called donor specific antibodies. These develop generally due to an earlier sensitising event such as a blood transfusion, pregnancy, or prior transplantation. If present at the time of transplantation, hyperacute rejection can occur.

What are unacceptable antigens and acceptable mismatches?

The antigens against which a recipient's anti-HLA antibodies are likely to bind are called unacceptable antigens for that recipient. A suitable recipient is selected based on the absence of anti-HLA antibodies against the donor's HLA-typing.

For highly sensitised individuals, a list of acceptable antigens against which anti-HLA antibodies are absent may help to increase the chances of finding a suitable donor.

How can virtual crossmatching be used in clinical practice?

Virtual crossmatch as opposed to CDC or flow cross-match would involve assessing the immunological risk between donor and recipient in-silico. Virtual crossmatching can be used efficiently at the time of organ allocation. Having a list of unacceptable antigens and acceptable mismatches for each recipient would help to exclude patients that are likely to have a positive crossmatch. Post organ allocation patients with negative DSA and no sensitisation history from the time of SAB test, CDC and flow crossmatch could be avoided and transplantation could proceed directly. Multiple studies have reported successful outcomes from this strategy without any evidence of hyperacute rejection even in highly sensitised patients. Avoiding pre-transplant crossmatch in deceased donor transplantation can significantly reduce the cold ischaemia time and improve the graft outcomes.

What are the pitfalls of virtual crossmatch?

For a patient who does not have any detectable DSA, CDC or flow-crossmatch may not be needed irrespective of the donor's HLA typing. An important caveat is that there should not be any sensitising events from the time of SAB assay. If such an event occurs, then virtual crossmatching should not be used to determine the immunological risk.

Further SAB assay has its own limitations leading to false negative results– absence of a particular HLA antigen in the bead assay (assays have predominantly Caucasian phenotypes), shared epitopes causing dilution of a particular antibody leading to a negative result, inhibitory factors present in the serum of the recipient inhibiting the detection of an antibody (prozone effect).

False positive results can also pose a problem. High sensitivity of the SAB tests can lead to identification of non-pathological antibodies which may not be clinically relevant. In such situations the organ may be refuted unnecessarily for a recipient who would otherwise have benefitted from it.

For the virtual cross match to be accurate detailed HLA phenotyping of at least to 2 field depth may be needed and getting this data within the shorter time frames of cadaveric kidney transplantation may be difficult.

The cost implications are significantly high and not many patients may be able to afford this test and this will prove to be a bottle neck in adapting this technique in the Indian setting. Further the test results may not be valid beyond three months and ideally should be repeated after every sensitising event.

How could virtual crossmatching be used in our set-up?

- Given the cost implications involved in doing SAB tests on all the recipients and the frequency with which they need to be done, perhaps this could be done only in patients who are on top of the wait list that are likely to receive an organ in the next few months.

- A clear and effective system in place to capture the sensitising events from the time of SAB testing to transplantation would help to improve the confidence in the result.
- Establishing the HLA phenotype of the donor at the time of declaring the brain death would expedite the entire process. The responsibility of obtaining and cascading this information should reside with a central body rather than with an individual institute.

