C3 Glomerulopathy: From Early Recognition to Individualized Targeted Therapy

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Faculty

Andrew Bomback, MD, MPH
Associate Professor of Medicine
Division of Nephrology
Co-Director, David Koch Jr. Glomerular Kidney Center
Columbia University Irving Medical Center
New York, New York

Disclosures

Consultant: Amgen, Apellis, Novartis

Learning Objectives

- Conduct a diagnostic evaluation for suspected C3G consistent with current guidelines.
- Review the safety and efficacy of iptacopan and pegcetacoplan for use in patients with C3G.
- Individualize targeted therapies in patients with C3G based on patient needs and characteristics and risk evaluation and mitigation strategy programs.

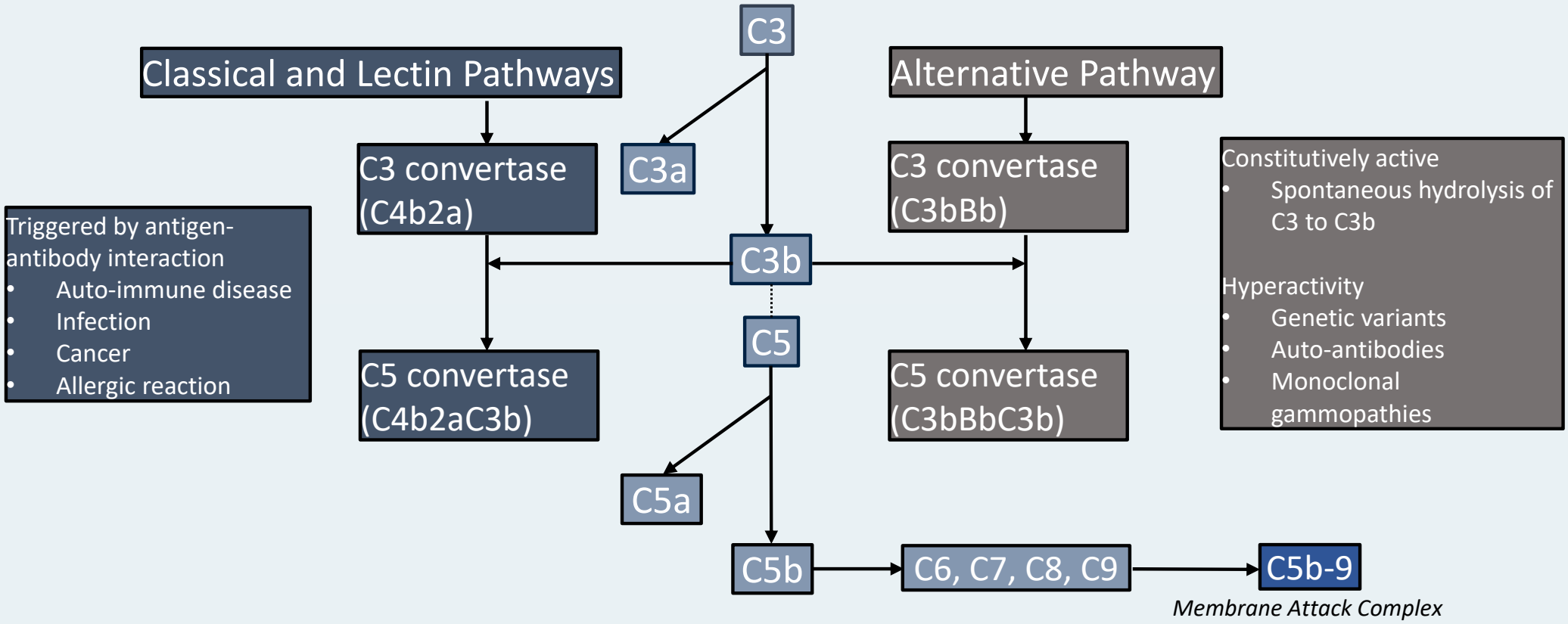
C3 Glomerulopathy (C3G)

