MULTI-HIT MODEL IN IgA NEPHROPATHY

THE ROLE OF COMPLEMENT ACTIVITY

IgA nephropathy (IgAN) is a highly heterogeneous disease with a wide array of clinical presentation that varies from patient to patient.

The pathophysiology of IgAN is made up of a multi-hit model which can include several inflammatory processes. In some cases, complement dysregulation is a key driver of glomerular inflammation in IgAN.

Here, we will discuss the role of the complement system in the pathogenesis of IgAN, kidney damage, and disease progression.

Deepen your understanding of IgAN with insights and perspectives from two thought leaders in nephrology, **Dr Lama Abdelnour** and **Dr Jared Hassler**.

IgA, immunoglobulin A.

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The perspectives provided within this white paper by Dr Abdelnour and Dr Hassler are their own and not reflective of their affiliations. The medical experts in this white paper have been paid by Novartis to provide their perspectives.

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THE DEMOGRAPHICS OF IgAN ARE HIGHLY HETEROGENEOUS

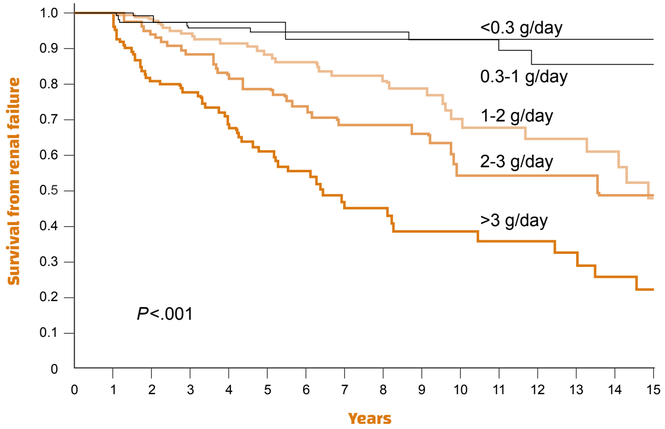
IgAN is the most common primary glomerulonephritis and greatly contributes to the burden of chronic kidney disease. It often affects younger adults between 20 and 30 years of age, who should be in the prime of their early adulthood. As many as 13 out of every million people in the United States are diagnosed with IgAN annually. Up to 40% of patients with IgAN develop worsening kidney function and progress to kidney failure within 10 to 20 years of diagnosis.

The heterogeneity of clinical and pathological features, as well as disease progression journey of IgA nephropathy, demands a tailored approach to care:

Clinical presentation:

- Asymptomatic: microscopic hematuria and/or proteinuria
- Symptomatic: gross hematuria, foamy urine, loin pain/discomfort, or nonspecific symptoms related to presence of hypertension and kidney decline
- Pathological features: The level of C3 accumulation in the glomeruli can vary between patients and may be an indicator of prognosis
- Disease progression: Progression to kidney failure following biopsy has ranged from ~5 years to ~30 years across ethnic populations

Renal survival by category of time-average proteinuria



Number of patients

<0.3 g/day	37	22	8	1
0.3-1 g/day	134	79	35	11
1-2 g/day	145	79	28	10
2-3 g/day	105	50	18	4
>3 g/day	120	44	13	6

Reich HN et al., Remission of proteinuria improves prognosis in IgA nephropathy, *J Am Soc Nephrol*, 18(12), 3179, https://journals.lww.com/jasn/fulltext/2007/12000/remission_of_proteinuria_improves_prognosis_in_iga.23.aspx

High proteinuria levels can indicate high risk for progression

According to a retrospective review of 542 patients with IgAN, time-averaged proteinuria was the most important predictor of renal function.*

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease Improving Global Outcomes.

*All patients who had biopsy-proven IgAN and were enrolled in the Toronto Glomerulonephritis Registry were considered (n=1373) and were excluded only when clinical data were incomplete (37 lacked proteinuria data, 18 lacked weight data), they were younger than 16 yr at presentation (n=54), they had 12 mo of follow-up (n=713), or they had a secondary cause of IgA deposition (n=9). A total of 542 patients were included in this retrospective Canadian review.