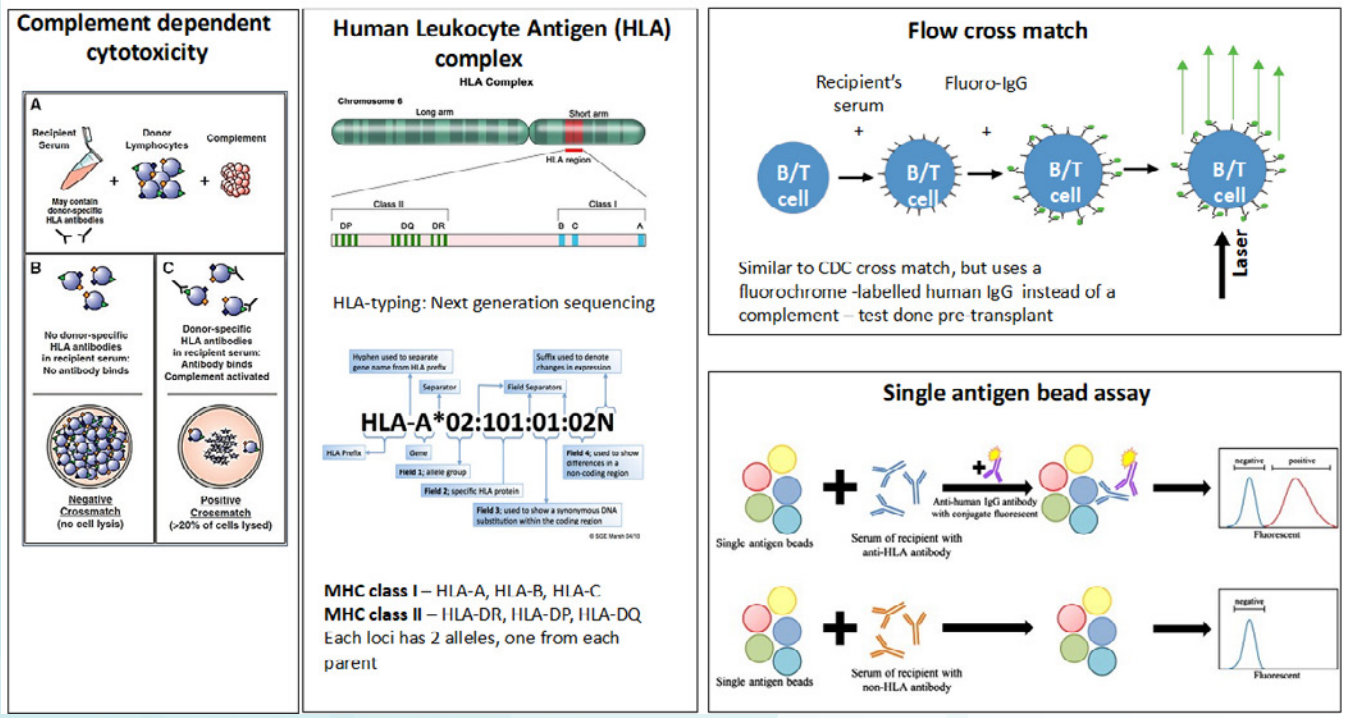


Figure showing various crossmatch techniques

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Bhaskaran MC, Heidt S, Muthukumar T. Principles of Virtual Crossmatch Testing for Kidney Transplantation. Kidney Int Rep. 2022 Mar 15;7(6):1179-1188.

Dr Seera Pani Gopaluni, MBBS, MRCP(UK), CCT(UK), PhD (Cambridge)

Senior consultant nephrologist and transplant physician

Citizen's Hospital, Hyderabad.

Publication Corner

Acetaminophen Exacerbates Hypertension

Acetaminophen (also known as paracetamol) is one of the options on the first rung of the World Health Organization analgesic ladder for treatment of cancer pain and it is the most commonly used analgesic worldwide. It is the perceived safety of acetaminophen that reassures doctors and patients regarding continuous long-term use. This remains true when compared with alternative over-the-counter analgesics such as nonsteroidal anti-inflammatory drugs, whose side effects are well known and include increased cardiovascular risk, hypertension, gastrointestinal ulceration, and acute kidney injury. The safety profile of acetaminophen has now been called into question. The Paracetamol Treatment in Hypertension-Blood Pressure (PATH-BP) trial was designed to compare the effect of acetaminophen versus placebo on BP in individuals with hypertension. It showed a 4.7 mm Hg increase in systolic BP when acetaminophen is used at a dose of 4 g per day for 2 weeks in patients with hypertension. This should lead us to be more cautious when recommending it, especially for patients with hypertension or increased cardiovascular risk.

John P, Popa C, Abbasi M, Teakell J, Hiremath S, Willows J. Acetaminophen Exacerbates Hypertension: A #NephJC Editorial on PATH-BP. Kidney Med. 2022 Jun 28;4(8):100515.

Macrophage polarization in kidney transplant patients

Macrophages can oscillate between two functionally distinct states: proinflammatory M1 and anti-inflammatory M2. Classically- activated M1 macrophages produce proinflammatory cytokines (TNF-α, IFN-γ, and IL-6), which ares associated with graft dysfunction/rejections. In contrast, alternatively-activated macrophages M2 produce anti-inflammatory cytokines (IL-10) that are involved in host defense, tissue repair/remodeling, debris scavenging, and immune regulation, thereby helps to improve long-term graft survival. In this study, authors have identified graft dysfunction or rejection by biopsies using immunohistochemistry. Flow cytometry was used to detect M1 (CD163+, CD206+, and CD200R+) and M2 (CD86+, CD80+, and CD68+) macrophages. Enzyme-linked immunosorbent assay (ELISA) was used to measure a panel of cytokines. Flow cytometry results showed that patients with graft rejection exhibited macrophages with decreased expression (33.28%) of M2 macrophage markers (CD163+, CD206+, and CD200R+) and reduced production of IL-10 (as detected using ELISA). However, 71.33% of the macrophages were found to have M1 markers (CD86+, CD80+, and CD68+; $p = 0.002$) and produced proinflammatory cytokines (TNF-α, IFN-γ, and IL-6) by ELISA ($p = 0.001$) when compared with the healthy control group. In contrast, stable kidney transplants had 65.58% M2 and 27.66% M1 macrophages ($p = 0.03$) and produced IL-10. These findings suggest that M1 macrophages dominate in kidney grafts with dysfunction or rejection, whereas M2 macrophages dominate in kidney grafts with stable function.

