IgAN

The role of complement in disease progression

In IgAN, overactivation of the alternative complement pathway can lead to kidney damage[1-4]

IgAN, immunoglobulin A nephropathy.

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IgAN IS AN AUTOIMMUNE DISEASE THAT CAN INFLICT BOTH PHYSICAL AND EMOTIONAL BURDENS ON PATIENTS[3,5]

COMPLEMENT-MEDIATED GLOMERULONEPHRITIS WITH CHALLENGING SIGNS AND SYMPTOMS

IgA nephropathy is a complement-mediated disease. It is the most common primary glomerulonephritis.[1,6]

Symptoms may include[7]*:

✓ Fatigue ✓ Edema ✓ Insomnia ✓ Hypertension

Laboratory findings may include[6,8]:

✓ Proteinuria ✓ Hematuria ✓ Declining eGFR

HETEROGENOUS PRESENTATION

The diverse clinical and pathological features, coupled with unpredictable disease progression, call for a tailored approach to management based on symptoms and C3 deposition in the glomeruli.[6,8]

"I can't stress enough the toll this disease takes on my life. EVERYTHING changed."

—Real patient with IgAN[7]

Patient portrayal.

*Based on patient insights.

C3, complement 3; eGFR, estimated glomerular filtration rate.

POTENTIAL PROGRESSION AND THE THREAT OF KIDNEY FAILURE MAY CAUSE CONCERN FOR THE FUTURE[5]

RISK OF PROGRESSION AND LIMITED OPTIONS

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

✓ Patients may face continued disease progression and burdens that may impact their day-to-day lives.[1]

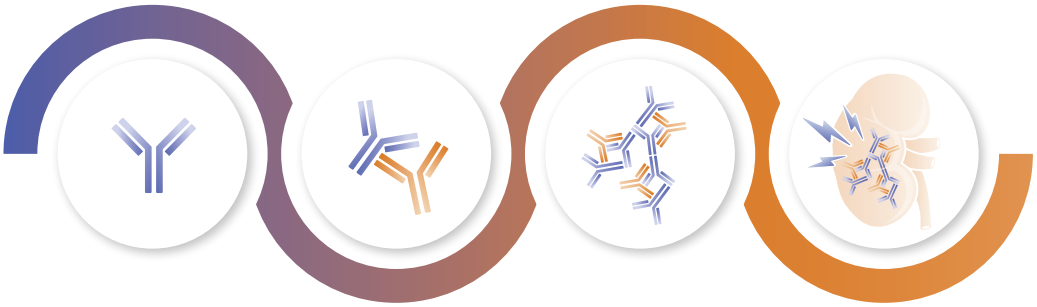
LIMITATIONS OF OPTIMIZED SUPPORTIVE CARE

Although current supportive care and treatment can help reduce proteinuria, they don't address a key pathogenic step in the progression of IgAN: the activation of the complement system.[9]

Additional research is required, but the need to address complement dysregulation remains unaddressed.[9,10]

COMPLEMENT SYSTEM DYSREGULATION* IS A KEY DRIVER OF KIDNEY INFLAMMATION AND CAN CONTRIBUTE TO IgAN DISEASE PROGRESSION[1-3, 11-13]

