KIDNEY KOLUMNS
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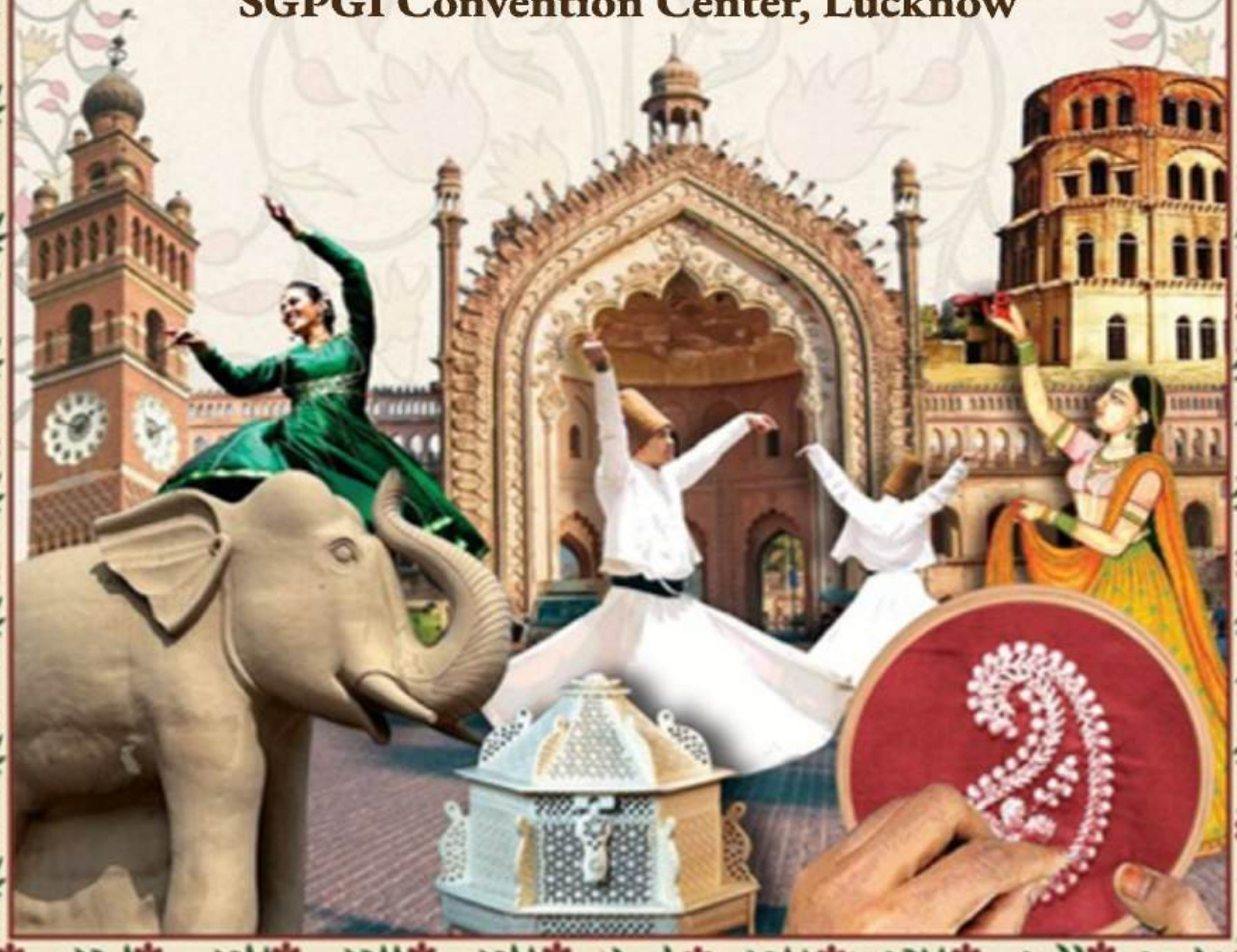
KIDNEY KOLUMNS VOL 4 | ISSUE 4 | OCT TO DEC 2025

Welcome to 54th ISNCON 2025 LUCKNOW

18th to 21st December 2025
SGPGI Convention Center, Lucknow



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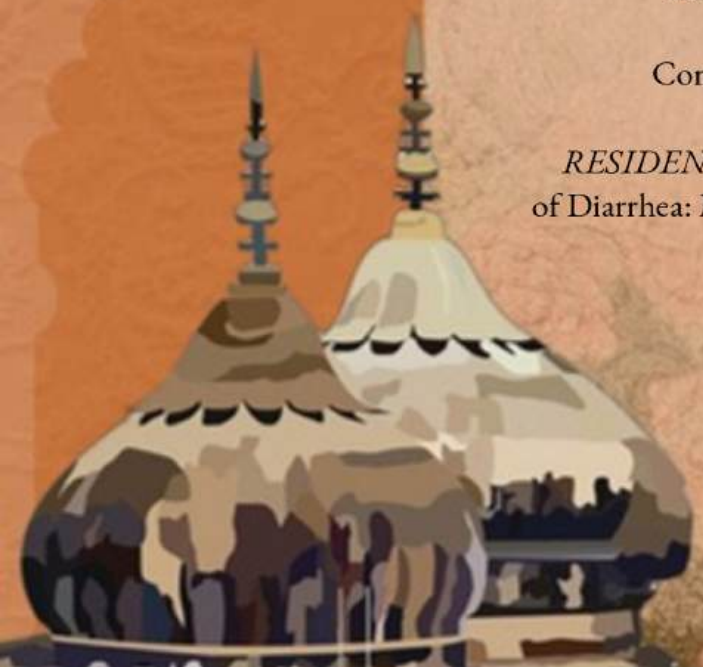

It is with
immense pleasure that we, the
Editors in Chief

present this new edition of Kidney Kolumns, marking our second anniversary as your dedicated source for the latest in Nephrology! Two years ago, we embarked on a journey to bring insightful and impactful content to your fingertips, and we are incredibly proud of the growth and engagement we've witnessed.

This celebratory edition is focused on an essential theme: Practice-Changing Newer Advances and Trials in Nephrology. We delve into the cutting-edge research and landmark clinical trials that are actively redefining patient care and shaping the future of our specialty.

Looking ahead, the coming year promises exciting developments. We are committed to an evolutionary change, planning to incorporate newer minds and fresh ideas to further improve Kidney Kolumns and take the newsletter to new heights of relevance and impact.

As we look forward, the promise of academic excellence continues. We eagerly anticipate the academic feast that awaits everyone at ISNCON 2025 in the historic city of Lucknow from December 18-21, 2025. This premier conference promises to be a hub of innovation, precision, and global collaboration, and we hope to see many of you there as we collectively strive to advance kidney care.

Thank you for your continued readership and support, and we trust you will find this edition.

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Greetings from the Indian SN secretariat!!

Dr Shyam B Bansal
Honorary Secretary, Indian SN

We are pleased to announce that the Final Program for the 54th Annual Conference of the Indian Society of Nephrology, ISNCON 2025, is now available online. The conference will be held from December 18-21, 2025, at the SGPGI Convention Centre in Lucknow, Uttar Pradesh.

The scientific committee of ISN has curated an enriching academic and networking event that promises to be a unique experience, combining an extensive scientific program with the warm hospitality and rich culture of Lucknow. Access the Final Program. The detailed scientific program, including schedules, speakers, and session details, can be accessed on the official conference websites:
Indian Society of Nephrology (ISN) Official Website - www.isn-india.org

Program Highlights

The conference features an academic feast with renowned national and international speakers , including experts from major global nephrology societies such as the ISN, ISGD, ASN, ERA-EDTA, and APSN.

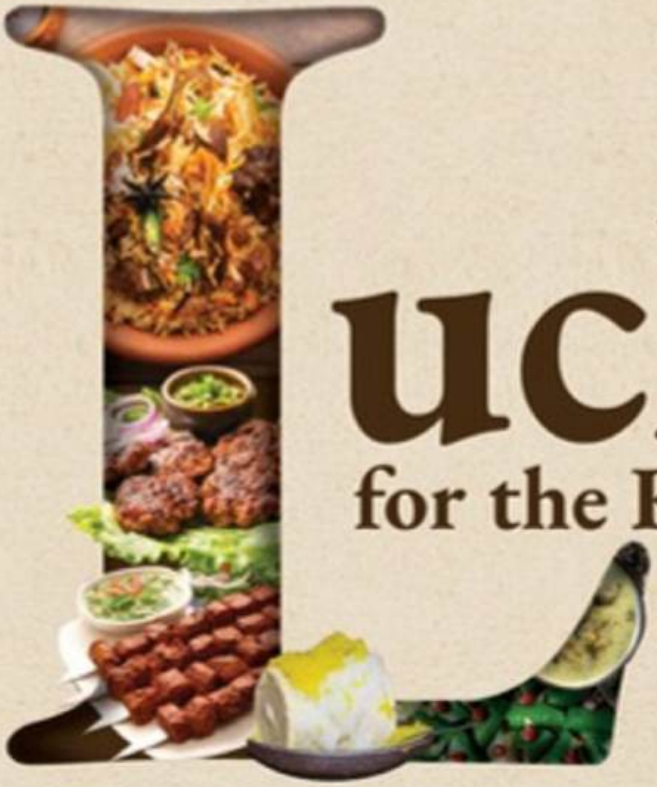
Key highlights include:

- Pre-conference Workshops (December 18): Hands-on workshops will cover essential areas, including Transplant Immunology, Interventional Nephrology, Pediatric Nephrology, Onconephrology and Renal Histopathology, and Critical Care Nephrology, including practical demonstration of Point-of-Care Ultrasound (POCUS) and Venous Excess Ultrasound (VEXUS).
- Cutting-edge Sessions: The main conference program will feature diverse sessions on Glomerular diseases with ISGD, CKM with ASN, advances in renal replacement therapy, AI in nephrology and Transplantation, AKI, and managing complex conditions like thrombotic microangiopathy, Bone disease, genetics in CKD to name a few.
- Renowned Speakers: Notable speakers such as Dr Katherine Tuttle (CKM, GLP-1 agonist), Dr Rajnish Mehrotra (peritoneal dialysis), Dr Jai Radhakrishnan (Glomerular diseases) Dr Rukshana Shroff (Nutrition in CKD, HDF), Dr Rulan Parekh (Precision health in CKD) Dr Vivekaknad Jha (Art and Science of Nephrology), Dr Carla M. Nester (Thrombotic Microangiopathy, C3 GN), Dr Roman Mueller (ADPKD, Genetics and CKD) Dr Marc Vervloet (CKD-MBD, GFR estimation), Dr Rupesh Raina (RRT, FSGS), Dr Balram Bhargava (HTN in India), Dr Prabir Roy Chaudhry (CKM, Policy), Dr S Swaminathan (AKI), Dr Rajiv Agrawal (HTN, CONFIDENCE Trial) Dr Vasishta Tatapudi (Xenotransplantation) Dr Amit Govil (AI in Transplantation) Dr Vandana Dua (POCUS in Nephrology) and Dr Silvi Shah (Obstetric AKI) deliver key sessions.
- Paper Presentation: With more than 500 abstracts submitted and 150 for oral and mini-oral presentations, this is the highest number of ISNCON presentation this time.
- Special Recognition: The Life time achievement award of Indian SN will be conferred to Dr M Rajapurkar and The ISN 2025 Pioneer Award for the South Asia region will be presented to Professor Amit Gupta at the conference.