- Form of glomerulonephritis caused by deposition of C3 complexes
  - C3 glomerulonephritis, dense deposit disease
- Prevalence
  - United States: 2-3 cases/million
  - Europe: 0.2-1 case/million
- Estimated 30%-50% progress to ESKD within 10 y of diagnosis
  - Post-transplant recurrence rate 80%-100%
  - Allograft failure

ESKD, end-stage kidney disease

Servais A, et al. *J Med Genet*. 2007;44(3):193–199.
Smith RJH, et al. *Nat Rev Nephrol*. 2019;15(3):129-143.
Ahmad SB, et al. *Adv Chronic Kidney Dis*. 2020;27(2):104-110.
Bomback AS, et al. *Kidney Int*. 2018;93(4):977–985.

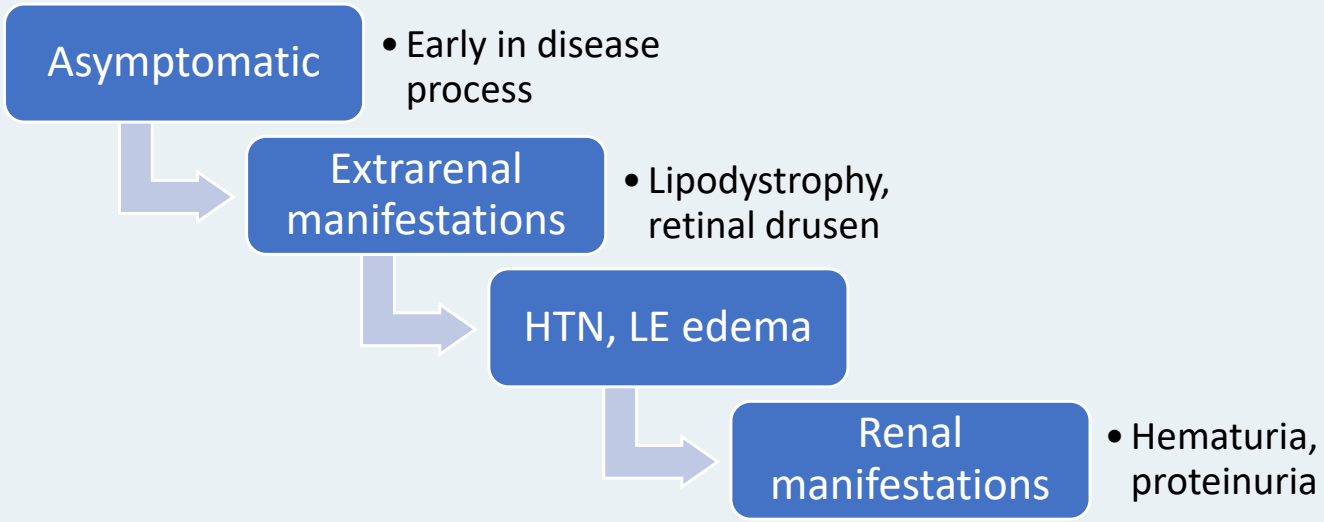
Pathogenesis



Bomback AS. *Adv Chronic Kidney Dis.* 2014;21(2):152-158.
Ahmad SB, et al. *Adv Chronic Kidney Dis*. 2020;27(2):104-110.