RISK OF PROGRESSION

High proteinuria levels can indicate high risk for progression. KDIGO guidelines define high-risk patients as those with proteinuria >0.75 to 1 g/day, despite three months of optimized supportive care.

Collaborating with an expert renal pathologist to interpret the pathology report is crucial to understanding a patient's unique prognosis and managing them accordingly. Initial management of IgA nephropathy, per KDIGO guidelines, involves supportive care, including a maximally tolerated dose of ACEi/ARB and lifestyle modifications.

For some of these high-risk patients, immunosuppressive therapy with glucocorticoids is an option. However, the risk of treatment-emergent toxicity with long-term use remains a concern.

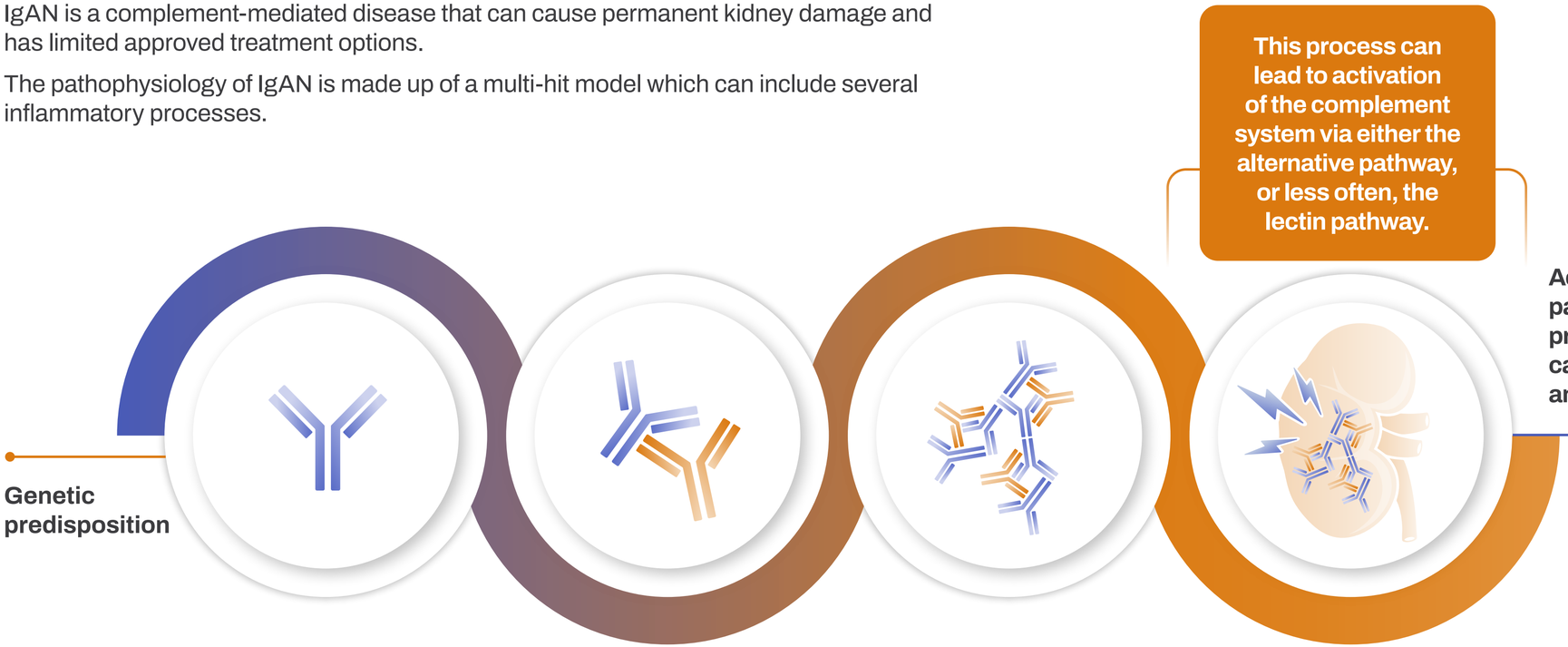
WHAT ARE SOME LIMITATIONS IN MANAGING IgAN?

