IgA NEPHROPATHY

As many as 13 out of every 1 million people in the United States are diagnosed annually with IgA nephropathy.[1]

Presentation can include but is not limited to[2-4]:

- Microscopic to gross hematuria
- Varying levels of proteinuria
- Presence or absence of hypertension

Up to 40% of patients with IgA nephropathy progress to kidney failure 10 to 20 years after diagnosis.[5]

Patients with a high risk of progression in IgA nephropathy have persistent proteinuria >0.75 to 1 g/day despite ≥3 months of optimized supportive care.[6]

IMPACT ON PATIENTS

For patients with IgA nephropathy, life outside your office can be more challenging than imagined.

“You may look well on the outside. Inside, you feel as if you are filled with lead. Even getting out of bed to get a drink of water can be difficult on a bad day.[7]”

Patient quote from an externally led focus group held by National Kidney Foundation with 94 patients with IgA nephropathy or caregivers on behalf of patients.

In patients with IgA nephropathy, additional strategies are needed to help achieve a comprehensive and personalized approach to the management of their disease[1,6]

Patient portrayal.
IgA, immunoglobulin A.

3/23 260656

DYSREGULATION BEHIND THE DISEASE

IN IgA NEPHROPATHY

MULTI-HIT HYPOTHESIS of IgA NEPHROPATHY[8-12]

HIT 1: Increase in galactose-deficient IgA1 antibodies

HIT 2: Induction of autoantibody production

HIT 3: Autoantibodies and antibodies bind to form immune complexes

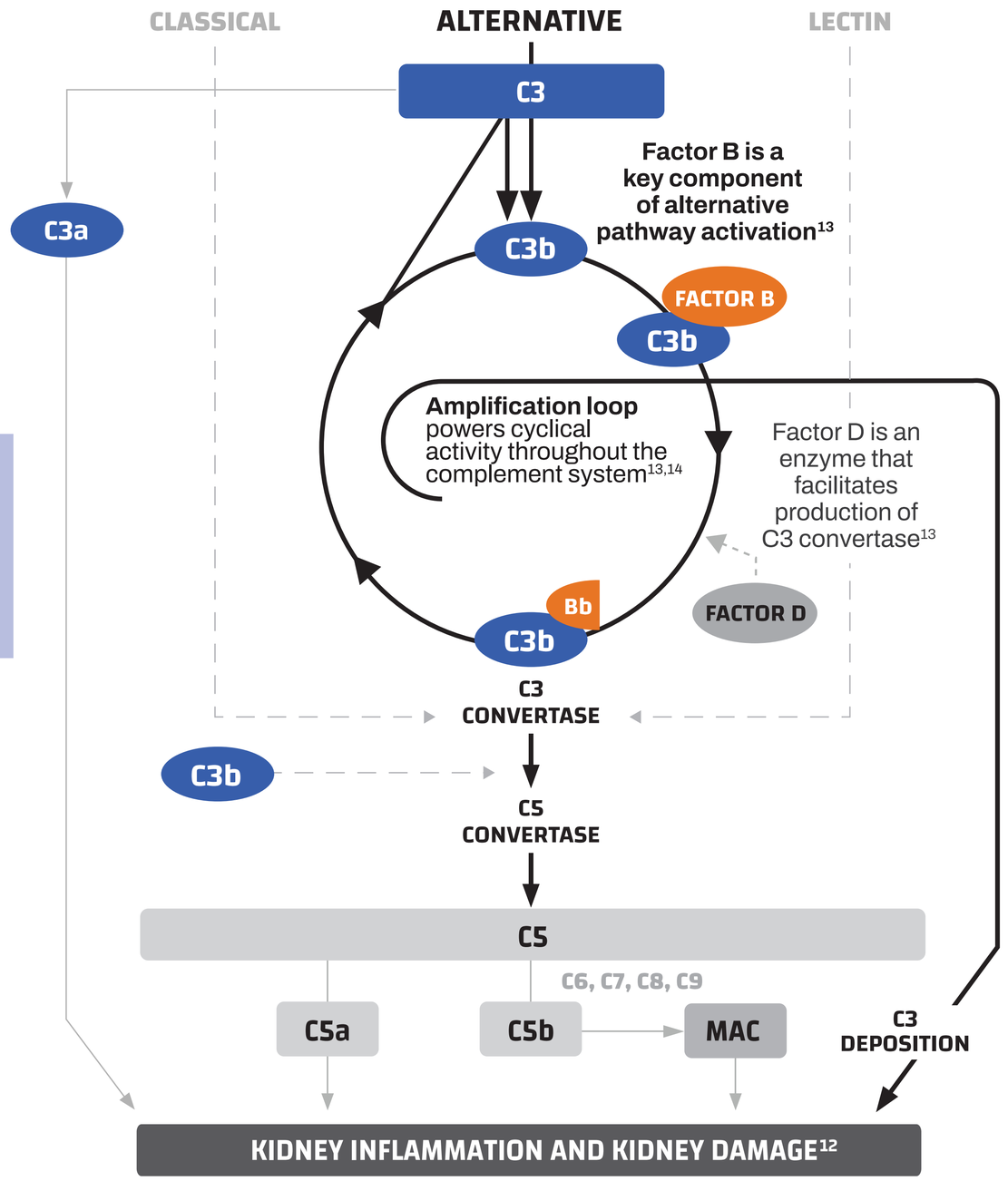
HIT 4: Immune complex deposition in the mesangium activates the complement system via the alternative pathway (or, less often, the lectin pathway)