Clinical Features

- Heterogenous based on disease severity and duration

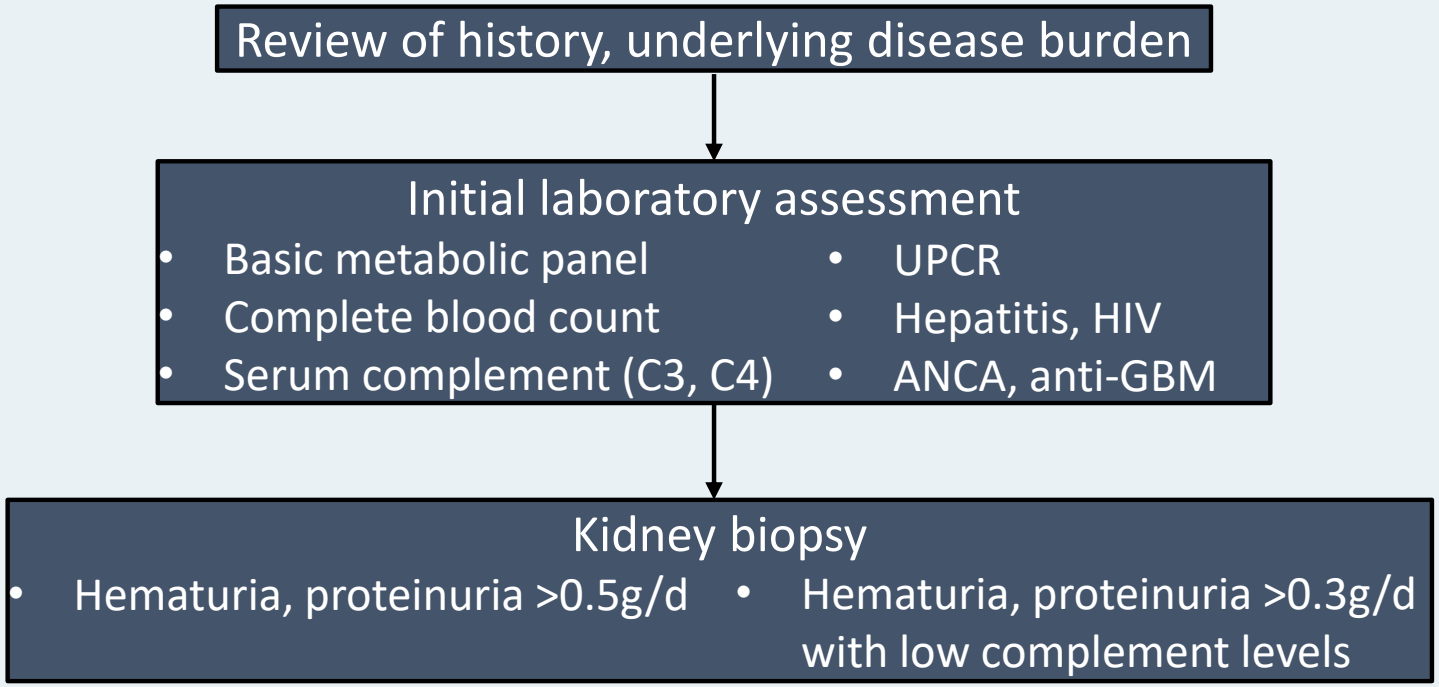


- C3G is not specific to one age range; it may present at any age
  - Average age at diagnosis is late teenage and early adulthood

LE, lower extremity

KDIGO Workgroup. *Kidney Int.* 2021;100(4S):S1-S276.
Mashayekhi M, et al. *Kidney Med.* 2026;8(3):101258.
Overwijk RH, et al. *Kidney Int Rep.* 2025;11(2):103681.

Diagnostic Evaluation



ANCA, antineutrophil cytoplasmic antibody; GBM, glomerular basement membrane; HIV, human immunodeficiency virus, UPCR, urine protein:creatinine ratio

KDIGO Workgroup. *Kidney Int.* 2021;100(4S):S1-S276.
Ahmad SB, et al. *Adv Chronic Kidney Dis.* 2020;27(2):104-110.