"In my clinical experience, **predicting the disease's course and response to treatment can be challenging**. The efficacy of current treatments, such as ACEi or ARBs, varies among patients, and some individuals may not respond well to them." **— Lama Abdelnour, MD**

THE 4-HIT HYPOTHESIS IN IgAN PATHOPHYSIOLOGY

IgAN is a complement-mediated disease that can cause permanent kidney damage and has limited approved treatment options.

The pathophysiology of IgAN is made up of a multi-hit model which can include several inflammatory processes.



The 4-HIT hypothesis in IgAN pathophysiology

HIT 1

Increase in galactose-deficient IgA1 antibodies

HIT 2

Induction of autoantibody production

HIT 3

Autoantibodies and antibodies bind to form immune complexes

HIT 4

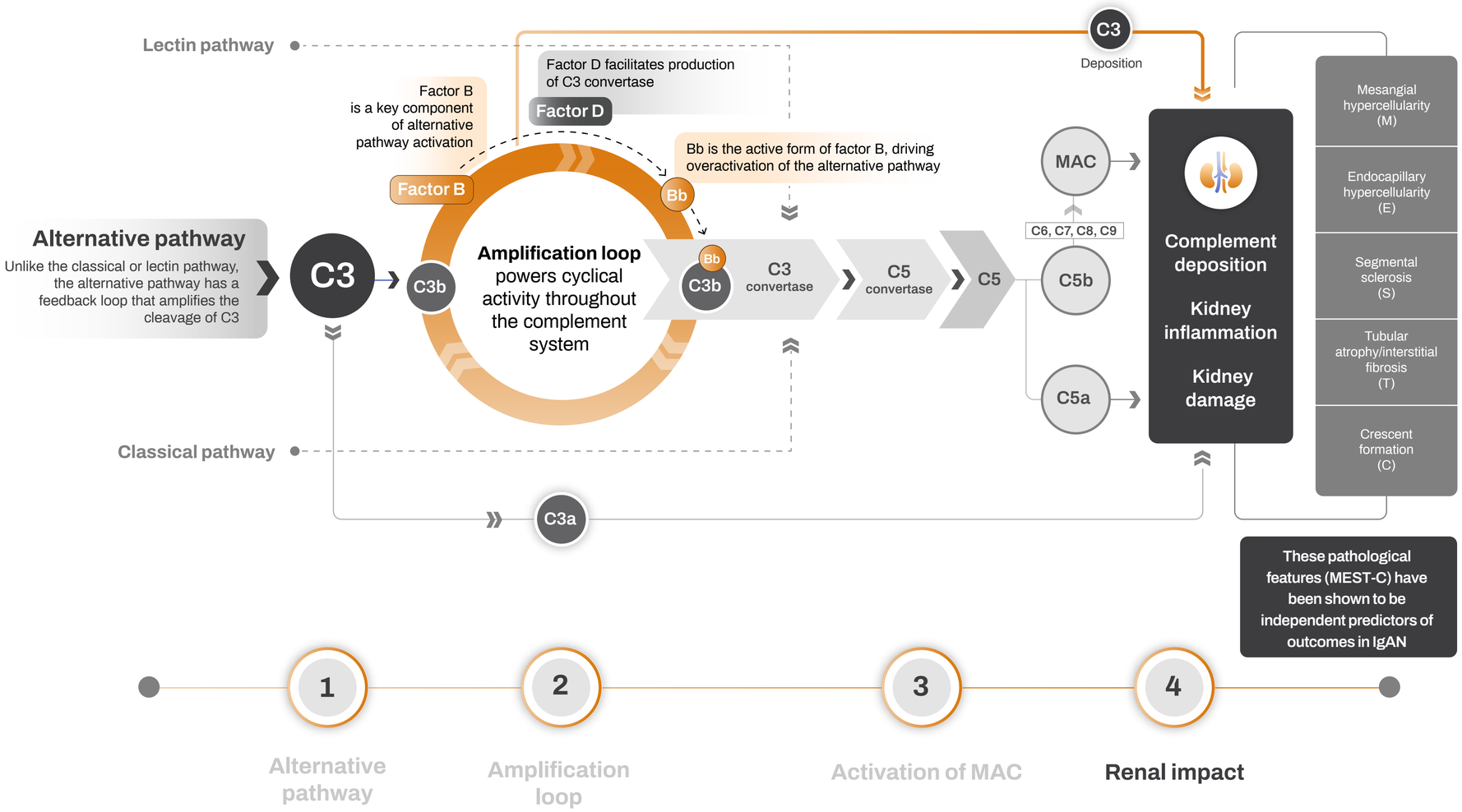
Immune complex deposition in the mesangium activates the complement system, contributing to kidney damage