Don't miss this opportunity to advance your knowledge and connect with peers.

Warm regards

Shyam Bansal



CULTURE, CUISINE, CAMPUSES & CHIKAN Lucknow

for the Kidney Connoisseurs

Authors:
Namrata Rao S, Additional Professor, Department of Nephrology, Dr RMLIMS, Lucknow
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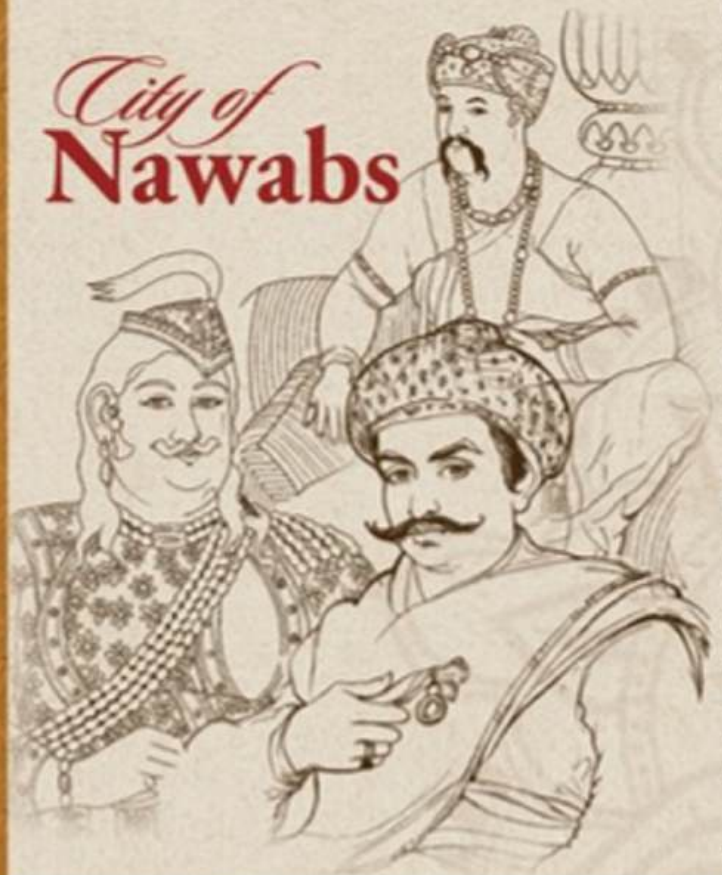
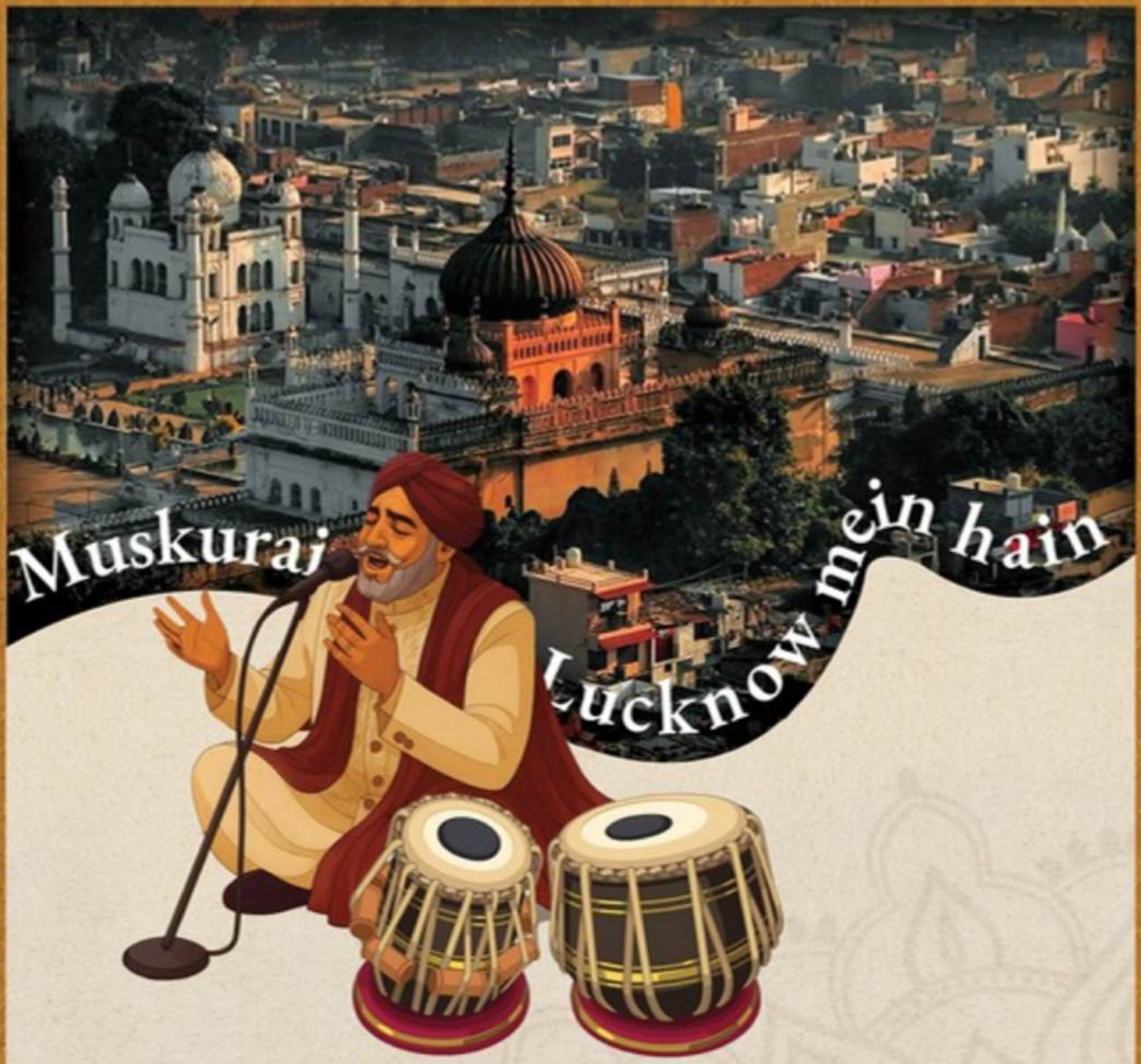
As you all pack your bags (with a few warm woollens) to Lucknow this December, this writeup from the local ISNCON SoMe team will add quite a few items to your to-do lists!



Beyond India's most famous labyrinth (the Bhool Bhulaiya), housed in the Bara Imambara, history and architecture buffs will surely find Satkhanda and Lal Pul of interest. And did you know even our railway station is steeped in history? Indeed, the Charbagh Railway Station built in the Indo-Saracenic style was the place where Mahatma Gandhi and Jawahar Lal Nehru first met, in the year 1916. Nestled in the city, is also an ancient Hanuman Mandir, considered a living symbol of communal harmony - where Hanumanji's idol, in fact, was discovered at a mound considered sacred by both the Hindu and the Muslim communities, and the temple having been built by Nawab Muhammad Ali Shah's wife.

If scenic walks on chilly winter mornings (or on glorious afternoons) are more your cup of tea – Lucknow boasts of both old-world (Sikandar Bagh, CSIR-NBRI Botanical Garden, and Begum Hazrat Mahal Park) and modern (Janeshwar Mishra and Lohiya) parks. Entries to most parks are free during morning hours. So folks, don't forget to pack a pair of sneakers! And while at it, you could soak in the Lucknow campus culture at the heritage campuses of KGMU, Lucknow University and Bhartendu Natya Academy.

For the gourmands of the Nephrology world – those who do not mind mincing the meat with extra sodium, potassium and protein – Lucknow's refined cuisine (like its revered dialect) awaits you at Tunday Kababi, Raheem's Kulcha-Nahari, Idris and Wahid's Biryani, the Mughal's Dastarkhwan and Ali Hussain's Sheermal. For the vegetarian aficionados – do check out Bajpai's Puris and Kachoris, Dixit, Shukla and Jain Chaat, Ratti Lal's Khasta Kachori, Purvanchal specials such as Baati Chokha and the Bollywood favourite, Royal Café's Basket Chaat. After the carb-loading, (gut-space notwithstanding) conference goers must end their food adventures on a sweet note – with Makkhan-Malai from Ram Asrey or Kulfi from Prakash ki Mashoor Kulfi. Those who fret for an evening tryst with Kulhad Chai – should check out Sharmaji ki Chai at LalBagh with a side of Bun-Makkhan.



No travel guide for women (and men who have to travel back home to their beloveds) is ever complete without picking up either a Chikan saree or kurtas. If you are a natural braveheart, you can head to the crowded markets of Chowk or Aminabad areas for learning to bargain with Tehzeeb. For authentic craftmanship, Lucknow Chikan Emporium and Chhangamal have the vote of the second and third authors of this writeup (you may ask for their expert opinion at the conference venue too). For those who wish for high-quality and stylish chikankari options, Nazrana Chikan at Janpath Market and Ada Designer Studio at Hazratganj are great places to check out. Not to forget, Hazratganj lights up like a beauty every evening, as you could stroll in with your shopping bags with locals on its heritage walkways, an activity lovingly called "Ganj"ing.