Devraj VM, Kalidindi K, Guditi S, Uppin M, Taduri G. Macrophage polarization in kidney transplant patients. Transpl Immunol. 2022 Sep 18:101717.

Pregnancy-related Acute Kidney Injury

Pregnancy-related acute kidney injury (PRAKI) is a common problem in the developing world. In this retrospective observational study at a tertiary care hospital in South India authors evaluated records for the maternal, fetal, and renal outcomes in women with PRAKI. Over a 10-year period, 395 patients of PRAKI were seen constituting 8.1% of all acute kidney injury (AKI). The mean age of patients was 27 ± 3 years. A total of 176 (44.5%) had pre-eclampsia, 132 (33.4%) had puerperal sepsis, 76 (19.2%) had antepartum hemorrhage or postpartum hemorrhage (APH 30/PPH 46), nine (2.2%) had hemolytic uremic syndrome (HUS). Obstruction was seen in two patients. Eleven had underlying glomerulonephritis out of three had lupus nephritis. Forty-five of 395 (11.39%) had hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, that is, 25.5% of those with pre-eclampsia. Sixteen (4.0%) had placental abruption. A total of 288 (72.9%) presented postpartum. Renal biopsy done in 103 (26%) showed patchy cortical necrosis (PCN) in 25 (22.3%), diffuse cortical necrosis (DCN) in 23 (20.3%), acute tubular necrosis (ATN) in 20 (19.4%), acute interstitial nephritis (AIN) in 10 (9.7%), while nine (8.7%) had thrombotic microangiopathy (TMA). Glomerular disease was seen in 11. Cortical necrosis (CN) was seen in 48 patients of which 10 (20.83%) had abruption placenta, 25 (52%) had puerperal sepsis, 11 (22.9%) had postpartum hemorrhage (PPH), and two (4.1%) had TMA. A total of 290 (73.4%) required dialysis. About 76% improved while 8.3% progressed to end-stage renal disease (ESRD). Maternal mortality (MM) was 5%. There were 42 intrauterine deaths and 30 deaths in the neonatal period.

Sahay M, Priyashree, Dogra L, et al. Pregnancy-related Acute Kidney Injury in Public Hospital in South India: Changing Trends. J Assoc Physicians India. 2022 Aug;70(8):11-12.

Extramedullary plasmacytoma of thyroid cartilage unmasking indolent multiple myeloma

Extramedullary plasmacytomas commonly occur in the upper aerodigestive tract. Most plasma cell neoplasms of the larynx represent solitary extramedullary plasmacytomas without multiple myeloma (MM). Thyroid cartilage infiltration in MM is very rare. This case report described a case of plasmacytoma of thyroid cartilage secondary to indolent MM with associated hypercalcemia and acute kidney injury (AKI), which recovered spontaneously with conservative therapy.

Etta PK, Gajare U, Guttikonda J, Kota M, Chakravarthi R. Neck Lump Unmasking Multiple Myeloma in a Patient with Acute Kidney Injury. Indian J Nephrol 2022;32:394-5.

Mucormycosis in a kidney transplant recipient

In India, we have witnessed an epidemic of mucormycosis (MM) during COVID-19 pandemic. This report presented a case of fatal rhino-orbital MM caused by Mucor at 2 years after kidney transplantation, following recovery from COVID-19 of moderate severity. Tissue biopsy from nasal sinuses showed broad, nonseptate filamentous fungal hyphae. Later, culture confirmed Mucor as the causative pathogen. The delay in diagnosis, surgical debridement, and antifungal therapy are associated with high mortality in MM.

Etta PK, Madhavi T, Panjwani RS. An unanticipated fatal infection after kidney transplantation. Indian J Transplant 2022;16:237-8.