> “Although all four hits are interconnected and contribute to the overall pathology of IgA nephropathy, it’s important to note that the specific contribution of each hit can vary among individuals, and the relative importance of these hits may also depend on genetic and environmental factors.”
>
> **— Lama Abdelnour, MD**

ECM, extracellular matrix; IgA1, immunoglobulin A1; IgAN, immunoglobulin A nephropathy.

THE ROLE OF COMPLEMENT IN THE PATHOPHYSIOLOGY OF IgAN

The alternative pathway is 1 of 3 pathways of the complement system, an innate component of the body's immune system.



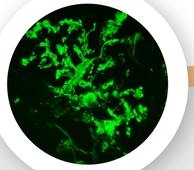
Bb, activated factor B; C, complement component; GN, glomerulonephritis; IgAN, immunoglobulin A nephropathy; MAC, membrane attack complex; MEST-C, mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis, and crescents.

WHAT ARE POTENTIAL CONSEQUENCES OF OVERACTIVATION OF THE COMPLEMENT PATHWAY?

"Based on my experience, **not all patients with IgA nephropathy will experience the same clinical consequences, and the rate of disease progression can differ**. Complement activation in the glomeruli can damage the structures responsible for filtering the blood in the kidneys."
— Lama Abdelnour, MD

"In my pathology practice, I see **activation of the complement system in multiple GNs, which indicates activation of this pathway has broad clinical implications and real significance** for patient outcomes."
— Jared Hassler, MD

MULTIPLE STUDY TYPES CONFIRM THE ACTIVATION OF THE COMPLEMENT PATHWAY IN IgAN



BIOPSY STUDIES

Co-deposition of IgA with C3 and properdin in IgAN biopsies highlights the role of the alternative pathway.

Progression in IgAN is associated with glomerular complement deposition.

C3 deposition is present in up to 90% of patients with IgAN.

In one study (n=60), biopsy evidence of lectin pathway activation was observed in 25% of patients with IgAN.

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IN VITRO STUDIES

Polymeric IgA1 serum activates the alternative pathway independently of the lectin pathway and leads to complement-mediated lysis of erythrocytes.

WHAT ROLE DOES THE COMPLEMENT SYSTEM PLAY IN PATIENT PROGNOSIS?

“Patients with higher levels of complement activation within the renal tissue may have a less favorable prognosis. **Complement-mediated inflammation can lead to more extensive kidney damage, a higher risk of kidney function decline over time, and exacerbation of proteinuria.**” **— Lama Abdelnour, MD**

Ba, factor B fragment a; Bb, activated factor B; C3, complement component 3; IgA, immunoglobulin A; IgA1, immunoglobulin A1; IgAN, immunoglobulin A nephropathy.

PER KDIGO GUIDELINES, DIAGNOSIS OF IgAN CAN ONLY BE MADE WITH A BIOPSY

HISTOPATHOLOGICAL RISK FACTORS FOR PROGRESSION INCLUDE: MEST-C SCORE (LIGHT MICROSCOPY) & C3 STAINING INTENSITY ON IMMUNOFLUORESCENCE

MEST-C SCORE

The MEST-C score is an indicator for diagnosis and prognosis in IgAN, and must be assessed via biopsy by a renal pathologist

M0-M1, percent of glomeruli with mesangial hypercellularity;

E0-E1, presence of glomeruli with endocapillary hypercellularity;

S0-S1, presence of segmental sclerosis within the glomeruli;

T0-T2, percent of the cortical area with tubular atrophy or interstitial fibrosis;

C0-C2, percent of glomeruli with crescent formation.