Here's to hoping for a memorable gathering of Kidney Connoisseurs and KK readers in the city we call home – Lucknow!

Critical Appraisal of Effects of Therapies on Proteinuria & eGFR in IgA Nephropathy - A Clinician's Perspective

DR MANJUNATH KULKARNI, Professor & Head,
Nephrology, Father Muller Medical College, Mangaluru

Emerging therapies in IgA nephropathy are a source of continuing excitement in nephrology circles, and should surely occupy pride of place, in Kidney Kolumns' year-end roundup too. With trials on both non-immunologic and immunologic therapies demonstrating efficacy in IgAN, we come to the crossroads question - how do these therapies fare in terms of proteinuria reduction and eGFR progression, and more fundamentally, which of these, may soon become the standard of care? This meta-analysis by Kim and colleagues published in CJASN tries to answer just these questions for us.

WHAT DID THE AUTHORS DO?

They conducted a systematic review including databases from inception through May 2025 including Phase 2b and 3 multicenter randomized controlled trials. They focused on trials evaluating therapies in adults with IgA nephropathy already on maximal supportive care, particularly RAS blockade. The outcomes of interest were proteinuria change at 6-12 months and eGFR slope over at least 12 months.

They identified 14 trials (3,843 participants) and organized these therapies into four distinct drug classes: nonimmunologic therapies (SGLT2 inhibitors, sparsentan, atrasentan), corticosteroids (methylprednisolone, budesonide), B-cell modulating agents (atacicept, sibeprenlimab, telitacicept), and complement inhibitors (cemdisiran, ravulizumab, iptacopan).

Their approach was methodologically sound - two independent reviewers screened studies, extracted data, and assessed quality using Cochrane's risk of bias (ROB) tool version 2. They pooled treatment effects using random-effects meta-analysis and explored heterogeneity both within and across drug classes.

WHAT DID THEY FIND?

Let us start with what grabbed our attention instantly. **All four drug classes reduced proteinuria**, but not equally. Corticosteroids showed the largest effect with 51% reduction, followed by B-cell modulators at 45%, nonimmunologic therapies at 34%, and complement inhibitors at 35%. The differences between classes were statistically significant.

For eGFR slope-the pattern shifted. B-cell modulators demonstrated the most impressive effect, improving eGFR slope by 4.3 ml/min/1.73m^2 per year (73% relative improvement). Corticosteroids came next with 2.3

ml/min/1.73m² per year (52% improvement), while nonimmunologic therapies showed a more modest but consistent 1.1 ml/min/1.73m² per year benefit (28% improvement).

WHAT WERE THE STRENGTHS OF THE STUDY?

Comprehensive and Timely: We were impressed by the authors' idea to design such a meta-analysis. They even incorporated results presented at conferences showing real commitment to completeness.

Pragmatic Outcome Selection: Choosing proteinuria and eGFR slope as primary outcomes can be considered pragmatic. (More about this later, see below)

Clinically Meaningful Subgroup Analysis: Organizing therapies by mechanism of action rather than individual drugs makes intuitive sense.

Safety as outcome measure: The systematic presentation of serious adverse events and treatment discontinuation rates is a highlight of this review. The safety data showing increased infection risk with full-dose corticosteroids but not with SGLT2 inhibitors directly translates to clinical practice.

WHERE DID WE GET CONCERNED?

Heterogeneity: While the authors report relatively low heterogeneity within drug classes, the populations across trials varied substantially. Baseline proteinuria ranged from approximately 0.9 g/day (DAPA-CKD) to 2.4 g/day (SANCTUARY trial). Mean eGFR spanned from 43 to 79 ml/min/1.73m². Some trials included 100% Chinese participants while others had primarily White or mixed Asian.

This heterogeneity matters because treatment responses differ by ethnicity, baseline proteinuria, and disease severity. The authors acknowledge this limitation. As an example, it seems uncertain if corticosteroids would have shown less benefit if more non-Chinese populations were included in the TESTING trial.

The Surrogate Endpoint Problem: Yes, proteinuria and eGFR slope are surrogate endpoints. But let's be honest about what we're seeing. Hard clinical outcomes,ie, kidney failure, dialysis initiation, death were reported in only a subset of these trials. The TESTING trial showed benefits on these clinical kidney outcomes, but most novel immunologic therapies haven't yet demonstrated this.

Moreover, the relationship between proteinuria reduction and kidney failure isn't perfectly linear or consistent across all interventions. The corticosteroid trials beautifully illustrate this problem: dramatic early proteinuria reduction at 12 months, but by 36 months, the effect had almost vanished. **Are we measuring a true disease-modifying effect or just a temporary suppression?** For drugs requiring indefinite therapy (SGLT2 inhibitors) versus time-limited courses (corticosteroids), this distinction becomes critical.

Limited Long-Term Data for Novel Agents: The eGFR slope data exists over 2 years for nonimmunologic therapies and corticosteroids, but for B-cell modulators and complement inhibitors, the agents showing the most impressive effects, we have mostly 9–12-month data, sometimes only 6 months. The sibeprenlimab data showing a 4.3 ml/min/1.73m² per year benefit looks phenomenal, but it's based on 12-month follow-up in the Phase 2 ENVISION trial with relatively small numbers. Will this magnitude of effect persist? Will there be late-emerging safety signals? We simply don't know.

The Network Meta-Analysis That Wasn't: The authors performed pairwise meta-analyses comparing

each drug class to placebo or standard care. What they didn't do and couldn't do given the data, is perform a formal network meta-analysis with head-to-head comparisons. **This means the "ranking" of effectiveness across drug classes comes with huge uncertainty.** Different baseline risks, different background therapies, different outcome definitions, all these factors prevent confident comparative effectiveness conclusions.

CONCERNS ABOUT STATISTICS AND METHODOLOGY

Outcome Timing Inconsistency: While the authors aimed to assess 9-month proteinuria and 2-year eGFR slope, they **used whatever timepoints were available.** Proteinuria was assessed anywhere from 6 to 24 months, and eGFR slopes came from periods ranging from 12 to 50+ months. They acknowledge trying to "prioritize the same time point within each therapeutic class," but **mixing these timeframes introduces temporal bias**.

Relative Versus Absolute Effects: The authors report both absolute differences in eGFR slope (ml/min/1.73m^2 per year) and relative percentage differences. While this dual reporting is commendable, the relative effects depend entirely on the baseline rate of decline in control arms, which varied substantially across trials (from -1.6 to -5.9 ml/min/1.73m^2 per year). The relative effect of 73% for B-cell modulators sounds more impressive than the absolute effect of 4.3 ml/min/1.73m^2 per year, but which number should guide our clinical decisions? Both are important, but neither tells the complete story.

Risk of Bias Assessment: The authors state that the overall risk of bias among the included studies was low to moderate. However, the specific details supporting this assessment are provided only in a supplemental table, making it difficult to fully evaluate their conclusions within the main text. It is important to note that several of the included trials were sponsored by industry, and in some cases, outcomes were derived from prespecified interim analyses of ongoing studies.

Another key methodological concern is that the risk of bias assessment was conducted at the study level rather than at the outcome level. This approach does not align with best practices, as outlined by the Cochrane guidelines, which recommend evaluating risk of bias for each outcome individually. Although some methodological limitations may have been outside the authors' control, a more thorough and outcome-specific risk of bias assessment could have been undertaken to strengthen the validity and transparency of the review.

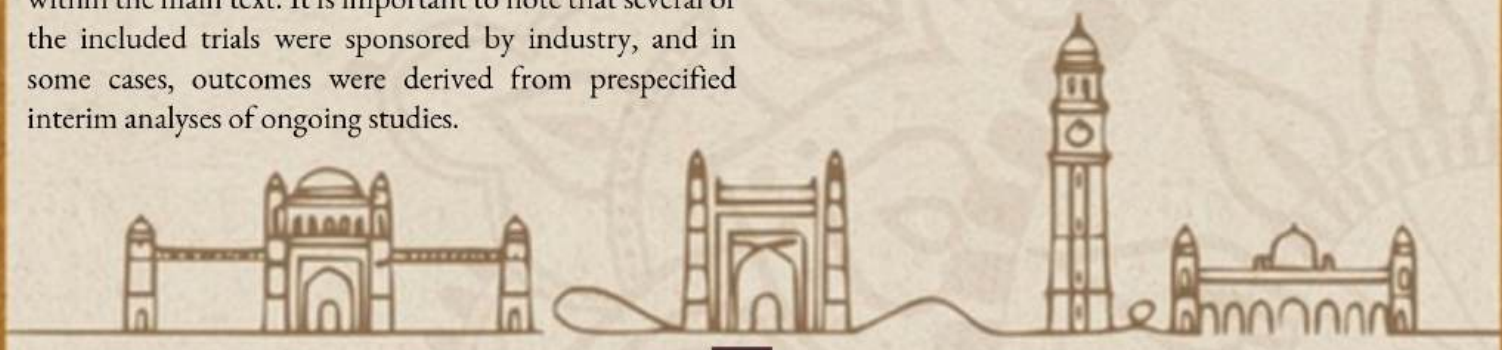
CAN WE TRANSLATE THE FINDINGS TO CLINICS?

Here's where we really struggle. The authors conclude that "all four drug classes improve kidney outcomes in IgA nephropathy" and suggest that "the varying mechanisms and effects of different therapies suggest a potential for combination therapy". But how do we use this information on Monday morning when we see a 35-year-old with IgA nephropathy, proteinuria of 1.5 g/day, eGFR of 45, and she/he asks us what treatment she/he should receive?

The meta-analysis tells us that, on average, multiple therapies work. But it doesn't tell us:

- Which therapy is best for her/him specifically?
- Whether combining an SGLT2 inhibitor with a B-cell modulator is safe and additive in effect?
- How long should she take these medications?
- What to do if the proteinuria doesn't improve after 6 months?
- Whether particular histologic features on biopsy should influence therapy choice?

These are the questions that matter at the bedside, and meta-analyses of aggregate data simply cannot answer them. We need individual patient data meta-analyses



and, ideally, head-to-head trials or platform trials testing combinations.

ARE THE RESULTS OF THE REVIEW APPLICABLE TO OUR SETTING?

The authors briefly mention that "most of these drugs, including those approved by the FDA, remain inaccessible for large parts of the world". This is not a minor footnote; it is a fundamental limitation of the entire analysis. If we practice in a resource-limited setting, knowing that complement inhibitors reduce proteinuria by 35% is academically interesting but clinically irrelevant if our patient cannot afford or access these medications.