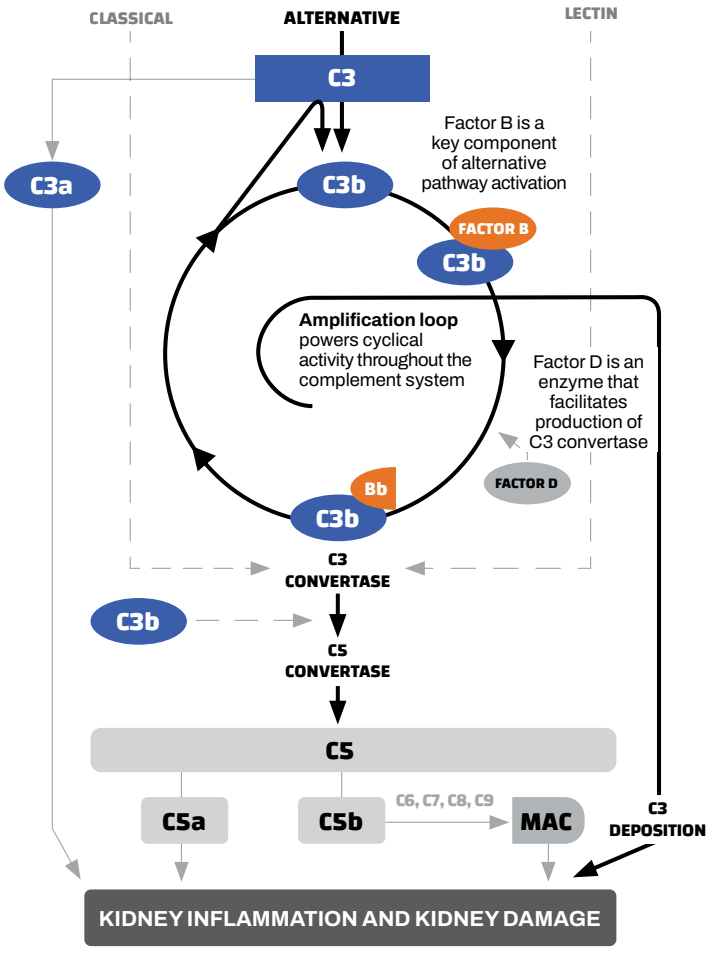
THE MULTI-HIT MODEL[2,3,14]



This process can lead to activation of the complement system via either the alternative pathway, or less often, the lectin pathway.

The 4-HIT hypothesis in IgAN pathophysiology

HIT 1	HIT 2	HIT 3	HIT 4
Increase in galactose-deficient IgA1 antibodies	Induction of autoantibody production	Autoantibodies and antibodies bind to form immune complexes	Immune complex deposition in the mesangium activates the complement system, contributing to kidney damage



*Not all cases

C3 DEPOSITION IN BIOPSIES CAN BE ASSOCIATED WITH PROGRESSIVE DISEASE[2,15]

PATHOGENETIC SEVERITY OF IgAN IS INFLUENCED BY ACTIVATION OF THE COMPLEMENT PATHWAY THROUGH THE ALTERNATIVE AND LECTIN ACTIVATION PATHWAYS AND IS ASSOCIATED WITH KIDNEY INJURY.[2,11]

Kidney biopsies from patients with progressive disease have more staining for C3b/iC3b/C3c, C3d, C4d, and C5b9.[2,10]