Further Evaluation of C3G

- Comprehensive assessment of complement cascade
  - Activation (Bb, sMAC, C3d)
  - Autoantibodies (nephritic factors, anti-factor B, anti-factor H)
  - Functional assays (CH50, AP50, factor H function)
  - Regulators (factor H, factor I, factor B, properdin)

- Genetic testing
  - Complement factor B, complement factor H, complement factor I, CFHR1-5 MLPA

AP50, complement alternate pathway activation 50%; Bb, activated factor B; C3d, complement component 3d; CH50, complement hemolytic activity 50%; CFHR1-5 MLPA, complement factor H-related protein 1-5 multiplex ligation-dependent probe amplification; sMAC, soluble membrane attack complex

KDIGO Workgroup. *Kidney Int.* 2021;100(4S):S1-S276.

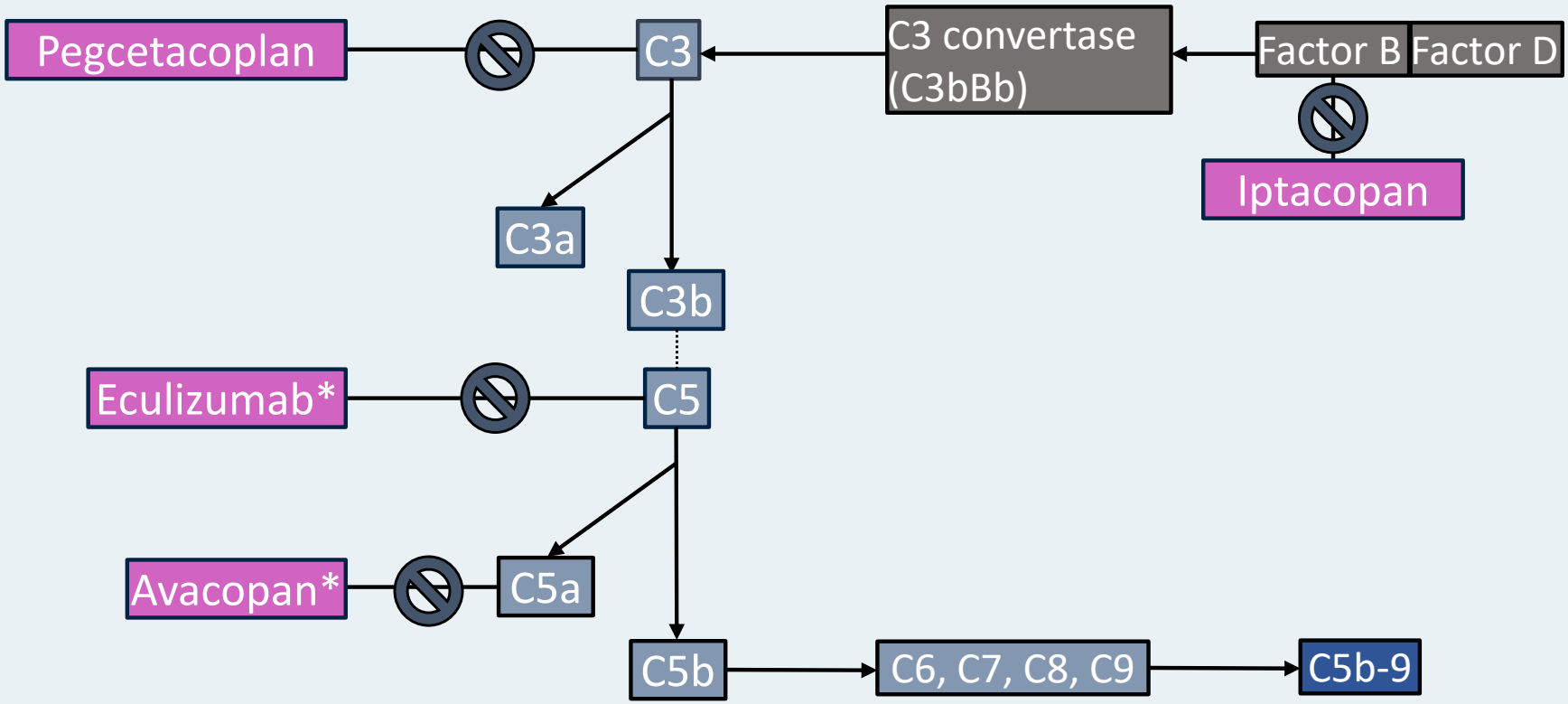
Treatment of C3G

- Identification and treatment of primary disease process
- ACEi or ARB* for proteinuria and blood pressure control