Generic corticosteroids remain the most accessible option globally, yet they carry the highest adverse event burden. The safety-efficacy trade-off looks very different depending on whether you're choosing between a Rs 500 per month corticosteroid and a Rs 80000 per month complement inhibitor. The analysis treats all therapies as equally available, which creates a disconnect between evidence and real-world applicability.

THE BOTTOM LINE

This meta-analysis confirms what many of us suspected: we now have multiple effective therapies for IgA nephropathy, each with distinct mechanisms, efficacy profiles, and safety considerations.

However, significant uncertainty remains. The magnitude of benefit varies across drug classes, but confidence in these comparative estimates is limited by population heterogeneity and methodological differences across trials. Long-term efficacy and safety data for the most promising novel agents, B-cell modulators and complement inhibitors, are not available. We lack evidence to guide combination therapy and treatment duration.

For now, SGLT2 inhibitors should be considered standard of care for most patients with IgA nephropathy and reduced eGFR or persistent proteinuria along with RAS blockade, given their proven benefits and excellent safety profile. Beyond that, treatment decisions require careful individualization weighing disease severity, risk factors, patient preferences, cost, and access to novel agents.

Before we conclude, we provide GRADE assessment of the systematic review for our readers.

GRADE assessment of the systematic review

Outcome	Effect Estimate	No of Participants (Studies)	Certainty of Evidence	Justification
Proteinuria reduction - Nonimmunologic therapies	-34% (95% CI: -42 to -26)	1,745 (4 trials)	⊕⊕⊕◯ MODERATE	Started HIGH (RCTs). Downgraded one level for inconsistency in baseline populations and some heterogeneity (I^2=52.9%)

Outcome	Effect Estimate	No of Participants (Studies)	Certainty of Evidence	Justification
Proteinuria reduction - Corticosteroids	-51% (95% CI: -56 to -46)	1,291 (4 trials)	⊕⊕⊕◯ MODERATE	Started HIGH (RCTs). Downgraded one level for concerns about durability of effect (diminished by 36 months) and geographic heterogeneity in treatment response.
Proteinuria reduction - B-cell modulators	-45% (95% CI: -55 to -35)	567 (4 trials)	⊕⊕◯◯ LOW	Started HIGH (RCTs). Downgraded two levels: one for indirectness (includes Phase 2 data with small sample sizes), one for imprecision (wide confidence intervals, few events) and heterogeneity (I2=49%).
Proteinuria reduction - Complement inhibitors	-35% (95% CI: -46 to -25)	347 (3 trials)	⊕⊕◯◯ LOW	Started HIGH (RCTs). Downgraded two levels: one for indirectness (short follow-up, interim analyses) and one for imprecision (small sample sizes, few trials)
Serious adverse events - Corticosteroids	Increased risk, particularly infections	1,291 (4 trials)	⊕⊕⊕⊕ HIGH	Well-established increased SAE risk with full-dose corticosteroids (16% vs 3% in TESTING), consistent across trials, biologically plausible

Outcome	Effect Estimate	No of Participants (Studies)	Certainty of Evidence	Justification
Serious adverse events - SGLT2 inhibitors	No significant difference vs placebo	1,071 (2 trials)	⊕⊕⊕⊕ HIGH	Large RCTs with extended follow-up (>2 years), consistent safety profile, well-characterized from broader CKD trials
Serious adverse events - Novel immunologic agents	No clear increase in short-term SAEs	816 (6 trials)	⊕⊕◯◯ LOW	Started HIGH. Downgraded two levels: one for indirectness (short follow-up periods 6-12 months) and one for imprecision (small number of events, insufficient power to detect rare SAEs)

Real-life Tolvaptan Use in ADPKD - Current Evidence at a Glance

DR J MARIA ALEX BABU
DM (Nephrology)

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disorder, characterised by progressive development and enlargement of renal cysts leading to loss of kidney function. Management focuses on delaying renal decline, controlling complications, and addressing systemic manifestations of the disease. Tolvaptan, a vasopressin V2 receptor antagonist, is currently the only disease-modifying drug shown to slow the growth of TKV and decline in eGFR, especially in progressive ADPKD. It has been evaluated in several randomised, controlled trials.

The TEMPO 3:4 study (1445 adult ADPKD patients), a 36-month randomised controlled trial, showed that tolvaptan treatment resulted in a 26% reduction in the rate of kidney function decline in patients with preserved kidney function. Also, the trial showed a 49% reduction in total kidney volume (TKV) growth (2.8%/year vs. 5.5%/year in placebo; P < 0.001]. A composite clinical-progression endpoint (worsening kidney function, pain, hypertension, or albuminuria) favoured the use of tolvaptan. The benefit was attributed to a reduction in the rate of kidney volume growth by tolvaptan. TEMPO 4:4 was an open-label extension trial of TEMPO 3:4. The early-treated group included individuals who received tolvaptan in TEMPO 3:4, and the delayed-treated group included those who received a placebo in TEMPO 3:4 and later initiated tolvaptan. TEMPO 4:4 demonstrated that the eGFR benefit, achieved at the end of TEMPO 3:4 in the early-treated subjects, was maintained for an additional 2 years in TEMPO 4:4. But it did not demonstrate a sustained expected beneficial difference in TKV achieved during TEMPO 3:4, suggesting that tolvaptan induces predominantly short-term effects on kidney volume, after which cyst growth continues at more or less the same rate as before treatment. These conflicting data make it clear that the long-term impact of tolvaptan on kidney volume growth needs to be investigated more thoroughly.

Real-life data on long-term tolvaptan treatment are sparse and limited by restricted follow-up, small patient groups or lack of a control group. A recent study by Gansevoort et al. investigated the long-term effects of tolvaptan on kidney function and growth in real-life patients and controls. For this analysis, data from the DIPAK (Developing Interventions to HALT Progression of ADPKD) and OBSERVA (Observing the Natural Course of ADPKD) cohorts were utilised. Criteria for initiating tolvaptan included a history of rapid eGFR decline and/or predicted rapid disease progression based on the PROPKD score. At the start of this analysis, the DIPAK and OBSERVA cohorts contained 670 and 160 patients, respectively. After excluding 215 patients due to the use of lanreotide (n = 121), nephrectomy (n = 12), or less than 6 months of follow-up (n = 82), 615 patients were included in the analyses. Of these patients, 105 were treated with tolvaptan (tolvaptan group), and 510 were not (no tolvaptan group). The mean duration of tolvaptan treatment was 6.1 ± 4.7 years, and patients received tolvaptan in a dose of 90/30 mg (84.8%), 60/30 mg (8.6%) or 45/15 mg (6.7%) daily. A matched cohort was formed based on 1:1 matching for age, sex, Mayo class, eGFR at baseline, eGFR slope before (theoretical)

start of treatment and follow-up time. eGFR slope before tolvaptan use was - 4.36 (- 4.97 to - 3.76) mL/min/1.73 m2/year, which significantly improved during chronic treatment [- 3.75 (- 4.35 to - 3.16), difference 14.0%, P = 0.03]. No significant change was noted in the control group during chronic treatment. It is worth noting that TKV growth in the tolvaptan group before treatment did not change significantly during chronic treatment [5.05 (3.06 to 7.10) versus 5.59 (3.45 to 7.71) %/year, P = 0.6]; In the no tolvaptan group, the same effect was noted. [4.79 (1.69 to 7.97) versus 3.85 (1.04 to 6.74) %/year, P = 0.5].

Although this finding conflicts with data from the TEMPO 3:4 study, it corresponds to the conclusions of the open-label TEMPO 4:4 study. This study suggests that tolvaptan's long-term effect on slowing kidney function decline may not be solely due to its impact on kidney volume. Other possible mechanisms include reduced glomerular hyperfiltration or V1 receptor stimulation from the compensatory rise in vasopressin during treatment. Subgroup analysis revealed that lower urine osmolality during treatment, higher daily osmolar intake, and the use of diuretics were determinants of better tolvaptan treatment efficacy. A critical limitation of this study was that TKV was both measured by the stereologic method and estimated using the Ellipsoid formula. Growth rates obtained using the Ellipsoid formula are more variable compared to measured volumes; however, a sensitivity analysis conducted by this group with only measured volumes yielded similar results.

In our setting, initiating Tolvaptan requires careful consideration of several practical challenges. Prescription rates remain low, and once treatment begins, stringent liver function monitoring is essential, with discontinuation warranted if transaminases exceed three times the standard limit. Risks include hypernatremia, dehydration, and interactions with potent CYP3A4 inhibitors. Women of childbearing potential require contraception and should avoid breastfeeding. Patients must also follow a sick-day plan during illnesses that cause fluid loss. Many may not reach the recommended dose in our setting, and the benefit of underdosing remains uncertain. These factors highlight the need for individualised decision-making when starting Tolvaptan therapy.

Keep the Blood Flowing

DR JAYANIVASH J
Interventional Nephrologist
SIMS Hospital, Chennai

Despite all the advantages of autologous arteriovenous fistulas, one major limitation to its widespread usage as the vascular access of choice is the high incidence of dysfunction caused by vascular stenosis within the fistula circuit, leading to inadequate hemodialysis. Unfortunately, despite many attempts to address stenoses in arteriovenous access circuits through endovascular approaches, the percentage of patients who undergo repeat intervention within 6 months has been estimated in systematic reviews and meta-analyses to be approximately 50%. The standard treatment, percutaneous transluminal angioplasty (PTA), suffers from high restenosis rates and an upgrade of PTA with usage of Bare metallic stents, Covered stents, grafts and drug coated balloons have been tried with variable success.

The need to explore new devices with better long-term patency and safety profiles is still large and real. The WAVE trial investigated a novel device called the cell-impermeable endoprosthesis (CIE), designed to overcome the limitations of existing covered stents by preventing transmural cellular growth that contributes to restenosis. The CIE incorporates a multilayer fluoropolymer graft with a cell-impermeable middle layer and a novel spun PTFE inner layer to limit fibrin and thrombus formation. It also features modifications in stent design to improve radial strength and compression resistance.