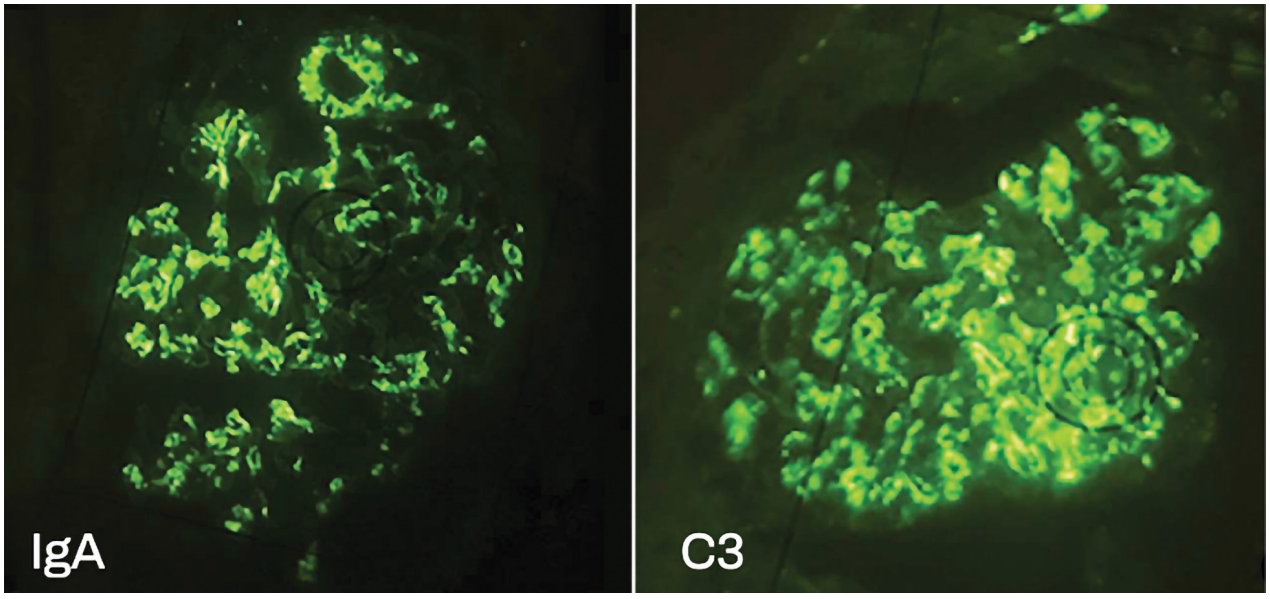
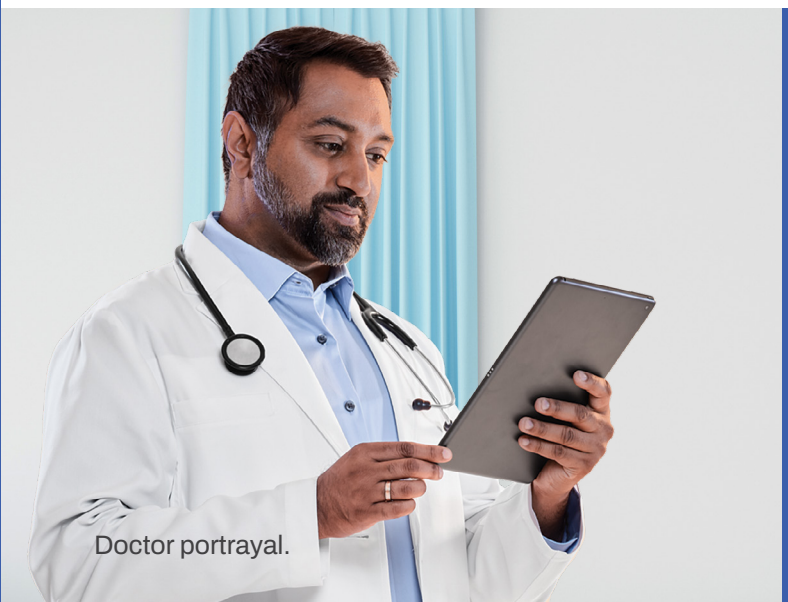


Image showing colocalization of C3 and IgA in a kidney biopsy

Image adapted from: Mastrangelo A, Serafinelli J, Giani M, Montini G. Clinical and pathophysiological insights into immunological mediated glomerular diseases in childhood. *Front Pediatr*. 2020;8:205. Published 2020 May 12. doi:10.3389/fped.2020.00205