↓

THE COMPLEMENT SYSTEM

IN C3G

THE COMPLEMENT SYSTEM[13]



PATHOPHYSIOLOGY OF C3G[13-21]

GENETIC OR ACQUIRED ABNORMALITIES of complement regulatory proteins

↓

UNCONTROLLED ACTIVATION of the alternative pathway: the primary driver of disease

↓

C3 DEPOSITION in the glomerular mesangium and along capillary walls

↓

DISRUPTED KIDNEY FUNCTION: inflammation, generation of the MAC, and release of inflammatory mediators

C3G, complement 3 glomerulopathy; MAC, membrane attack complex.

References: 1. Kwon CS, Daniele P, Forsythe A, Ngai C. A systematic literature review of the epidemiology, health-related quality of life impact, and economic burden of immunoglobulin A nephropathy. *J Health Econ Outcomes Res*. 2021;8(2):36-45. **2.** Rajasekaran A, Julian BA, Rizk DV. IgA nephropathy: An interesting autoimmune kidney disease. *Am J Med Sci*. 2021;361(2):176-194. **3.** Yeo SC, Goh SM, Barratt J. Is immunoglobulin A nephropathy different in different ethnic populations? *Nephrology (Carlton)*. 2019;24(9):885-895. **4.** Gutierrez E, Praga M, Rivera F; Spanish Registry of Glomerulonephritis. Changes in the clinical presentation of immunoglobulin A nephropathy: data from the Spanish Registry of Glomerulonephritis. *Nephrol Dial Transplant*. 2018;33(3):472-477. **5.** Xie J, Kiryluk K, Wang W, et al. Predicting progression of IgA nephropathy: new clinical progression risk score. *PLoS One*. Published online June 14, 2012. doi:10.1371/journal.pone.0038904 **6.** Rovin BH, Adler SG, Barratt J, et al; Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. 2021;100(suppl 4):S1-S276. **7.** Feldman DL, White EM, Julian B, et al. *The Voice of the Patient: Externally Led Patient-Focused Drug Development Meeting on IgA Nephropathy*. National Kidney Foundation; 2020. **8.** Lafayette RA, Kelepouris E. Immunoglobulin A nephropathy: advances in understanding of pathogenesis and treatment. *Am J Nephrol*. 2018;47(suppl 1):43-52. doi:10.1159/000481636 **9.** Lai KN, Tang SCW, Schena FP, et al. IgA nephropathy. *Nat Rev Dis Primers*. Published online February 11, 2016. doi:10.1038/nrdp.2016.1 **10.** Rizk DV, Maillard N, Julian BA, et al. The emerging role of complement proteins as a target for therapy of IgA nephropathy. *Front Immunol*. Published online March 19, 2019. doi:10.3389/fimmu.2019.00504 **11.** Barratt J, Feehally J. IgA nephropathy. *J Am Soc Nephrol*. 2005;16(7):2088-2097. **12.** Xie M, Zhu Y, Wang X, et al. Predictive prognostic value of glomerular C3 deposition in IgA nephropathy. *J Nephrol*. Published online July 4, 2022. doi:10.1007/s40620-022-01363-4 **13.** Harris CL. Expanding horizons in complement drug discovery: challenges and emerging strategies. *Semin Immunopathol*. 2018;40(1):125-140. **14.** Willows JW, Brown M, Sheerin NS. The role of complement in kidney disease. *Clin Med (London)*. 2020;20(2):156-160. **15.** Ravindran A, Smith RJH, Fervenza F, et al. Genetic abnormalities in complement regulating proteins in C3 glomerulopathy. *Am J Clin Pathol*. 2018;150:S129-S133. doi:10.1093/ajcp/aqy102.313 **16.** Merle NS, Noe R, Halbwachs-Mecarelli L, Fremeaux-Bachi V, Roumenina LT. Complement system part II: role in immunity. *Front Immunol*. Published online May 26, 2015. doi:10.3389/fimmu.2015.00257 **17.** Caravaca-Fontán F, Lucientes L, Cavero T, Praga M. Update on C3 glomerulopathy: a complement-mediated disease. *Nephron*. 2020;144(6):272-280. **18.** Schena FP, Esposito P, Rossini M. A narrative review on C3 glomerulopathy: a rare renal disease. *Int J Mol Sci*. 2020;21(2):525. doi:10.3390/ijms21020525 **19.** Smith RJH, Alexander J, Barlow PN; Dense Deposit Disease Focus Group. New approaches to the treatment of dense deposit disease. *J Am Soc Nephrol*. 2007;18(9):2447-2456. **20.** C3 glomerulopathy: dense deposit disease and C3 glomerulonephritis. National Organization for Rare Disorders (NORD). Accessed September 24, 2022. https://rarediseases.org/rare-diseases/c3-glomerulopathy-dense-deposit-disease-and-c3-glomerulonephritis/ **21.** Medjeral-Thomas NR, O'Shaughnessy MM, O'Regan JA, et al. C3 glomerulopathy: clinicopathologic features and predictors of outcome. *Clin J Am Soc Nephrol*. 2014;9(1):46-53. **22.** Lu DF, Moon M, Lanning LD, McCarthy AM, Smith RJH. Clinical features and outcomes of 98 children and adults with dense deposit disease. *Pediatr Nephrol*. 2012;27(5):773-781. **23.** Servais A, Noël LH, Roumenina LT, et al. Acquired and genetic complement abnormalities play a critical role in dense deposit disease and other C3 glomerulopathies. *Kidney Int*. 2012;82(4):454-464. **24.** Bomback AS, Santoriello D, Avasare RS. C3 glomerulonephritis and dense deposit disease share a similar disease course in a large United States cohort of patients with C3 glomerulopathy. *Kidney Int*. 2018;93(4):977-985. **25.** Martín B, Smith RJH. C3 glomerulopathy. In: Adam MP, Mirzaa GM, Pagon RA, et al, eds. GeneReviews® [Internet]. University of Washington; 2007. Updated April 5, 2018. Accessed July 28, 2022. https://www.ncbi.nlm.nih.gov/books/NBK1425/ **26.** Smith RJH, Appel GB, Blom AM, et al. C3 glomerulopathy - understanding a rare complement-driven renal disease. *Nat Rev Nephrol*. 2019;15(3):129-143. **27.** Sethi S, Fervenza FC, Zhang Y, et al. Atypical postinfectious glomerulonephritis is associated with abnormalities in the alternative pathway of complement. *Kidney Int*. 2013;83(2):293-299. **28.** Hou J, Markowitz GS, Bomback AS, et al. Toward a working definition of C3 glomerulopathy by immunofluorescence. *Kidney Int*. 2014;85(2):450-456. **29.** Feldman DL, Bomback A, Nester CN. *Voice of the Patient: Report of Externally Led Patient-Focused Drug Development Meeting on Complement 3 Glomerulopathy (C3G)*. National Kidney Foundation; 2018.

