



INTRODUCTION

- The complement system plays a key protective role in innate and adaptive immunity, but its dysregulation can contribute to CMKDs, which include the following¹⁻⁵:
 - Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis
 - Antiglomerular basement membrane (anti-GBM) disease
 - Atypical hemolytic uremic syndrome (aHUS)
 - C3 glomerulopathy (C3G)
 - IgA nephropathy
 - Immune complex-mediated membranoproliferative glomerulonephritis (IC-MPGN)
 - Lupus nephritis (LN)
 - Membranous nephropathy (MN)

Many CMKDs are rare conditions

In contrast, IgA nephropathy is the most common form of primary glomerulonephritis



PATHOPHYSIOLOGY

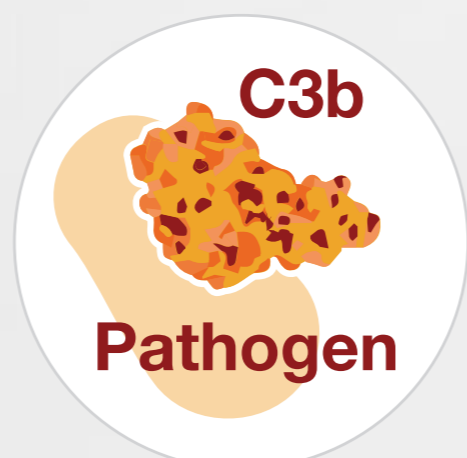
The complement system comprises the classical, lectin, and alternative pathways, with activation leading to^{5,10,11}:



Inflammation via release of anaphylatoxins



Cell injury via the assembly of the membrane attack complex



Immune-cell targeting and cell injury via opsonization

- In some CMKDs, complement dysregulation is caused by genetic mutations or acquired abnormalities (ie, autoantibodies)^{2,3}
- Dysregulated complement activity can progressively damage the kidneys, which may be particularly vulnerable due to their^{3,11}:
 - Glomerular structure
 - Immune complex deposition in the mesangium and capillary wall

- Increased local production of complement proteins
- Local lack of complement regulator expression