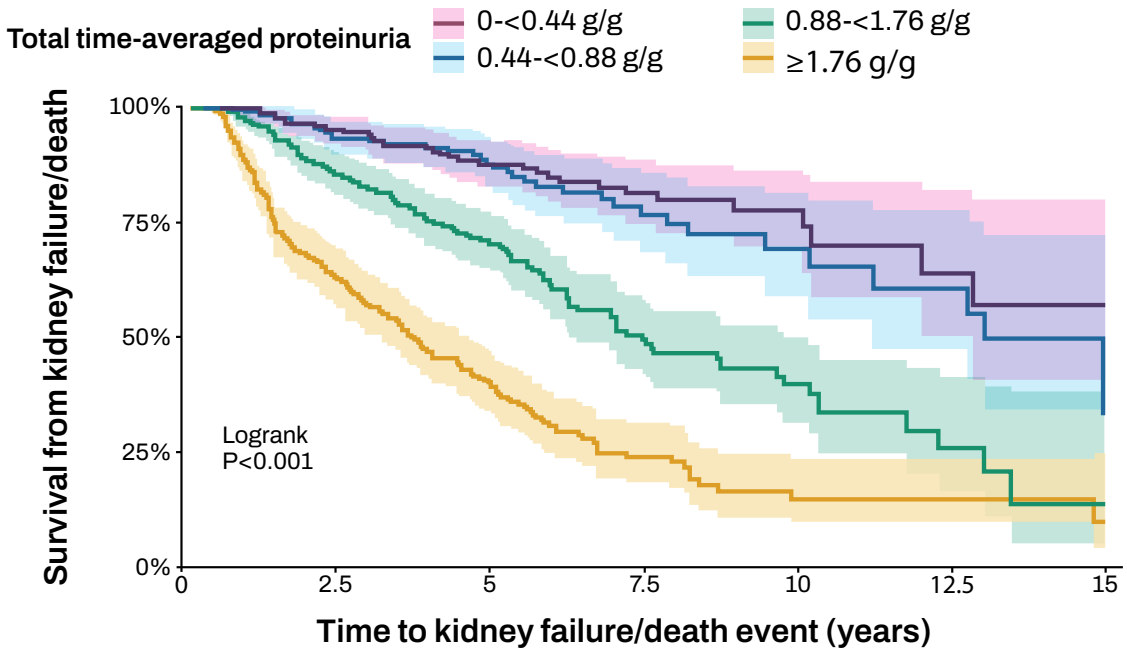


Doctor portrayal.

Complement component C3 was colocalized with IgA in greater than 90% of biopsies positive for IgAN

TIME AVERAGED PROTEINURIA AND SURVIVAL DATA FROM A UK RETROSPECTIVE COHORT

In all age groups, the majority of patients developed kidney failure in 10 to 15 years[16]



0-<0.44 g/g	215	176	114	57	22	10	6
0.44-<0.88 g/g	175	147	94	40	20	11	1
0.88-<1.76 g/g	251	195	120	51	20	7	1
≥1.76 g/g	246	142	66	24	10	5	2

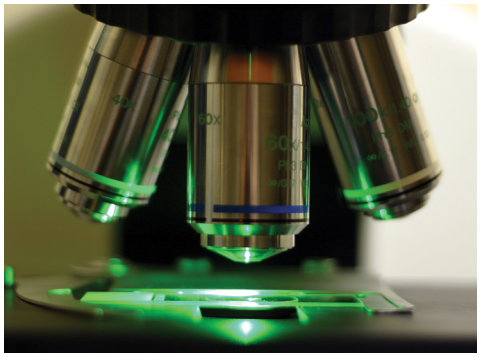
Image adapted from: Pitcher D, Braddon F, Hendry B, et al. Long-term outcomes in IgA nephropathy. *Clin J Am Soc Nephrol*. 2023;18(6):727-738. doi:10.2215/CJN.0000000000000135

*<1g/day is approximately <0.88 g/g.[16]

†Data from United Kingdom retrospective cohort of 2299 adults and 140 children with IgAN of the UK National Registry of Rare Kidney Diseases (RaDaR). Patients enrolled had a biopsy-proven diagnosis of IgA nephropathy plus proteinuria >0.5 g/day or eGFR <60 mL/min per 1.73 m^2 at any time in their history of their disease. Analyses of kidney survival were conducted using Kaplan–Meier and Cox regression. Recruitment into RaDaR was initiated in 2013. Availability of patient medication and blood pressure data was a limiting factor in this study.

INDICATORS OF PROGRESSION CAN HELP PERSONALIZE PATIENT MANAGEMENT[6,17]

COMPLEMENT ACTIVITY AND PATHOHISTOLOGICAL FINDINGS



C3 deposition in the glomeruli can indicate accelerated disease progression for patients with IgAN.[15]

The MEST-C score is an indicator for prognosis in IgAN and must be assessed via biopsy by a renal pathologist.[18]

DECLINING KIDNEY FUNCTION

The International IgAN Prediction Tool estimates the long-term risk of worsening kidney function, measured as a 50% reduction in eGFR or the progression to kidney failure.[6]

Patients may struggle emotionally with the uncertainty of outcomes and the potential for progression to kidney failure.[1,5]

Patient portrayal.

MEST-C, mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T), and crescents (C).

IgAN

THE ROLE OF COMPLEMENT IN PROGRESSION AND ITS IMPACT ON PATIENTS

Patients with IgAN may struggle with both clinical and emotional burdens[5,6]

Patients with persistent proteinuria are at high risk of progression[5]

Complement system dysregulation is a key driver* of glomerular inflammation, and it can contribute to IgAN disease progression[1-3, 11-13]

Patient portrayal.

A retrospective cohort found that

30% of patients with a time-averaged proteinuria range of

0.5 g/day to <1 g/day reached kidney failure within 10 years.[†,‡]

Additional research is required, but the need to address complement dysregulation remains unaddressed.[9,10]

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*Not all cases

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