Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/medical-industry-feature/the-role-of-april-and-the-4-hit-process-in-the-pathogenesis-of-iga-nephropathy/29539/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

The Role of APRIL and the 4-Hit Process in the Pathogenesis of IgA Nephropathy

ReachMD Announcer:
You're listening to ReachMD.

This medical industry feature, titled "The Role of APRIL and the 4-Hit Process in the Pathogenesis of IgA Nephropathy," is sponsored by Otsuka. And now, here's Dr. Edgar Lerma and Dr. Luis Vélez.

Dr. Lerma:
Coming to you live from Houston, Texas at ASN Kidney Week 2025, this is ReachMD. I'm Dr. Edgar Lerma, a Clinical Professor of Medicine at the University of Illinois Chicago. I'm joined today by my colleague, Dr. Luis Vélez, and together, we'll be discussing the role and clinical relevance of APRIL in the 4-hit process of IgA nephropathy.

I'm looking forward to our conversation, Dr. Vélez.

Dr. Vélez:
Likewise, Dr. Lerma. Glad to be here.

Hi everyone, my name's Luis Vélez, and I am a nephrologist with the South Texas Renal Care Group in San Antonio, Texas. I'm very excited to be here to discuss this very important topic, IgA Nephropathy. Dr. Lerma?

Dr. Lerma:
So let's jump right in. Now we know IgA nephropathy, or IgAN, is a progressive, immune-mediated, chronic kidney disease.[1,2] In years past, it's been thought of as a slow progressing disease, because many patients are asymptomatic until significant damage to or loss of nephrons has already occurred.[1,3-5]

Prognostic factors including proteinuria, decline in eGFR and these are essential to monitoring disease progression in IgAN.[2,6,7] But even so, typically more than 50 percent of nephrons are already damaged at the time of diagnosis.[4]

So there is a real need to improve detection and enable earlier diagnosis by kidney biopsy to help preserve nephrons and maintain kidney function.

Dr. Vélez:
I couldn't agree with you more, Dr. Lerma. nephron and kidney damage happens before eGFR decline is detected, which is why IgAN is so difficult to catch early.[4,5]

Usually by the time nephrology sees these patients, the damage has already been done. I believe the inflammatory process has likely been going on for months, sometimes even years, especially if they didn't have symptoms. So our therapeutic window becomes very small.

IgAN tends to affect younger people.[3] And if you're in your 20s or 30s or even 40's and feeling fine, you're probably not rushing to see a doctor. It's that "if it ain't broken, don't fix it" mentality, so that may be the cause for some of the delay in diagnosis that we see.

But the reality is that, in my experience, a majority of patients are at stage three, four, or five when I see them in the office.

At that point, when we look at the histopathological findings in biopsies from patients with IgAN, we can see the damage to the

glomeruli.[8,9]

Proliferation of cells in the mesangium and endocapillaries, reflecting acute immune activity and inflammation.[10,11] The development of crescents, indicating severe, active injury,[12,13] and then progressive scarring, such as segmental glomerulosclerosis, tubular atrophy and interstitial fibrosis of cortical area, which represents irreversible chronic damage.[10]

So we're able to classify both active inflammation and chronic scarring, and the MEST-C system gives clinicians a structured way to assess that.[10]

To understand the pathogenesis of the disease, we need to look at the immune processes driving this damage caused by the disease and that brings us to the 4-hit hypothesis, which shows why and how IgAN progresses on the immunological level.[3,7,13-18]

So let's take a closer look at this process. It starts with the body making a pathogenic form of IgA1, called galactose-deficient IgA or Gd-IgA1—that is hit 1. Then, in hit 2, the immune system reacts by making antibodies againstgalactose-deficient IgA 1 . Those two things together set up hit 3, where the autoantibodies bind to galactose-deficient IgA 1and form pathogenic immune complexes. Finally, in hit 4, those complexes are deposited in the kidney's filtering units, the mesangium, triggering inflammation which causes mesangial and endocapillary hypercellularity.[10,14]

And that's where the connection really comes together. The immune complexes deposited during hit 4 correspond to what we see as high M and E score in the MEST-C scoring system, showing active inflammation. Over time, as inflammation continues, this leads to scarring and structural damage, which show up as higher S and T scores, and can ultimately lead to kidney failure.[10,14]

But there's been more discussion into key drivers of the 4-hit process, specifically before hit-1. Can you tell us about those Dr. Lerma?