DIAGNOSIS AND PRESENTATION

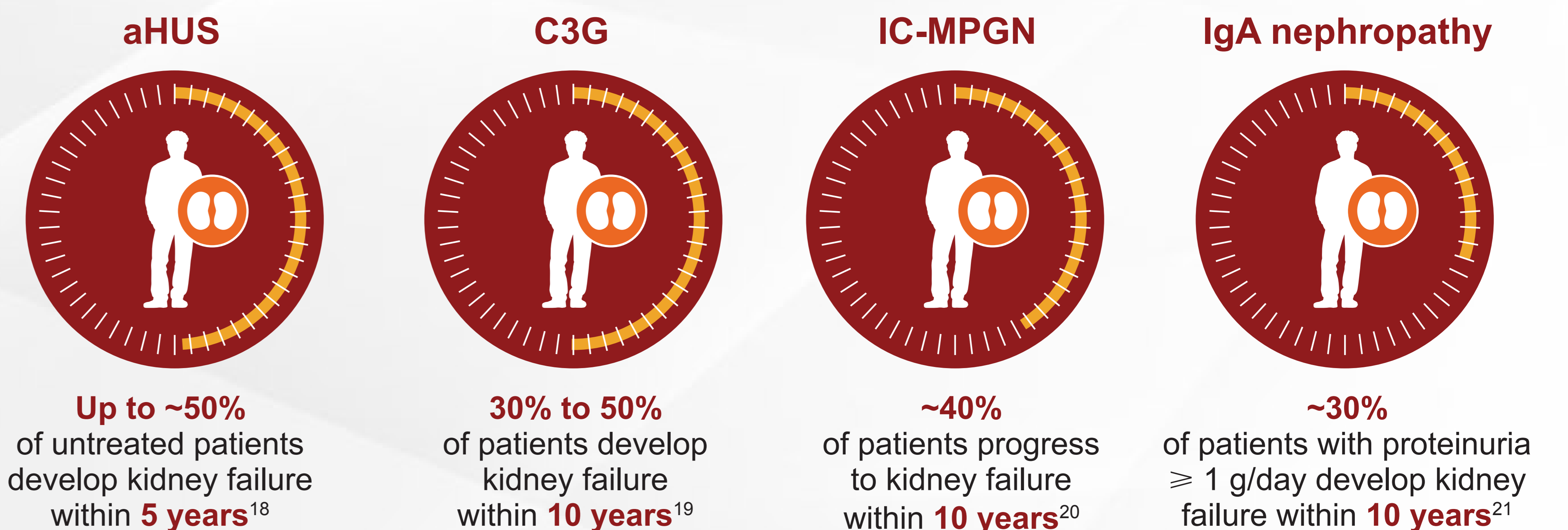


- Diagnosis can be challenging due to disease rarity, as well as delays in and heterogeneity of clinical presentation¹²⁻¹⁵
- Kidney biopsy is the “gold standard” for diagnostic evaluation of glomerular disease, which can reveal characteristic patterns of injury and complement/immunoglobulin deposits and may be supported by autoantibody, genetic, and serum complement testing^{2,16,17}
- Clinical signs are diverse but can involve hematuria, proteinuria, and decreased glomerular filtration rate (GFR)^{12,15}



OUTCOMES

Many CMKDs may eventually progress to chronic kidney disease and kidney failure



The role of the complement system in CMKD progression is increasingly recognized but remains to be fully elucidated^{5,10}

aHUS, atypical hemolytic uremic syndrome; ANCA, antineutrophil cytoplasmic antibody; C3, complement 3 protein; C3G, complement 3 glomerulopathy; C5, complement 5 protein; C5b-9, membrane attack complex; CMKD, complement-mediated kidney disease; GBM, glomerular basement membrane; GFR, glomerular filtration rate; IC-MPGN, immune complex-mediated membranoproliferative glomerulonephritis; IgA, immunoglobulin A; LN, lupus nephritis; MN, membranous nephropathy.

1. Zipfel PF et al. *Cell Tissue Res*. 2021;385(2):355-370. doi:10.1007/s00441-021-03485w 2. Poppelaars F, Thurman JM. *Mol Immunol*. 2020;128:175-187. doi:10.1016/j.molimm.2020.10.015 3. Thurman JM, Nester CM. *Clin J Am Soc Nephrol*. 2016;11(10):1856-1866. doi:10.2215/CJN.01710216 4. Killick J et al. *Semin Immunopathol*. 2018;40(1):37-48. doi:10.1007/s00281-017-0644-y 5. Mathern DR, Heeger PS. *Clin J Am Soc Nephrol*. 2015;10(9):1636-1650 doi:10.2215/CJN.06230614 6. Yan K et al. *Clin Epidemiol*. 2020;12:295-305. doi:10.2147/CLEP.S245642 7. Wong EKS et al. *Clin J Am Soc Nephrol*. 2021;16(11):1639-1651. doi:10.2215/CJN.00320121 8. Sim JJ et al. *Am J Kidney Dis*. 2016;68(4):533-544. doi:10.1053/j.ajkd.2016.03.416 9. Swaminathan S et al. *Clin J Am Soc Nephrol*. 2006;1(3):483-487. doi:10.2215/CJN.00710805 10. Bomback AS et al. *Kidney Int Rep*. 2016;1(3):148-155. doi:10.1016/j.ekir.2016.06.005 11. Thurman JM. *Adv Chronic Kidney Dis*. 2020;27(2):86-94. doi:10.1053/j.ackd.2019.10.003 12. Smith RJH et al. *Nat Rev Nephrol*. 2019;15(3):129-143. doi:10.1038/s41581-018-0107-2 13. Goodship T et al. *Kidney Int*. 2017;91(3):539-551. doi:10.1016/j.kint.2016.10.005 14. McGrogan A et al. *Nephrol Dial Transplant*. 2011;26(2):414-430. doi:10.1093/ndt/gfq665 15. Lafayette RA, Kelepouris E. *Am J Nephrol*. 2018;47(suppl 1):43-52. doi:10.1159/000481636 16. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. *Kidney Int*. 2021;100(4S):S1-S276. doi:10.1016/j.kint.2021.05.021 17. Angioi A et al. *Kidney Int*. 2016;89(2):278-288. doi:10.1016/j.kint.2015.12.003 18. Schaefer F et al. *Kidney Int*. 2018;94(2):408-418. doi:10.1016/j.kint.2018.02.029 19. Ahmad SB, Bomback AS. *Adv Chronic Kidney Dis*. 2020;27(2):104-110. doi:10.1053/j.ackd.2019.12.003 20. Servais A et al. *Kidney Int*. 2012;82(4):454-464. doi:10.1038/ki.2012.63 21. Reich HN et al. *J Am Soc Nephrol*. 2007;18(12):3177-3183. doi:10.1681/ASN.2007050526