DIVE DEEPER

For more information or to sign up for updates and resources, visit **GlomTalk.com** or scan the QR code

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

3/23

260656

3/23 260656

COMPLEMENT 3 GLOMERULOPATHY

- **Estimated worldwide annual prevalence of 1 to 2 cases per 1 million people**[18]
- **Often presents in children and young adults but can affect all ages**[22-24]

C3G can be challenging to diagnose and distinguish from other more common glomerulonephritis.[6,18-20,25-27]

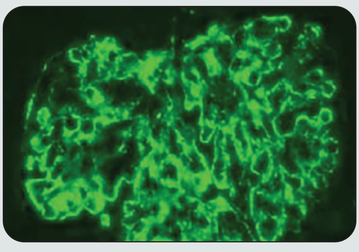
Approximately 50% of patients progress to kidney failure within 10 years of diagnosis.[20,21,25]

EXPERT BIOPSY ANALYSIS

Timely analysis by an expert pathologist is essential to confirmatory diagnosis and early intervention.[25,26,28]

In biopsy, C3 accumulation appears as[25,26]:

- **intensity of C3 staining ≥2 orders of magnitude vs other immunoreactants**
- no to low presence of immunoglobulin and components of the classical pathway



IMMUNOFLUORESCENCE C3-DOMINANT STAINING

Image Credit: Martín B, Smith RJH. C3 Glomerulopathy. 2007 Jul 20 [Updated 2018 Apr 5]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1425/

IMPACT ON PATIENTS

Patients face the possibility of disease progression and kidney failure.[26]

“You can’t plan for the future…you don’t know where you’ll be next year.”[29]

Patient quote from an externally led focus group held by National Kidney Foundation with 59 patients with C3G or caregivers on behalf of patients.

Ask your patients about the physical and emotional challenges they may be facing as they navigate managing C3G.

Patient portrayal.

3/23 260656