Dr. Lerma:
Yes, actually, a proliferation-inducing ligand, also called APRIL, has been identified as a key driver in initiating the 4-hit process of IgAN.

But to understand its role, we will have to take a step back to even before hit 1.

So APRIL mediates B cells switching antibody classes through TACI, or the transmembrane activator and calcium-modulator interactor, signaling and interacts with the B-cell membrane antigen, or BCMA, to protect plasma cell survival and both of these are responsible for producing the pathogenic Gd-IgA1 antibody.[19,20]

So by supporting B cells and plasma cells, APRIL helps sustain and promote the production of Gd-IgA1, and subsequently, the problematic immune complex formation.[19,21] Over time, this process fuels inflammation, fibrosis, and progressive kidney damage. This makes APRIL a key initiator and amplifier of the disease mechanism in IgAN.[14]

So, we actually see clinical evidence of this – higher levels of APRIL are associated with higher risk for end-stage kidney disease, or ESKD. Patients with IgAN have been shown to have elevated plasma levels of APRIL, which have been shown to correlate with Gd-IgA1 levels and may be associated with adverse kidney outcomes.[20,22]

And there's also genetic evidence, right?. A large, genome-wide association study, or GWAS, looked at over 10,000 patients with IgAN and 28,000 control participants. They found that two genes, APRIL and TACI, are linked to an increased risk of developing IgAN.[23,24]

So I personally believe that increasing awareness of key immunological drivers of IgAN progression will shape the understanding of this disease.

So, Dr. Vélez, now that we have a better understanding of this 4-hit process, how do you think this knowledge could impact how we think about managing IgAN?

Dr. Vélez:
Great question Dr. Lerma. When we think about treatment, our primary goal is to protect nephrons from the very start of diagnosis in order to preserve kidney function and avoid kidney failure.

The 2025 KDIGO guidelines bring a few important updates. They now recommend a more liberal kidney biopsy policy and aim for tighter control of proteinuria — specifically keeping it below 0.5 grams per day, and ideally under 0.3 grams per day — all while maintaining a stable eGFR.[25]

But one of the biggest shifts is the call to address both drivers of kidney damage at the same time. That means starting treatment not just with supportive care, which are things like controlling blood pressure, optimizing ACE inhibitors or ARBs, but encouraging healthy

lifestyle habits, and lowering cardiovascular risk as well. Also, therapies that reduce the production of galactose-deficient IgA 1 and preventing immune complex formation.[2,25]

Now that's my perspective. Dr. Lerma, what is your take on the therapeutic direction for IgAN in 2025?

Dr. Lerma:
Well I think that's a great summary. But remember, back in 2021, the KDIGO guidelines placed most of the emphasis on supportive care.[26]

Now, with the updated guidelines, there is a paradigm shift, we now recognize that both the chronic kidney disease process and the immune-mediated injury must be targeted together and earlier, depending on a patient's risk profile. Approaches that leverage supportive care, together with these therapies directed at inflammation and pathogenic IgA1 synthesis, represent a more comprehensive path forward.[4,25]

The challenge—and opportunity—now lies in integrating these advances into practice. We have to bridge what we now know from academic centers into real-world community nephrology, where most patients are actually managed. Until there are widely available therapies that target the underlying immune drivers of IgAN, there remains an unmet need in IgAN care.[4,27]

If we have novel therapies that may significantly impact the trajectory of this disease earlier on in the process, it behooves us to think that perhaps, identifying the patients even earlier than they present to the nephrologist would be ideal. So if you think about this, I think we should also educate the primary care providers who, in my opinion, I think they are the first line of defense as they are the ones who see the patients even earlier on. We have had what supportive care to offer these patients in the past, and we now have new therapies, backed by randomized controlled trials, that have been shown to actually curve the trajectory of the disease.[4]

Dr. Vélez:
I agree with you, Dr. Lerma. We also need to take what's known in academic medicine and bring it into everyday clinical practice. Many front-line nephrologists aren't familiar with what's happening on the academic frontlines, and so the urgency around changing how we approach IgAN hasn't really sunk in yet.