- MMF plus glucocorticoids*
  - Initial treatment for moderate to severe disease (proteinuria >1g/d, hematuria for 6 mos)
- Eculizumab*
  - Alternative treatment with failure of MMF plus glucocorticoids
- Clinical trial enrollment
- Kidney transplantation

**Not approved for the treatment of C3G*
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MMF, mycophenolate mofetil

KDIGO Workgroup. *Kidney Int.* 2021;100(4S):S1-S276.

Treatment Targets

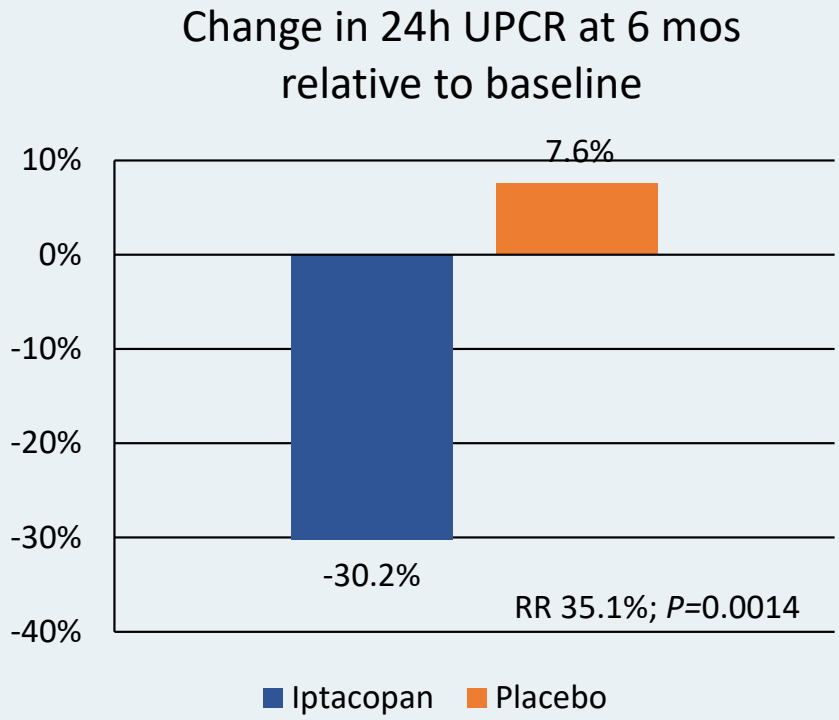


*Not approved for the treatment of C3G

Mashayekhi M, et al. *Kidney Med.* 2026;8(3):101258.

Iptacopan

- APPEAR-C3G
  - Patients with native kidney C3G randomized to iptacopan vs. placebo
  - Reduction in proteinuria observed as early as day 14 and sustained at 12 mos
- NCT 03955445
  - Long-term extension study evaluating efficacy and safety in patients with C3G and IC-MPGN