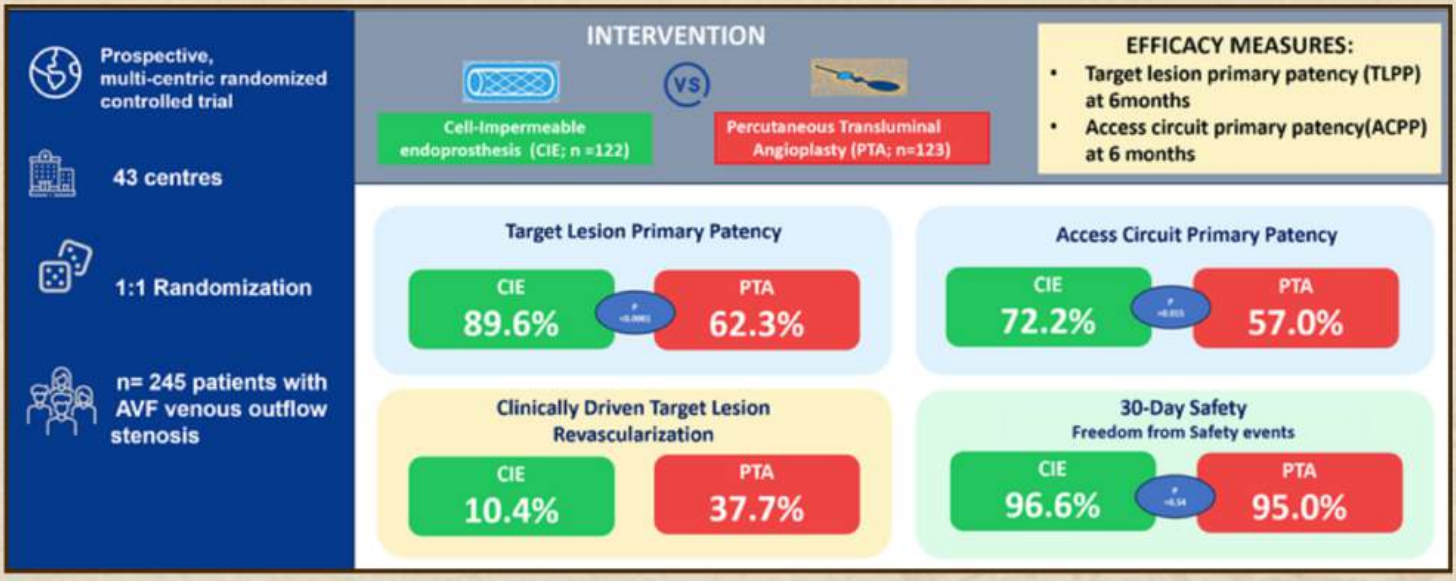
This multicenter, prospective, randomized controlled trial enrolled 246 hemodialysis patients with dysfunctional AVFs due to venous outflow stenosis that met strict angiographic and clinical criteria. After successful predilatation with high-pressure balloons, patients were randomized 1:1 to receive either the CIE or standard PTA. The primary efficacy endpoint was target lesion primary patency (TLPP) at 6 months, defined as freedom from clinically driven revascularization or thrombosis at the treated site. The primary safety endpoint was freedom from adverse access-related events within 30 days post-procedure that required rehospitalization, reintervention, or caused death. Secondary endpoints included access circuit primary patency (ACPP), clinical and procedural success, and rates of reinterventions.

The results were highly optimistic, the CIE cohort demonstrating a significantly higher TLPP of 89.6% compared to 62.3% in the PTA cohort, reflecting a 27.3% absolute improvement at 6 months. Similarly, ACPP was significantly better in the CIE group at 72.2% versus 57.0% with PTA. Clinically driven target lesion revascularization was markedly lower among CIE-treated patients (10.4% vs. 37.7%). Procedural and clinical success rates were high and comparable between cohorts, and the mean number of interventions needed to maintain patency was significantly fewer in the CIE group. Safety outcomes through the first 30 days showed no significant difference in adverse events, with freedom from safety events at 96.6% for CIE and 95.0% for PTA, confirming non-inferiority of the novel device.

In a typical Indian scenario, the loss of functional vascular access means creating a new temporary access with a non-tunnelled dialysis catheter and creation of a new permanent access placing an additional clinical and socio economic burden on patients. Any manoeuver that helps in maintaining AVF patency in hemodialysis patients, with significantly lower rate of re-intervention requirement is a life saver. Compared with historical data, the CIE showed superiority over PTA, a standard therapy

with known limitations. Given that restenosis is a major challenge limiting long-term AVF functionality, the cell-impermeable design of the CIE may provide a significant advantage by reducing neointimal hyperplasia and negative remodeling, which were supported by preclinical animal studies and observatory human trials.

The key limitations of the study included the inability to blind operators due to the nature of the interventions, stringent eligibility criteria affecting generalizability. The trial is on-going with planned 24-month follow-up to further assess long-term outcomes. In conclusion, the WAVE trial demonstrates that CIE offers superior 6-month efficacy in maintaining target lesion and access circuit patency compared to standard PTA without compromising safety. These promising results suggest that the CIE may improve vascular access durability in patients undergoing hemodialysis, potentially reducing the burden of repeat interventions and enhancing patient care in this vulnerable population.



Conclusions

The CIE was superior to PTA with respect to six month TLPP and ACPP with no observed difference in 30-day primary safety events

Ref: Razavi MK et al, Kidney Int, 2024
PMID: 41271307
VA by: Dr Subashri MD, DM @happiedoc

Targeting Complement Factor B in C3 Glomerulopathy: The Promise of Iptacopan

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BACKGROUND

C3 glomerulopathy (C3G) is an exceptionally rare form of chronic glomerulonephritis, affecting mainly people under 40 years and diagnosed in one to two individuals per million annually. It is associated with considerable clinical heterogeneity and requires a kidney biopsy to confirm the diagnosis. The outlook is grim, with about half of all patients developing kidney failure within a decade. The pathogenesis of C3G centres on uncontrolled activation of the alternative complement pathway in both the plasma and the glomerular environment, leading to the deposition of C3 activation products in the glomeruli. This process causes significant kidney inflammation and injury. Complement factor B is a critical player in this pathway, serving as a logical target for new therapies. Traditional treatments—such as renin-angiotensin system blockers, corticosteroids, and general immunosuppression - have, up to now, offered only limited help, as they do not address the root cause of complement overactivation.

RATIONALE

Iptacopan is a new oral drug that acts as a complement inhibitor with selective activity against complement factor B. Its mode of action involves blocking the formation and activity of the C3 convertase (C3bBb), which is central to the alternative pathway's amplification. By silencing this pathway while sparing the classical and lectin arms of the complement system, Iptacopan aims to limit kidney injury driven by complement overactivation and preserve vital immune functions.

TRIAL DESIGN AND POPULATIONS

The APPEAR-C3G clinical trial was a multicenter, double-blind, randomized, placebo-controlled, phase 3 study. It recruited 74 adults, with biopsy-proven C3G, proteinuria exceeding 1 gram per day, and relatively stable kidney function (eGFR at least 30 mL/min/1.73 m^2). Participants were randomly assigned to either Iptacopan 200 mg twice daily or placebo for a period of six months. After the initial double-blind phase, an open-label extension allowed continued treatment for up to twelve months. The primary assessment focused on changes in the 24-hour urine protein-to-creatinine ratio (UPCR) at

six months, a direct marker of kidney disease severity.

RESULTS AND OUTCOMES

The APPEAR-C3G trial brought forth strong clinical evidence showing that Iptacopan can selectively and effectively inhibit the alternative complement pathway. The primary endpoint was met with relative reduction in 24 hour UPCR at 6 months for Iptacopan vs placebo of 35.1% (13.8 to 51.1; P=0.014). The oral administration of Iptacopan provides a practical benefit for patients and distinguishes itself from the general side effects of nonspecific immunosuppressants.

LIMITATIONS AND FUTURE DIRECTIONS

While this commentary is optimistic regarding Iptacopan and other targeted complement inhibitors, the need for longer-term data and broader clinical experience remains. Further research is needed in pediatric populations to define safety and pharmacokinetics, combination therapy with C5 inhibitor for full cascade blockade, sequential therapy with Pegcetacoplan for induction and Iptacopan for maintenance.

Pegcetacoplan (VALIANT programme; regulatory reports/press): phase-3 data reported large and durable proteinuria responses (reports cite ~68% reduction in UPCR at 26 weeks in VALIANT versus placebo, with sustained benefit through 1 year and biopsy evidence of C3 clearance), stabilization of kidney function, and an acceptable safety profile in adolescents and adults.

Pegcetacoplan is a C3 inhibitor (targets C3/C3b) that blocks central C3 activation and therefore has a broader effect on all complement activation that converges at C3.

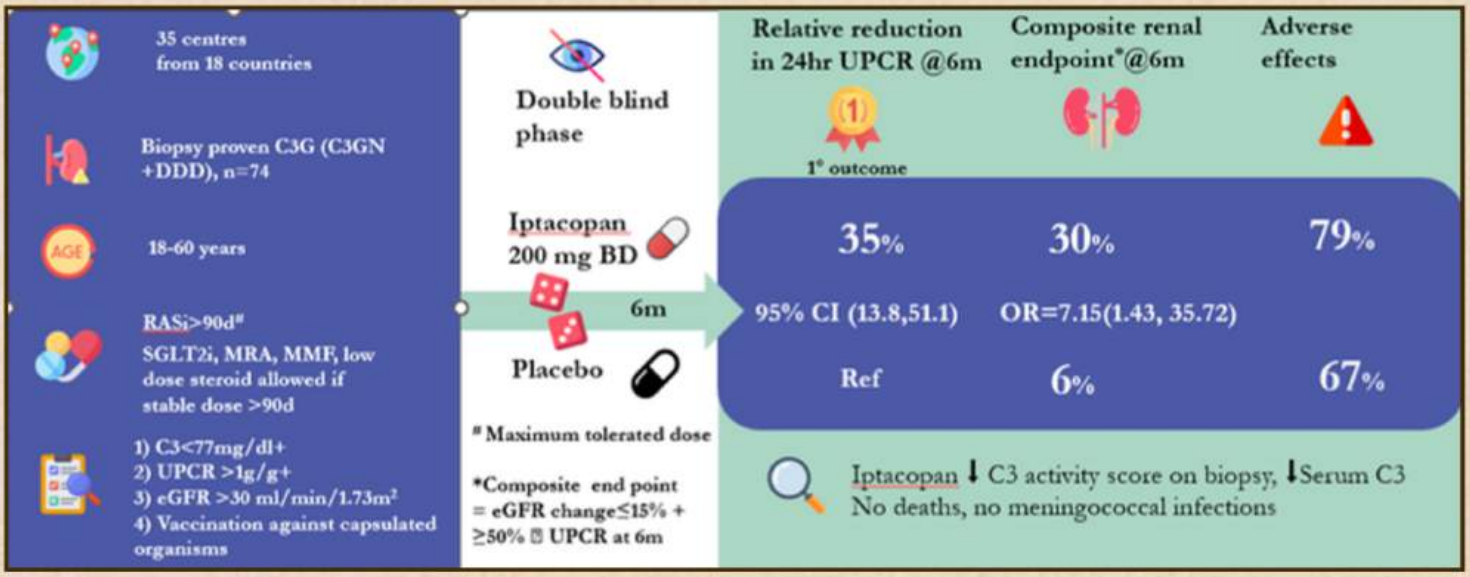
This difference has predictable implications:

- **Site of blockade:** pegcetacoplan has a more proximal, central block and therefore may produce larger and faster reductions in C3 activation products and tissue C3 deposition in some patients. Reported UPCR reductions with pegcetacoplan (VALIANT, ≈68% at 26 weeks) appear numerically larger than the 35% relative reduction reported for iptacopan at 6 months, though cross-trial comparisons are imperfect due to differences in baseline proteinuria, inclusion criteria, age ranges, duration, and background therapy.