Post-transplant diabetes mellitus in physician's perspective

Post-transplant diabetes mellitus (PTDM) is a common problem among solid organ transplant recipients contributing to morbidity and affecting patient as well as graft survival adversely. It can occur at any period following transplantation, but maximum incidence is observed in the first few months, with a second peak after a few years after transplantation. The pathogenesis is complex and poorly understood,

however, it is associated with both dysfunctional beta-cells and insulin resistance. Both nonpharmacologic and antidiabetic therapies are important for adequate glycemic control. This point of view article provides a short review on PTDM in solid organ transplantation (SOT) recipients from a general physician's perspective.

Etta PK. Post-transplant Diabetes Mellitus: What Physicians Need to Know. J Assoc Physicians India 2022;70:11-2.

Achievements
(academic and non-academic)

Dr KS Nayak, Chief Nephrologist at Virinchi Hospital, is selected for 'Guru Dronacharya' award by AVATAR board

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Dr Manisha Sahay received certificate of appreciation from IMA Hyderabad City Branch on the event of National Doctors Day. She had delivered few lectures in various National conferences. Few of them are - "Unmet need in management of Anemia in CKD" at ISN Frontiers meeting held at New Delhi on 23/9/22; "Hypertension and kidney - Culprit or Victim" at IMA meeting on 25/9/22; "Iron talks" webinar on 25/9/22 and International webinar ISN WIN on "PRAKI" on 30/8/22.

Dr Sree Bhushan Raju received appreciation from Arogyasri Trust on the event of National Doctors Day

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Dr G Swarnalata is promoted as Professor of Nephrology at NIMS (Unit 3) Nephrology.

Dr Srikanth Bathini has finished GlomCon Fellowship in 2022

Dr Vikram Kumar, Dr Bhavya, Dr Deepthi, Dr Payal, Dr Chandini, Dr Kajaree, Dr Megha, Dr Siddharth and Dr Anitha got selected for GlomCon fellowship, a Virtual Glomerular Disease Fellowship for year 2022-23.

Dr V Bukka, Dr Swarnalatha Guditi, Dr Gangadhar Taduri and Dr R Kalidindi from NIMS presented a poster titled "Clinical Outcomes in IRGN - A Single Centre Experience in 21 Patients From South India" at the ISN-Frontiers Meeting on Infections & the kidney conducted in New Delhi from 22nd to 25th September 2022

Dr Praveen Kumar Etta presented one oral paper titled 'Font chart for the detection of PD peritonitis using remote monitoring' and three posters titled 1) Role of Ulinastatin, a protease inhibitor, in peritoneal dialysis-related peritonitis, 2) Emergent-start peritoneal dialysis: The preferred modality to increase PD therapy adoption, 3) Standard peritoneal equilibration test: Is it really needed? at the International Society for Peritoneal Dialysis Congress, held from 11th to 14th August 2022, at Suntec, Singapore.

Dr Praveen Kumar Etta authored two chapters recently 1) 'Amyloidosis' published in a book 'API Text Book of Medicine', 12th Edition and 2) 'Peritoneal Dialysis in Intensive Care Unit' published in a book 'ISCCM Manual of RRT and ECMO in ICU' by the Indian Society of Critical Care Medicine.

Dr Praveen Kumar Etta was invited as a faculty to present a topic titled "Approach to Kidney Failure - Case Based Discussion" at the Indian Association of Clinical Medicine Annual Conference held at Agartala on 11th September 2022.

Dr Praful Chege presented a poster titled "A Study of Clinical characteristics and outcomes of patients with Acute Pyelonephritis in a Tertiary Care Centre in South India" at the ISN-Frontiers Meeting on Infections & the kidney conducted in New Delhi from 22nd to 25th September 2022.

Dr Devidas Bantewad presented a poster titled "HCV Seroconversions in Dialysis Patients under Hub & Spoke model - a study from South India" at the ISN-Frontiers Meeting on Infections & the kidney conducted in New Delhi from 22nd to 25th September 2022.

Dr Soundarya presented a poster titled "Clinical features and Outcomes of SARS-CoV-2 infection in geriatric patients with renal dysfunction in tertiary care hospital" at the ISN-Frontiers Meeting on Infections & the kidney conducted in New Delhi from 22nd to 25th September 2022.

Dr Harsha Guptha presented a poster titled "Spectrum of renal disease in patients with retroviral disease at tertiary care centre" at the ISN-Frontiers Meeting on Infections & the kidney conducted in New Delhi from 22nd to 25th September 2022.

Dr. Ashwinikumar Aiyangar had finished gruelling 226 km endurance Ironman Triathlon (Swim 3.8 km + Cycling 180 km + Run 42.2 km) held at Kazakhstan in August 2022, in 13h:52m:59s.