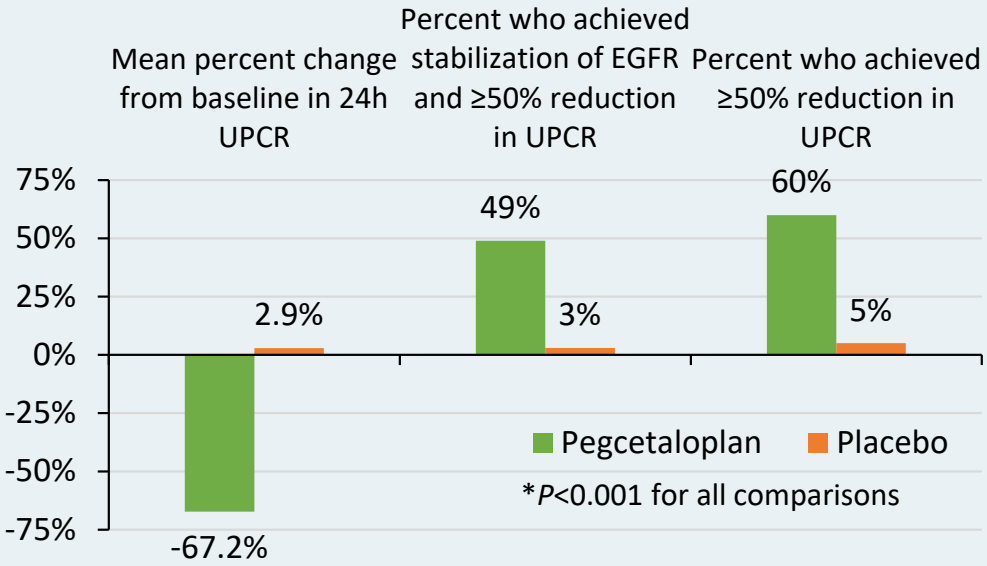


IC-MPGN, idiopathic immune-complex membranoproliferative glomerulonephritis; RR, relative reduction

Pegcetacoplan

- VALIANT
  - Patients with C3G or IC-MPGN randomized to pegcetacoplan vs. placebo
  - Significantly greater reduction in proteinuria with pegcetacoplan
- VALE
  - Long-term extension study evaluating efficacy and safety in patients with C3G and IC-MPGN

Results at Week 26*



EGFR, estimated glomerular filtration rate

Fakhouri F, et al. *N Engl J Med*. 2025;393(22):2210–2220.
Apellis Pharmaceuticals, Inc. Updated April 2, 2026. https://clinicaltrials.gov/study/NCT05809531

Benefits of Targeted Treatment

- Shift from non-specific immunosuppression to targeted treatment options
- Address limitations of non-specific historical treatment targeting C3G pathogenesis
- Superior clinical and similar safety outcomes compared with supportive care and historical treatment approaches

Kavanagh D, et al. *Lancet*. 2025;406(10512):1587-1598.
Fakhouri F, et al. *N Engl J Med*. 2025;393(22):2210–2220.
Caravaca-Fontan F, et al. *Clin J Am Soc Nephrol.* 2020;15(9):1287-1298.
Le Quintrec M, et al. *Am J Kidney Dis.* 2018;72(1):84-92.

Treatment Goals

- Reduce proteinuria
  - ≥50% reduction in proteinuria over 6 mos
  - Proteinuria to <500 mg/d to preserve long-term kidney function

KDIGO Workgroup. *Kidney Int.* 2021;100(4S):S1-S276.
Caravaca-Fontan F, et al. *Kidney Int Rep.* 2025;11(2):103671.

Iptacopan & Pegcetacoplan: Safety

- Increased risk of encapsulated bacteria infections
  - *S. pneumoniae*, *N. meningitidis*, *H. influenzae* type b
- Complete meningococcal and pneumococcal vaccination at least 2 wks prior to first dose of iptacopan or pegcetacoplan[†]
- In urgent situations, provide antimicrobial prophylaxis and administer vaccinations as soon as possible
- Available through Risk Evaluation and Mitigation Strategy program

[†]*According to current Advisory Committee on Immunization Practices (ACIP) recommendations*

Fabhalta. Prescribing Information. Novartis Pharmaceuticals Corporation; 2025. Accessed August 17, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/218276s007lbl.pdf -
Empaveli. Prescribing Information. Apellis Pharmaceuticals; 2025. Accessed August 17, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/215014s011lbl.pdf -

Interprofessional Approach