- **Benefit v/s Risk:** Iptacopan's alternate-pathway selectivity could theoretically preserve some classical/lectin-mediated host defense and immune functions; pegcetacoplan's central C3 blockade is broader and may carry different infection or immunologic risks.

CONCLUSION

Targeting complement factor B via Iptacopan offers genuine hope for patients with C3 glomerulopathy, marking the first time a therapy tackles the disease's underlying mechanism. With ongoing investigation, this strategy may herald a new era of disease-modifying treatments for those affected by this previously refractory kidney disease.



FDA approved in March 2025 to reduce proteinuria in adults with C3G. First and only treatment approved for this condition.

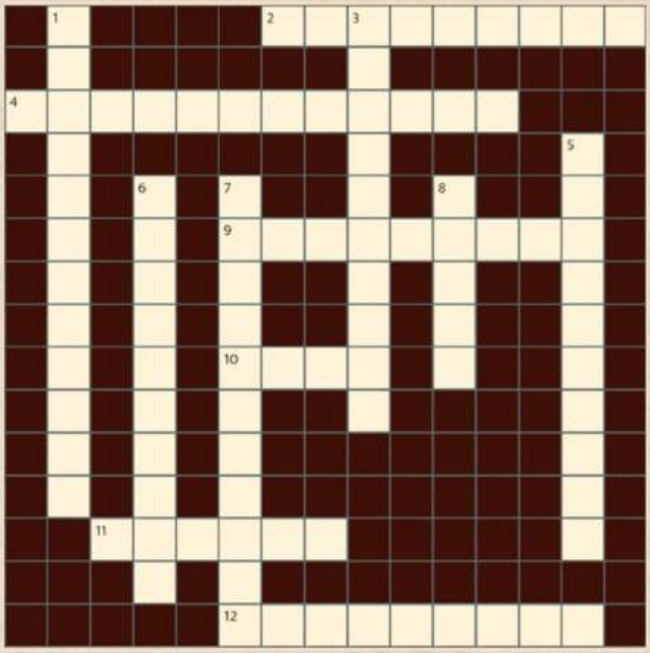
Kavanaugh D et al, Lancet 2025. Visual abstract by Dr Pallavi Prasad @DrPallaviPrasad

KK Crossword

VOL 4, ISSUE 4
OCTOBER TO DECEMBER 2025

NEO NEPHRONS

DR PALLAVI, DR SUBASHRI, DR SANDHYA, DR AMBILY



ACROSS

2 This trial compared mortality benefit of bicarbonate therapy versus control in AKI with severe acidosis

4 _____ is an IL-6 inhibitor for patients with cardiovascular disease and chronic kidney disease (CKD) who have inflammation.

9 This drug was tested in C3GN in the APPEAR trial and in IgAN in the APPLAUSE trial

10 This protein can be considered a marker for DDD in C3 glomerulopathy

11 This trial showed a mortality benefit of fish oil versus corn oil in dialysis patients

12 This multicenter, unblinded, randomized superiority trial studied conservative dialysis strategy and kidney function recovery in dialysis-requiring acute kidney injury

DOWN

1 In October 2025, the FDA approved this drug for the treatment of active Lupus Nephritis

3 Till date, the longest surviving xenotransplant kidney in a human is from which species?

5 This study showed that, in CKD with DM, Finerenone-Empagliflozin combination led to greater reduction of UACR than either treatment alone

6 _____ is a double-blind, randomized, single-centre, placebo-controlled trial assessing efficacy of inorganic nitrate in CIN prevention in at-risk patients presenting with ACS

Solve the crossword ONLINE

7 Name the Renal Autologous Cell Therapy being tested in a phase 2 RCT to slow the progression of diabetic CKD

8 Mary E Brunkow and Fred Ramsdell, (Nobel prize 2025) discovered that mutation in this gene is associated with the autoimmune disease, IPEX

KK Crossword Answers @ Pg 32

Renal TMA in TAFRO Syndrome: A Form of Idiopathic Multicentric Castleman Disease

Revealing Rarest of Rare

DR ANJALI KRISHNANANDAN
Government Medical College, Kottayam

TAFRO syndrome is an extremely rare form of idiopathic MCD characterised by thrombocytopenia, anasarca, fever, reticulin fibrosis on bone marrow biopsy and organomegaly. Renal involvement is also a common presentation in patients with TAFRO syndrome. MPGN like injury, and thrombotic microangiopathy (TMA) are the most reported histopathological findings of renal biopsy. Several molecular mechanisms like abnormal production of IL-6, VEGF, have been postulated. Proposed mechanism of renal thrombotic microangiopathy in a patient with TAFRO syndrome is circulating autoantibodies or cytokines produced by specific lymphocyte clones within lymphadenopathy interfere with VEGF diffusion flux or directly act on vascular endothelial cells causing damage. Elevated serum VEGF breaks the concentration gradient of VEGF across the glomerular basement membrane, impeding the nursing effect of VEGF produced by podocytes. Severe diuretic-resistant anasarca with mild proteinuria and severe glomerular endotheliopathy were common characteristics of renal dysfunction due to TAFRO syndrome.

CASE PRESENTATION

We report a 39 year old male native of Bihar, with no past medical history and addictions presenting with complaints of bilateral lower limb swelling for the past 3 years, frothing of urine 6 months, and abdominal distension for 3 months. Pedal edema was insidiously progressing over the last 6 months and involved the whole of both lower limbs. He had a history of loss of appetite and weight for the last 6 months along with low grade fever once or twice in a month for that period. He had no jaundice, malena, hematemesis, no gross hematuria and decreased output.

On examination is emaciated with BMI 17.6, pallor and bilateral pitting pedal edema present and bilateral cervical axillary inguinal and left supraclavicular enlarged firm in consistency and mobile. Vitals stable with BP 140/90 mmHg, No other peripheral signs of CLD, no external markers of tuberculosis. Systemic examination of the

abdomen revealed hepatosplenomegaly with shifting dullness and chest examinations bilateral reduced breath sound with stony dullness suggestive of pleural effusion. Blood investigation at presentation

Blood investigation at presentation		
Hb: 8.5. ESR: 47	TC: 9440	PLT: 2.46 L
TP/ ALB: 7.3/ 3.3	OT/PT: 24/28	TB/CB: 0.4/ 0.16
RFT: 34/0.9	PT INR , APTT: 14.8/ 34	Total cholesterol 150 CRP: 103
Urine routine Albumin: 3+ RBC: 10-12 PC: 1-2 No cast	USG abdomen Liver enlarged size 17.8 cm, normal echoes Portal vein normal caliber, normal colour flow Spleen enlarged, 13 cm Moderate ascites Right kidney: 10.3 cm Left kidney: 10.6 cm Bilateral increased echoes and preserved CMD	Echo: No RWMA good biventricular function
24 hour urine protein: 3.4 gram/ 2.2 liter volume	Ascitic fluid study: TC 60 cells (N 80 L 20) SAAG: 1.14 Protein: 4.2 high Ada negative Culture sterile Cytology no abnormal cells Afb and gram stain negative OGD scopy: moderate corpus gastritis Colonoscopy: normal	Anemia workup Smear: normocytic normochromic anemia Serum LDH: normal Recticulocyte count: normal Dct negative Stool occult blood: negative

Patient underwent renal biopsy for nephrotic range proteinuria, active urinary sediments CECT abdomen thorax for malignancy workup: intra abdominal nodes of paracaval, para aortic, aortocaval, iliac, and inguinal largest 13.5mm. Hepatoslenomegaly, moderate ascites, bilateral pleural effusion.

Smear showed dimorphic anemia, and thrombocytopenia with no fragmented cells. Serum LDH and reticulocyte count were normal. Patient had intermittent fever spikes through the week. Bone marrow showed hypercellular marrow with megakaryocytes and reticulin fibrosis. Lymph node biopsy done suggestive of Castleman disease with IHC favouring Castleman disease hyaline vascular type.

For the evaluation of Castleman disease - HHV8 staining on lymph node biopsy was negative, retroviral negative, no autoimmune markers positive, no evidence of POEMS syndrome.

	Presentation	7th day	10th day
Hb	8.5	7.9	7.2
Mcv	88		
TC	8500	4450	5600
Plt	1.6 lakh	92000	60000
Rbs	104		
RFT	34/0.9	101/2.25	169/6.1
SE	132/ 4.4	130/3.9	133/4.5
TB/CB	0.5/ 0.2		
TP/Alb	6.5/3.3		
OT/PT	24/ 28		

Patient routines while awaited results over a week

So it was a HHV 8 negative, idiopathic MCD, with TAFRO symptoms such as thrombocytopenia, anasarca, fever, reticulin fibrosis on bone marrow and organomegaly.

Hence the patient was started on pulse steroid and later to oral steroid and for the targeted therapy, anti IL-6 therapy was considered. But considering the frailty and based on hematologist's advice rituximab was given weekly once for 4 weeks. Post therapy over a month, the patient's blood counts and renal dysfunction normalised.