My Ironman Journey by Dr. Ashwinikumar Aiyangar

After entering medical school there was no thought other than completing assignments and trying to barely scrape through the only-so-many tests and exams. The funny part is that in medical school, this never ends. One successful degree opens doors to pass through yet another gruel to be dogged down and stay oblivious to the oh-so-fast changing universe around us. Once the minimum required learning is complete and adequately miniscule knowledge is acquired it is time to put learning into practice. The never-ending hours in daily clinical practice makes me wonder on how deftly most doctors defy the laws of time.

In 2015 something happened which made me want to spend some time exercising or start running. I completed my first 10K run in Hyderabad Marathon 2015. The enthusiasm was immense, but then a small accident put me off running till 2018. Gradually trudged on rocky paths and I managed to complete my first Half Marathon Run in December 2018. This was when a friend showed me an advertisement of a Half Ironman Triathlon scheduled to be held in Goa in Oct 2019. Until then, I had completed one Half Marathon run and a couple 100km cycle rides but couldn't yet swim a single long lap of 25m without stopping for breath. I worked on my swim form, rhythm, and speed, visited Mysuru (Thonnur) and Goa (in May 2019) for open water swim experience. I could dedicate an hour or so of training 4-5 times a week. I was able to complete the Half Ironman 70.3 comprising of 1.9km swim + 90km bike ride + 21.1km run in 8 hours.

The question then was, "What's next?" Until then I always thought that attempting a Full Ironman Triathlon (3.8km swim + 180km bike ride + 42.2km run) was only for crazy people and regular mortals are not cut out for it. After completing the 70.3 (70.3 miles total distance in a half ironman), it dawned on me that a Full Ironman 140.6 is not impossible and that I can be among those crazy people. The distances were exactly double. A 42km run felt ok, but I had to work on to complete a 3.8 km swim and 180km cycle ride.

In 2020 and early 2021 due to covid, training took a back seat, pools were closed, and work and family needed more attention. I finally started training seriously again since Nov-Dec 2021. Needed to commit 5 to 6 days in a week for training with 1 ˝ to 2 ˝ hours on weekdays and 4-7 hours on Sundays. All this without disrupting time at work, family time, kids' studies, and rest. Wake up time would be at 4am, training from 4:45am to around 7am. If I missed the morning workout, I would compensate by doing it at night after 9:30pm. Training made me more disciplined, made me get more tuned to listen to my body. I became more conscious of the nutrition that I consumed, the amount of rest that I took. Workouts were graded, incremental effort levels of 5-7 % were targeted every subsequent week. Gradually I realised that I was finally getting ready for D-day.

There were few days when I needed to participate in few athletic events as a test of preparation, in Hyderabad and outside. I am ever indebted to my colleagues Dr. Shaista Hussaini, Dr. Vamsi and Dr Praveen who helped cover my work at times when I needed to take off. This served as a sort of motivation

too to go with a free mind and not have to worry about work that would be pending.

Race week finally dawned. The venue was in Kazakhstan having an average water temperature of 20 degrees C and min air temperature of 11 degrees C and maximum temperature of 24 degrees C. I reached there 4 days prior to the event to get used to the cold waters and the relatively cooler ambience.

The race was scheduled to start at 6:00am with 3.8km swim at the start in the pleasant waters of the flowing Ishim River followed by the 180km bike ride and then the 42.2km run. I woke up at 3:30am, had a good breakfast of two cheese veg sandwiches, cornflakes, and coffee at 4am keeping enough time for gastric emptying before jumping into the river. The swim was done in 1 hour 45 mins, changed into my bike wear, pulled out the bike and set out for the 180km gruel. Every 10-12 minutes I was sipping on electrolyte fluids and had carbohydrate gels every 40-45 minutes. I completed the ride in 6 hours. Quickly parked my bike, I changed into my running shoes, had a banana which I had kept in my changing bag and got onto the running track. The run route was a curvy 10.5km loop, 4 loops for completion. They had nutrition stations at every 3.5km which served fruits, gels, biscuits, water, and electrolytes. I finally completed my 42.2km run in around 5 hours and 45 minutes. Total time including the transition breaks was 13:52:50 hours.

Whew! Made it finally! There were many moments in the race when I felt like giving up, but it was sheer mental strength and the thoughts of what all sacrifices my colleagues and family made so that I could pursue the training as needed. The most ecstatic moment was when I was in the last 100 metres, the finish line in sight, holding aloft the India Flag with both hands, I heard the crowd cheering 'Indiaaaa … Indiaaaaaa …', this built up a strange nationalistic emotion which helped me push through to the end, a feeling so surreal!

