Cold Agglutinin Disease

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Cold agglutinin disease (CAD) is a rare autoimmune hemolytic anemia in which cold-reactive, typically monoclonal IgM antibodies bind to red blood cells and activate the classical complement pathway, resulting in complement-mediated hemolysis. Clinically, CAD presents with chronic hemolysis and anemia, fatigue, and cold-induced circulatory symptoms. As CAD pathophysiology has been clarified as a dual mechanism—"a clonal B-cell disorder plus complement-driven hemolysis"—therapeutic strategies have evolved toward targeted B-cell therapy and complement inhibition.

The diagnosis of CAD is established by evidence of hemolysis (anemia, elevated LDH and bilirubin, decreased haptoglobin) together with a direct antiglobulin test (DAT) showing **C3d positivity (±IgG)**, supportive cold agglutinin testing (commonly a titer ≥1:64), and assessment of thermal amplitude. Proper pre-analytical handling is essential to avoid falsely misleading results, including preventing specimen cooling during collection and transport (e.g., maintaining samples around 37°C). Once CAD is confirmed, evaluating **secondary causes (cold agglutinin syndrome, CAS)** is critical, with particular attention to infections and lymphoproliferative disorders.

Management consists of supportive care and pharmacologic therapy. Given the cold-dependent nature of hemolysis, supportive measures—cold avoidance and warming strategies, warmed transfusions and IV fluids, folate supplementation, and consideration of thrombotic risk during exacerbations—remain fundamental. Corticosteroids are generally ineffective in CAD and are therefore not recommended. Pharmacologic therapy can be broadly categorized into two approaches. First, therapies targeting the pathogenic B-cell clone include rituximab monotherapy and combination regimens such as rituximab plus bendamustine, with clinically meaningful response rates and durable responses reported. Second, complement-directed therapy has emerged as an important option; the C1s inhibitor sutimlimab demonstrated improvements in hemoglobin and hemolysis markers and meaningful reduction in fatigue in clinical trials. More recently, complement C3 inhibition (e.g., pegcetacoplan) has shown potential activity in both CAD and warm AIHA, expanding the therapeutic landscape.

In conclusion, understanding CAD through the two key axes—complement-mediated hemolysis and an underlying clonal B-cell disorder—enables a streamlined diagnostic and therapeutic approach. After confirming CAD and excluding secondary causes, treatment should be individualized based on symptom burden, severity of anemia and transfusion need, and the therapeutic goal (rapid control of hemolysis versus long-term remission).

Reference

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