Idiopathic MCD is an uncommon disorder with unique clinical features. TAFRO syndrome is an extremely rare subtype of idiopathic MCD with a specific clinical presentation. The diagnosis and management of these disorders are challenging. Comprehensive and collaborative research work could provide an opportunity to clarify the pathophysiologic mechanism of these unique diseases. Endothelial changes mediated via interleukin (IL)-6 and vascular endothelial growth factor (VEGF) that lead to vascular hyperpermeability and water leakage might contribute to anasarca, because molecular-targeting therapy directed against IL-6 or VEGF improved renal dysfunction and severe endothelial damage.

Keywords

TAFRO syndrome; idiopathic multicentric Castleman disease (MCD); IL-6; VEGF; renal thrombotic microangiopathy (TMA)

Renal Cortical Necrosis: A Rare, Life-Altering Complication of Plasmodium vivax Malaria

DR AKSHATA AGRAWAL
DR NIKHIL SAXENA

A 19-year-old female presented with high-grade fever and multiple episodes of vomiting for two days. There was no history of hematuria, cola-colored urine, dysuria, hypotension, drug intake, arthralgia, rash, or bleeding from any site. During hospitalization she developed oliguria, which progressed to anuria by day 3. Laboratory evaluation confirmed *Plasmodium vivax* malaria. Her hemoglobin dropped from 12.5 g/dL to 6.7 g/dL, and serum creatinine rose from 1.1 mg/dL to 6.78 mg/dL over three days. Peripheral smear showed hypochromic microcytic RBCs with occasional fragmented cells. ANA was 1+ mixed pattern, LDH was 828 IU/L, and complement C3 levels were normal. [Table 1]

The patient developed fluid overload and refractory metabolic acidosis, requiring initiation of hemodialysis. A renal biopsy was performed to evaluate non-recovering AKI.

RENAL BIOPSY FINDINGS

Twenty glomeruli were sampled, of which approximately 80% showed global tuft sclerosis. There was coagulative necrosis of adjacent tubules, and several viable arteries demonstrated luminal thrombotic occlusion - findings consistent with renal cortical necrosis. The necrotic process involved 40 - 45% of the sampled cortical area. Immunofluorescence was negative.

A tunneled cuffed catheter was inserted, and the patient was discharged on maintenance hemodialysis thrice weekly. Genetic testing for thrombotic microangiopathy could not be performed due to financial limitations.

Traditionally, P. vivax malaria has been considered relatively benign compared to P. falciparum. However, emerging data show that P. vivax can present with severe complications including cerebral malaria, hepatic dysfunction, ARDS, thrombocytopenia, anemia, and acute kidney injury. AKI in malaria may result from hemodynamic instability, tissue hypoxia, interstitial nephritis, mesangioproliferative glomerulonephritis, or pigment-induced tubular injury.

R Kumar et al. reported a 17-year-old female with P. vivax malaria who developed hematuria and fluid overload. Renal biopsy showed coagulative necrosis in 9 of 15 glomeruli, with tubular RBC casts, and negative immunofluorescence. She was discharged with a serum creatinine of 2.6 mg/dL.

Naqvi et al. analyzed 5,623 patients with acute kidney injury; 673 (11%) had malaria, including 109 cases of P. vivax. Renal replacement therapy was required in 82 patients; complete recovery occurred in 69 patients, while 14 died. Renal biopsy was performed in 15 patients and showed acute tubular necrosis (6), cortical necrosis (4), tubulointerstitial nephritis (2), and crescentic GN (2). Among the four patients with cortical necrosis, three had partial recovery while one progressed to end-stage kidney disease.

Management of malaria-associated AKI includes early initiation of appropriate antimalarial therapy, judicious fluid resuscitation, diuretics where indicated, and timely renal replacement therapy. Nephrotoxic agents such as ACE inhibitors, NSAIDs, aminoglycosides, and certain cephalosporins should be avoided. Modern intensive care practices, early dialysis initiation, and avoidance of nephrotoxic exposures are central to preventing progression to irreversible renal damage.

Cortical necrosis, although rare, is a catastrophic complication of P. vivax malaria and should be strongly considered in patients with severe or non-recovering AKI.

Table 1: Trend of lab investigations and their clinical implication

Parameter	Value / Trend	Clinical Interpretation
Hemoglobin	12.9 → 6.7 → **5.5** → 8–9 g/dL	Significant anemia likely from hemolysis + bone marrow suppression Received 3 unit PRC transfusion
Platelets	**12k** → 45k → 75k → 1.5–3.5 lakh	Severe thrombocytopenia early; recovery with disease control
BUN (mg/dl)	13 → **98** → Dialysis dependent	Sharp rise indicating severe AKI; fluctuates with dialysis
Creatinine (mg/dl)	1.1 → **6.7** → Dialysis dependent	Marked AKI, partial improvement, later deterioration; consistent with cortical necrosis
Liver Enzymes (AST/ALT)	21/11 → 25/12 U/L	Mild rise; no significant hepatic injury
Bilirubin (T/D)	0.4 / 0.1 mg/dL	Normal; rules out hemolytic jaundice or hepatic involvement
Urine Protein	**2+**	Suggestive of tubular/ischemic injury; not nephrotic range
Urine RBCs / Casts	Negative	No evidence of GN or hemoglobinuric pigment nephropathy

Parameter	Value / Trend	Clinical Interpretation
Peripheral Smear	Microcytic, hypochromic RBCs; fragmented cells	**Suggests hemolysis** and microangiopathic component
ANA	1+ mixed pattern	Low-titer nonspecific positivity; **unlikely autoimmune cause**
C3 Complement	121 mg/dL	**Helps exclude immune complex GN** or complement-mediated TMA
LDH	828 IU/L	High; **supports hemolysis or tissue necrosis**
Malaria Test	**P. vivax positive**	Confirms secondary cause of AKI
Urine Cultures	No growth	
Blood Cultures	No growth	
Renal Biopsy	**40 - 45% cortical necrosis; thrombotic occlusion**; 80% global sclerosis; IF negative	Diagnostic of **renal cortical necrosis**; poor recovery expected

Unforeseen Aftermath of Diarrhea: Myoglobin Cast Nephropathy Unveiled

DR NAMAN JAIN
DR MAYURI TRIVEDI

ABSTRACT

BACKGROUND

Rhabdomyolysis is a potentially life-threatening condition that may lead to acute kidney injury (AKI) due to myoglobin-induced nephropathy. Multiple factors including electrolyte disturbances, hypovolemia and endocrine disorders can contribute to its development.

CASE PRESENTATION

We report the case of a 58-year-old female with no prior comorbidities who presented with acute gastroenteritis with AKI. On admission, she was in shock with anuria, metabolic acidosis, and severe hypokalemia (serum K 2.6 mmol/L). Laboratory evaluation revealed elevated creatinine, hyperuricemia, hyperphosphatemia. Despite adequate hydration and inotropic support, the patient remained anuric, metabolic acidosis worsened and also developed fluid overload, requiring initiation of hemodialysis.Additional workup confirmed newly diagnosed diabetes mellitus and hypothyroidism.Renal biopsy done in view of non recovering AKI revealed acute tubular injury with coarse granular pigmented casts positive for myoglobin, consistent with myoglobin cast nephropathy. Over subsequent days, urine output improved and serum creatinine began declining. With supportive therapy, the patient's renal function gradually recovered, with serum creatinine declining to 1.9 mg/dL at 1 month and 1.1 mg/dL at 2 months.

CONCLUSION

This case illustrates rhabdomyolysis-induced myoglobin cast nephropathy precipitated by severe hypokalemia, hypovolemia, and hypothyroidism. Clinicians should maintain a high index of suspicion for rhabdomyolysis in patients presenting with unexplained AKI in the setting of diarrheal illness and metabolic derangements, as timely recognition and intervention are essential for renal recovery.

Unforeseen Aftermath of Diarrhea: Myoglobin Cast Nephropathy Unveiled

INTRODUCTION

Rhabdomyolysis is the breakdown of skeletal muscle fibers leading to release of intracellular myoglobin into the circulation. While it can present as asymptomatic elevations of muscle enzymes to life-threatening complications like acute kidney injury (AKI) due to myoglobin-induced tubular toxicity and cast formation [1,2]. Common precipitating factors include trauma, strenuous exercise, drugs, electrolyte disturbances, and endocrine abnormalities [3,4]. Renal biopsy, although not routinely required, may provide a definitive diagnosis in patients with unexplained or nonresolving AKI. Here, we present a case of biopsy-proven myoglobin cast nephropathy in a previously healthy female who developed severe AKI following acute gastroenteritis with hypokalemia, hypovolemic shock, and hypothyroidism.

CASE PRESENTATION

A 58-year-old female with no prior comorbidities (no history of diabetes mellitus, hypertension, coronary artery, cerebrovascular, or kidney disease) presented with watery diarrhea (20–30 episodes/day), multiple episodes of non-bilious vomiting, reduced urine output, generalized body ache and lethargy. On admission, the patient was hypovolumic and in circulatory shock—her blood pressure was unrecordable, central venous pressure was zero.

Initial laboratory evaluation showed: hemoglobin 17.7 g/dl, total leukocyte count 11,000/μL, platelet count 3.19 × 105/μL, serum sodium 135 mmol/L, serum potassium 2.6 mmol/L, total bilirubin 0.5 mg/dl, SGOT 28 U/L, SGPT 32 U/L, serum calcium 8.7 mg/dl, phosphate 8.8 mg/dl, uric acid 19.1 mg/dl, and serum creatinine 3.9 mg/dl. These findings were consistent with AKI, severe hypokalemia, metabolic acidosis, hyperuricemia, and hyperphosphatemia. [Table 1]

Over the next three days, the diarrheal episodes resolved. Stool cultures including the hanging-drop test were negative.Despite adequate hydration, inotropic support, and hemodynamic stabilisation, the patient remained anuric. Urine output did not improve even after a trial of furosemide. Serum creatinine rose to 8.1 mg/dl, metabolic acidosis worsened and the patient developed fluid overload requiring hemodialysis.