This completion didn't make me feel as crazy anymore. It wasn't as difficult or impossible as I had thought it to be. I now genuinely believe that the human body is the best machine made till date. It is extremely malleable and can be moulded the way one desires. The magic ingredients necessary are scientific systems of training, persistence, dedication, and discipline.

Dr Ashwinikumar Aiyangar

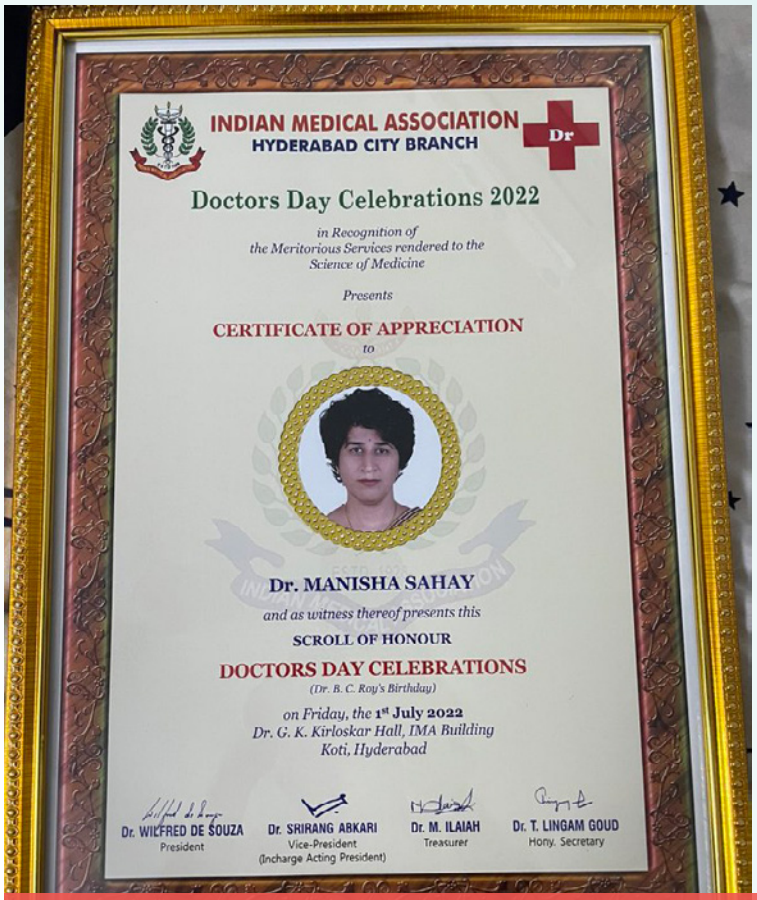