We're still trying to get the message out that IgAN isn't a slow progressing disease and it needs to be managed more aggressively. That means lower proteinuria targets and providing clarity on where these different therapies work.

Now we're just about out of time for today, but before we close, I'd like for us both to share some final thoughts from our discussion.

Why don't you start us off, Dr. Lerma?

Dr. Lerma:
I'd be happy to. I want to reiterate the importance of understanding the 4-hit process and the different players in IgAN progression. APRIL has been shown to be a key driver in Gd-IgA1 production.[3,7,14,15,21,28]

As nephrologists, whether you are in academician or a community nephrologist, we have novel therapies that are backed by evidence and science, that will enable the preservation of kidney function in these patients affected by IgAN, now recognized as a progressive autoimmune cause of CKD.[4]

So you know those are some of my takeaways, but I'll give you the final word, Dr. Vélez.

What key points would you like everyone tuning in today to take back to their practices?

Dr. Vélez:
Dr. Lerma, I think the biggest takeaway for physicians— and especially nephrologists—is I think that IgAN is no longer considered a benign disease. From my perspective, supportive care will always be important, but it can't be the whole story. Every patient we see is already at the "HIT 4" stage, meaning that the damage has occurred, and that's why it's crucial we treat it. The good news is that we now have more treatment options than ever before. So it's an exciting time, but we still need to shift our mindset and act with urgency.

So, clinicians should intervene earlier and more comprehensively by combining supportive strategies with treatments that address the root immunologic drivers.[4] That is how we move forward.

With those final thoughts in mind, I'd like to thank Dr. Lerma for sharing his insights on understanding the 4-hit process, and APRIL's role in driving IgAN progression.

Dr. Lerma, it was a pleasure speaking with you today and recording this live at ASN Kidney Week 2025.

Dr. Lerma:
You as well.

And I'd also like to thank Dr. Vélez for discussing the importance of early and more comprehensive intervention.

Dr. Vélez, it's been a pleasure.

ReachMD Announcer:
This program was sponsored by Otsuka. If you missed any part of this discussion, visit Industry Features on ReachMD.com, where you can Be Part of the Knowledge.

References:

1. Caster DJ, Abner CW, Walker PD, et al. Clinicopathological characteristics of adult IgA nephropathy in the United States. *Kidney Int Rep*. 2023;8(9):1792–1800.
2. Rajasekaran A, Julian BA, Rizk DV. IgA nephropathy: An interesting autoimmune kidney disease. *Am J Med Sci*. 2021;361(2):176–194.
3. Lai KN, Tang SC, Schena FP, et al. IgA nephropathy. *Nat Rev Dis Primers*. 2016;2:16001.
4. Barratt J, Lafayette RA, Floege J. Therapy of IgA nephropathy: time for a paradigm change. *Front Med (Lausanne)*. 2024;11:1461879.
5. Sharma A, Mucino MJ, Ronco C. Renal functional reserve and renal recovery after acute kidney injury. *Nephron Clin Pract*. 2014;127(1-4):94–100.
6. Cheung CKB, J. K. F.; Feehally, J. Evaluation and management of IgA nephropathy. *Clin Med*. 2012;12(6):s27–s31.
7. Cattran DC, Floege J, Coppo R. Evaluating progression risk in patients with immunoglobulin A nephropathy. *Kidney Int Rep*. 2023;8(12):2515–2528.
8. Haaskjold YL, Bjorneklett R, Bostad L, Bostad LS, Lura NG, Knoop T. Utilizing the MEST score for prognostic staging in IgA nephropathy. *BMC Nephrol*. 2022;23(1):26.
9. Pattrapornpisut P, Avila-Casado C, Reich HN. IgA Nephropathy: Core Curriculum 2021. *Am J Kidney Dis*. 2021;78(3):429–441.
10. Wendt R, Sobhani A, Diefenhardt P, Trappe M, Volker LA. An updated comprehensive review on diseases associated with nephrotic syndromes. *Biomedicines*. 2024;12(10)
11. Trimarchi H, Barratt J, Cattran DC, et al. Oxford Classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group. *Kidney Int*. 2017;91(5):1014–1021.
12. Shen XH, Liang SS, Chen HM, et al. Reversal of active glomerular lesions after immunosuppressive therapy in patients with IgA nephropathy: a repeat-biopsy based observation. *J Nephrol*. 2015;28(4):441–9.
13. Rodrigues JC, Haas M, Reich HN. IgA Nephropathy. *Clin J Am Soc Nephrol*. 2017;12(4):677–686.
14. Suzuki H, Kiryluk K, Novak J, et al. The pathophysiology of IgA nephropathy. *J Am Soc Nephrol*. 2011;22(10):1795–803.
15. Perše M, Večerić-Haler Ž. The role of IgA in the pathogenesis of IgA nephropathy. *Int J Mol Sci*. 2019;20(24)
16. Xu L, Yang HC, Hao CM, Lin ST, Gu Y, Ma J. Podocyte number predicts progression of proteinuria in IgA nephropathy. *Mod Pathol*. 2010;23(9):1241–50.
17. Floege J, Barbour SJ, Cattran DC, et al. Management and treatment of glomerular diseases (part 1): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2019;95(2):268–280.
18. Gutierrez E, Carvaca-Fontan F, Luzardo L, Morales E, Alonso M, Praga M. A personalized update on IgA nephropathy: A new vision and new future challenges. *Nephron*. 2020;144(11):555–571.
19. Cheung CK, Barratt J, Liew A, Zhang H, Tesar V, Lafayette R. The role of BAFF and APRIL in IgA nephropathy: pathogenic mechanisms and targeted therapies. *Front Nephrol*. 2023;3:1346769.
20. Zhai YL, Zhu L, Shi SF, Liu LJ, Lv JC, Zhang H. Increased APRIL expression induces IgA1 aberrant glycosylation in IgA nephropathy. *Medicine (Baltimore)*. 2016;95(11):e3099.
21. El Karoui K, Fervenza FC, De Vriese AS. Treatment of IgA nephropathy: A rapidly evolving field. *J Am Soc Nephrol*. 2024;35(1):103–116.
22. Han SS, Yang SH, Choi M, et al. The role of TNF superfamily member 13 in the progression of IgA nephropathy. *J Am Soc Nephrol*. 2016;27(11):3430–3439.
23. Kiryluk K, Sanchez-Rodriguez E, Zhou XJ, et al. Genome-wide association analyses define pathogenic signaling pathways and prioritize drug targets for IgA nephropathy. *Nat Genet*. 2023;55(7):1091–1105.
24. Yeo SC, Barratt J. The contribution of a proliferation-inducing ligand (APRIL) and other TNF superfamily members in pathogenesis and progression of IgA nephropathy. *Clin Kidney J*. 2023;16(Suppl 2):ii9–ii18.
25. KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A

Vasculitis (IgAV). *Kidney Int*. 2025;108(4S):S1–S71.
26. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases.*Kidney Int*. 2021;100(4S):S1–S276.
27. Pitcher D, Braddon F, Hendry B, et al. Long-term outcomes in IgA nephropathy. *Clin J Am Soc Nephrol*. 2023;18(6):727–738
28. Mathur M, Chan TM, Oh KH, et al. A PRoliferation-Inducing Ligand (APRIL) in the pathogenesis of immunoglobulin A nephropathy: A review of the evidence. *J Clin Med*. 2023;12(21)

 January 2026 21US25EBP0036