Evaluation for rapidly progressive glomerulonephritis was negative (Anti-GBM, Anti-MPO, Anti-PR3 ELISA, ANA). She was also noted to have elevated fasting and postprandial glucose levels; HbA1c measured at 6.8%, leading to a new diagnosis of diabetes mellitus without retinopathy. Thyroid evaluation revealed TSH of 11.26 μIU/ml, establishing a diagnosis of hypothyroidism. Kidney ultrasonography demonstrated normal-sized kidneys with preserved corticomedullary differentiation.

The patient was continued on alternate day hemodialysis for next ten days and a renal biopsy was performed in view of non recovering acute kidney injury. Light microscopy revealed non-proliferative glomeruli and diffused severe acute tubular injury.The tubular compartment contained coarse granular pigmented casts that stained positive for myoglobin on immunohistochemistry. Immunofluorescence was negative for significant immune deposits. [Image 1]

The diagnosis of myoglobin cast nephropathy was established on renal biopsy with immunohistochemical staining for myoglobin, which is considered confirmatory. Additional biochemical markers such as creatine phosphokinase, though useful, were not essential for

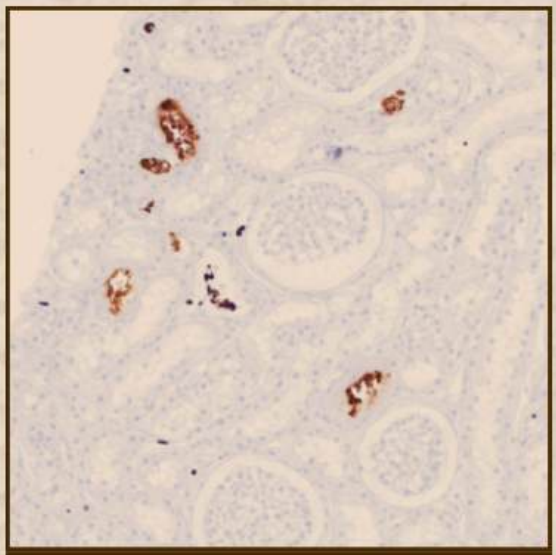


Image 1: Histopathology section showing coarse granular, pigmented casts positive for myoglobin on Immunohistochemistry

Gradually the patient's urine output improved over the next week thus the hemodialysis was withheld and serum creatinine also began trending downward. The patient was discharged in stable condition at serum creatinine of 3.2mg/dl and adequate urine output. On follow-up serum creatinine further reduced to 1.9 mg/dl by next month and 1.1 mg/dl by the end of third month - indicating near-complete recovery of renal function.

Table 1: Lab investigations of patient on presentation and on follow up

Laboratory Parameter	On Admission	At Discharge	Follow-up (1 Month)	Follow-up (3 Months)
Sodium (mmol/L)	135	136	138	140
Potassium (mmol/L)	2.6	3.8	4.1	3.9
Creatinine (mg/dl)	3.9	3.2	1.9	1.1
Uric Acid (mg/dl)	19.1	8	5.6	5.2
Phosphate (mg/dl)	8.8	5.8	4.2	3.8
Calcium (mg/dl)	8.7	8.8	9.1	9
pH / Acid–Base Status	Metabolic acidosis	Corrected	Normal	Normal
TSH (μIU/mL)	11.26	—	5.8	4.2
HbA1c (%)	6.8	—	—	—

DISCUSSION

In our case, several factors could have contributed to rhabdomyolysis. Severe hypokalemia is a well-recognized cause of rhabdomyolysis; potassium depletion leads to impaired muscle perfusion, membrane excitability defects, and increased susceptibility to ischemia-induced injury [5,6]. In addition, prolonged diarrhea and circulatory shock resulted in profound hypovolemia, further predisposing the patient to muscle ischemia. Metabolic derangements including acidosis and hyperphosphatemia may also have aggravated skeletal muscle injury [7]. Hypothyroidism, diagnosed during hospitalization, has also been implicated as a rare precipitant of rhabdomyolysis due to impaired muscle energy metabolism and increased susceptibility to injury [8] [Table 2]. Thus, in our patient, the combined effect of hypokalemia, severe volume depletion with shock, and underlying hypothyroidism likely resulted in rhabdomyolysis, leading to myoglobin cast nephropathy. Early recognition and adequate supportive care were crucial for renal recovery.

CONCLUSION

This case highlights rhabdomyolysis-induced AKI with biopsy-proven myoglobin cast nephropathy precipitated by hypokalemia, hypovolemia and shock from diarrheal illness and underlying hypothyroidism. Early recognition, prompt hemodynamic stabilization, electrolyte corrections and renal replacement therapy were crucial in ensuring renal recovery. In patients presenting with unexplained and non resolving AKI, particularly with risk factors such as severe electrolyte

Table 2: Factors contributing to development of Rhabdomyolysis

Contributing Factor	Mechanism	Impact
Hypokalemia	Impaired muscle perfusion, membrane excitability defects	Muscle injury → rhabdomyolysis
Hypovolemia + Shock	Ischemia of muscle and kidneys	Muscle breakdown + AKI
Metabolic Acidosis / Hyperphosphatemia	Increased cellular stress	Exacerbates muscle injury
Hypothyroidism	Impaired muscle energy metabolism	Increased susceptibility to rhabdomyolysis
Myoglobin Release	Direct tubular toxicity, cast formation	**Myoglobin cast nephropathy → AKI**

disturbances and hypothyroidism, rhabdomyolysis should be considered as a differential diagnosis. Timely intervention can significantly improve outcomes and prevent long-term renal sequelae.

ACKNOWLEDGEMENT

Renal biopsy reporting was done by Dr Alok Sharma Director, Renal Pathology and Electron Microscopy and Head (R&D) at Dr Lal PathLabs

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Crossword

ACROSS

2 BICARICU2: This French multicentre trial randomised 640 patients with AKI and severe acidosis pH <7.2 to 4.2% sodium bicarbonate to target a pH of 7.3 versus control. The primary outcome of 90 day mortality showed no significant difference between the two arms (62.1% vs 67.1%, absolute diff 0.4, 95% CI, −7.2 to 8.0) Amongst secondary outcomes, kidney replacement therapy was used in 35% in bicarbonate group versus 50% in controls (absolute difference, −15.5; 95% CI, −23.1 to −7.8)

4 ZILTIVEKIMAB: A novel anti–IL-6 ligand antibody, in patients on hemodialysis with rs855791, a single nucleotide polymorphism of the TMPRSS6 gene that is hypothesized to heighten susceptibility to IL-6–mediated inflammatory effects

9 IPTACOPAN: This is an oral highly selective factor B inhibitor. It is now FDA approved for use in adults with C3GN as per APPEAR trial and has accelerated approval for use in IgAN as per evidence from APPLAUSE trial

10 ApoE: Laser microdissection of deposits in DDD, demonstrated high levels of ApoE. IHC for ApoE can be used as a marker for DDD in cases of C3G. Dense deposits also have 6-9 fold higher levels of deposition of terminal complement pathway proteins versus C3 glomerulonephritis

11 PISCES: This multicentric trial randomised 1288 patients on maintenance hemodialysis in a 1:1 ratio to daily supplementation with fish oil (4g/day) or corn oil. The rate of serious cardiovascular events (primary endpoint)at 3.5 years of follow-up was significantly lower in the fish-oil group than in the placebo group (hazard ratio, 0.57; 95% CI], 0.47 to 0.70).

12 LIBERATE-D: The primary study end point was unadjusted kidney function recovery at hospital discharge, defined as being alive and not receiving dialysis, with at least 14 consecutive days without dialysis (including after discharge). Two prespecified key secondary end points were the number of dialysis sessions per week and the number of dialysis-free days to day 28. A conservative dialysis strategy in dialysis-requiring acute kidney injury resulted in a shorter time to and higher rates of recovery of kidney function in the unadjusted analysis. Given uncertainty regarding the estimated effect size, this approach should be tested in a larger study population.

DOWN

1 OBINUTUZUMAB: Based on data from the phase II NOBILITY trial and the phase III REGENCY trial, Obinutuzumab was approved for the treatment of active LN on standard therapy - only the 3rd drug approved specifically for LN after Belimumab and Voclosporin.

3 CHIMPANZEE: Early experiments in xenotransplantation utilised kidneys from non-human primates. In the 1960s, Dr. Keith Reemtsma conducted 13 kidney transplants from chimpanzees to humans with one patient, Edyth Parker, surviving almost 9 months. Tim Andrews holds the record for longest surviving pig kidney transplant till date with the graft being removed at 271 days in October 2025.

5 CONFIDENCE: patients with CKD (eGFR 30-90ml/min/1,73m2), albuminuria (UACR 100 to ≤5000mg/g), and type 2 DM, who were already on RAAS inhibitor, were randomised to receive finerenone, empagliflozin, or a combination of both. At day 180, reduction in UACR with combination therapy was 29% greater than that with finerenone alone and 32% greater than that with empagliflozin alone.

6 NITRATE-CIN: In patients at risk of renal injury undergoing coronary angiography for ACS, a short (5 day) course of once-daily inorganic nitrate reduced CIN, improved kidney outcomes at 3 months, and MACE events at 1 year compared to placebo.

7 RILPARENCEL: Rilparencel is an investigative autologous cell product composed of bioactively selected renal cells (SRC) isolated from a participant's own kidney cortex tissue, which takes part in kidney repair and restoration. Eligible participants with type 1 or 2 diabetes and CKD, eGFR 20 - 50 mL/min/1.73 m2, urine albumin-to-creatinine ratio (UACR) 30–5,000 mg/g, hemoglobin >10 g/dL, and glycosylated hemoglobin <10% were enrolled. After a percutaneous kidney biopsy and bioprocessing ex vivo expansion of selected renal cells, participants were randomized 1:1 into two cohorts determined by the dosing scheme. Cohort 1 receives 2 cell injections, one in each kidney 3 months apart, and cohort 2 receives one injection and the second dose only if there is a sustained eGFR decline of ≥20 mL/min/1.73 m2 and/or UACR increase of ≥30% and ≥30 mg/g, confirmed by re-testing.

8 FOXP3: Mary E. Brunkow and Fred Ramsdell discovered the mutation in the FOXP3 gene in Scurfy mice and mutation in the human equivalent of this gene is associated with IPEX and were awarded the Nobel prize for Physiology or Medicine in 2025 (with Shimon Sakaguchi)

Shout out... Fastest Fingers

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Dr G P Preeti, Delhi

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