Senior Consultant Nephrologist

Apollo Hospitals, Secunderabad

Photo Gallery

Dr KS Nayak receiving 'Guru Dronacharya' award by AVATAR board

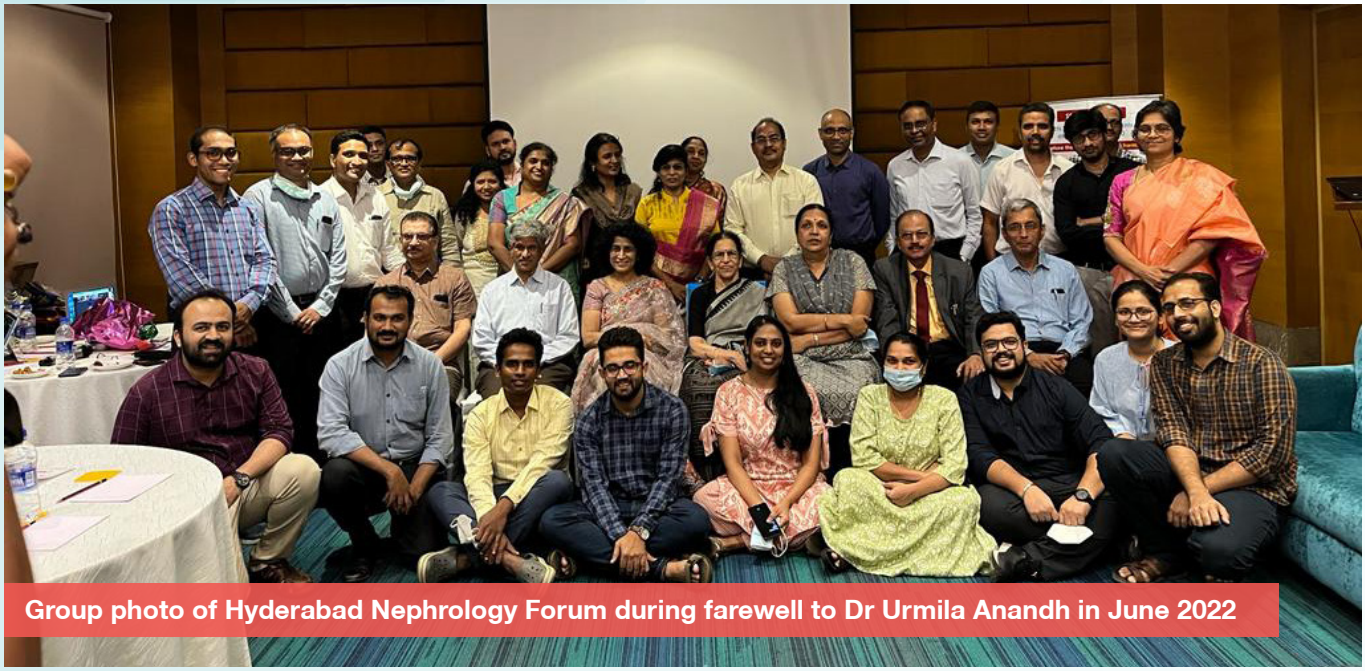
Dr KS Nayak as a faculty at the International Society for Peritoneal Dialysis Congress, held at Singapore



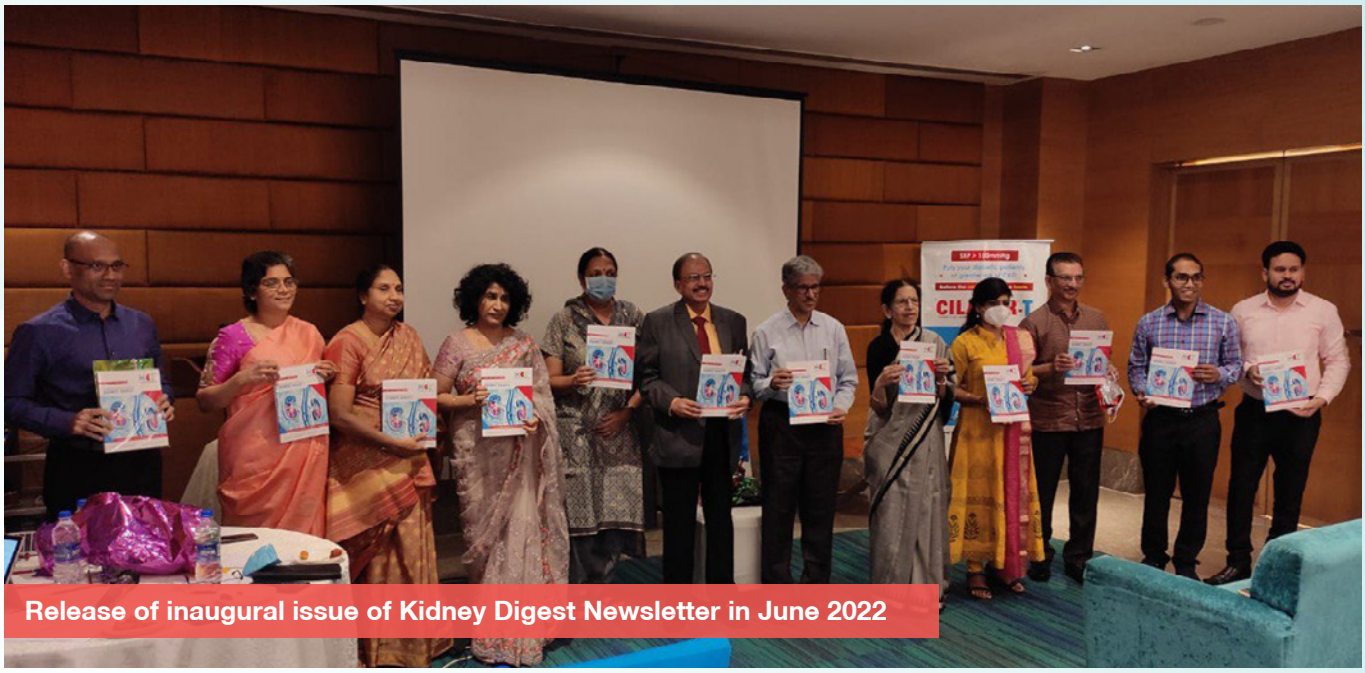
Dr Manisha Sahay received certificate of appreciation from IMA Hyderabad City Branch on the event of National Doctors Day