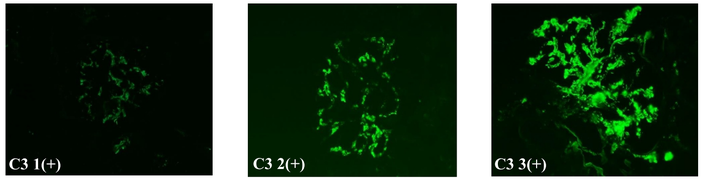
These pathological features (MEST-C) have been shown to be independent predictors of outcomes in IgAN

C3 DEPOSITION

- Progression in IgAN is associated with glomerular complement deposition
  - C3 deposition is present in up to 90% of patients with IgAN

Some studies have found that intensity of C3 staining on kidney biopsy is associated with increased progression to kidney failure

Collaborating with an expert renal pathologist to interpret the pathology report is crucial to understanding a patient's unique prognosis and managing them accordingly.



Immunofluorescent staining of mesangial C3 deposits 1+ to 3+

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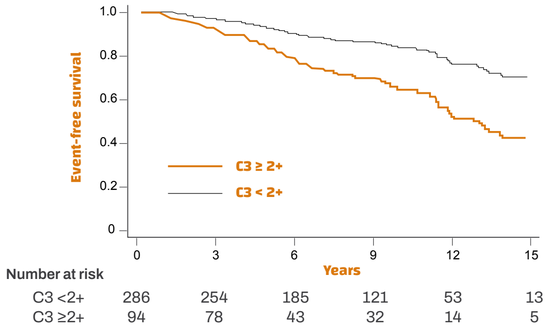
A study showed the risk of reaching a 30% decline in eGFR or ESRD- significantly higher in patients with mesangial deposition of C3 ≥ 2+*



Number at risk

C3 <2+	286	254	185	121	53	13
C3 ≥2+	94	78	43	32	14	5

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*Adjusted Kaplan-Meier analyses of cumulative renal survival of patients with IgAN according to mesangial C3. Immunofluorescence staining was quantified using software and graded according to the intensity of mesangial C3 deposits (0 to 3+). Patients were classified into two groups: those with mesangial C3 deposits of <2+ and those with mesangial C3 deposits of ≥2+.

C3, complement component 3; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; IgAN, immunoglobulin A nephropathy; MEST-C, mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis, and crescents.

IN WHAT WAY DOES MEST-C SCORING INFORM HOW YOU APPROACH IgAN IN YOUR PRACTICE?

"As a pathologist, **I try to provide as much information as possible in the biopsy report,** so that nephrologists have a comprehensive picture when making a diagnosis. MEST-C is useful in some areas—the more tubular interstitial scarring seen means a worse prognosis for the patient." **— Jared Hassler, MD**

"Patient stratification based on histopathological findings guides my treatment decisions, such as the choice of medications (eg, immunosuppressive agents), intensity of therapy, and the frequency of follow-up monitoring. **MEST-C scoring helps me tailor treatment plans to individual disease severity and risk profiles**. In some instances, I find that MEST-C scores may not always correlate perfectly with disease progression, but they remain a valuable tool in the management of IgAN that should be used in conjunction with clinical judgement." **— Lama Abdelnour, MD**

COMPLEMENT SYSTEM DYSREGULATION IS A KEY DRIVER* OF GLOMERULAR INFLAMMATION, AND MAY CONTRIBUTE TO IgAN DISEASE PROGRESSION

*Not in all cases

"In my opinion, I would place greater emphasis on assessing complement system activity in the diagnostic workup. I believe clinicians should stay informed about the latest developments in the field and be open to incorporating new diagnostic modalities into their practice." **— Lama Abdelnour, MD**

"I firmly believe that alternate pathway activation and the amplification loop worsen kidney damage and progression of IgAN."
— Jared Hassler, MD

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IgAN, immunoglobulin A nephropathy.

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