Dr Sree Bhushan Raju received certificate of appreciation from Arogyasri Trust on the event of National Doctors Day

Felicitation during farewell to Dr Urmila Anandh in June 2022



Group photo of Hyderabad Nephrology Forum during farewell to Dr Urmila Anandh in June 2022



Release of inaugural issue of Kidney Digest Newsletter in June 2022

Dr Srikanth Bathini has finished GlomCon Fellowship in 2022

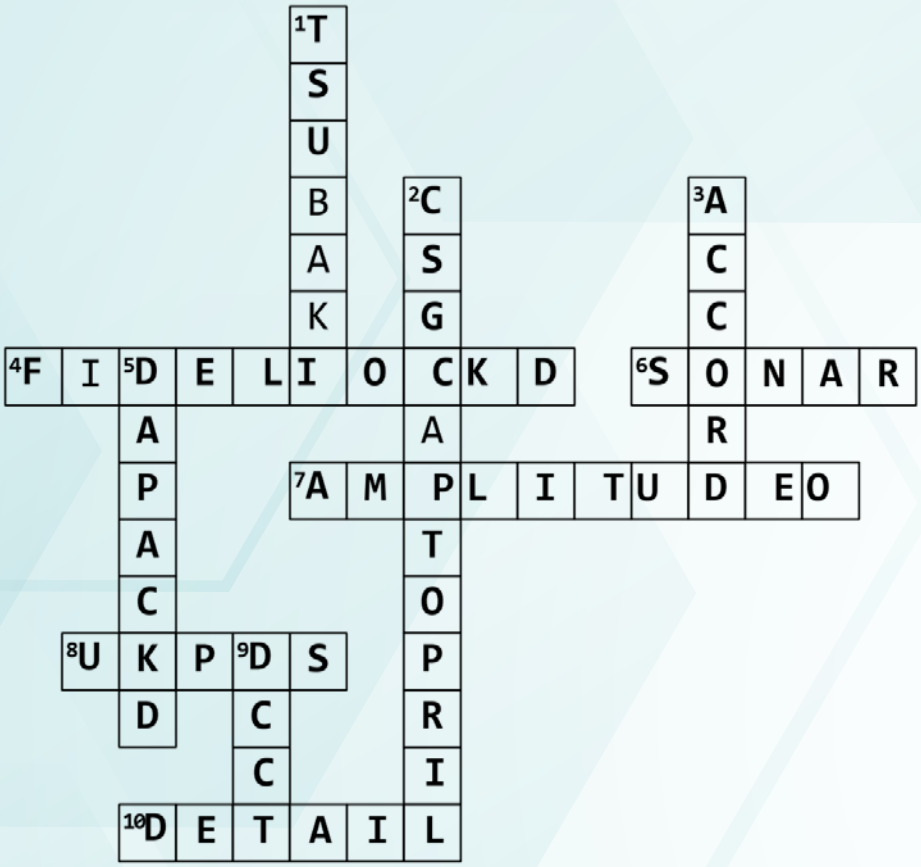
Dr Praveen Kumar Etta presenting one of the three posters at the International Society for Peritoneal Dialysis Congress, held at Suntec, Singapore

Dr Praveen Kumar Etta presenting a topic at the Indian Association of Clinical Medicine Annual Conference held at Agartala, Tripura on 11th September 2022.

Dr Vijaychandar from NIMS presented a poster titled “Clinical Outcomes in IRGN - A Single Centre Experience in 21 Patients From South India” at the ISN-Frontiers Meeting conducted in New Delhi from 22nd to 25th September 2022

Dr. Ashwinikumar Aiyangar had finished gruelling 226 km endurance Ironman Triathlon (Swim 3.8 km + Cycling 180 km + Run 42.2 km) held at Kazakhstan in August 2022, in 13h:52m:59s.

Answers to the Crossword Puzzle on trials in Diabetic Nephropathy



Contributed by

Dr Deepthi Ayanavelli

Consultant Nephrology

ESIC Superspeciality Hospital

Hyderabad

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*SOT : Solid Organ Transplant
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Hyderabad Nephrology Forum

Hyderabad, Telangana India

M +91 99892 90234

E hyderabadnephrologyforum@gmail.com

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