Chapter 2: Developments in the Diagnosis and Treatment of Cold Agglutinin Disease

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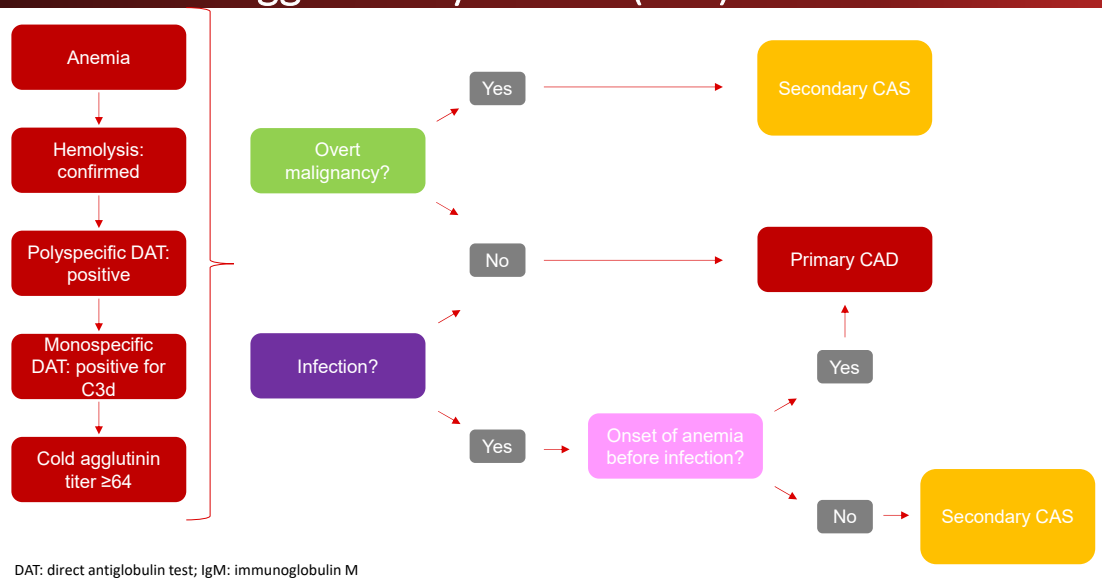
Diagnostic algorithm: cold agglutinin disease (CAD) versus cold agglutinin syndrome (CAS)



DAT: direct antiglobulin test; IgM: immunoglobulin M

Berentsen S, Tjønnfjord GE. *Blood Rev.* 2012;26(3):107-115.

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Agglutination

- As the red blood cells circulate into the peripheral vascular system, where temperatures are below core body temperature, **cold agglutinin** (IgM autoantibody against red blood cell antigens that bind at cold temperatures)[1] binds to the red blood cell membrane polysaccharide antigens I or i.
- In the case of IgM antibodies, as IgM forms pentamers, red blood cells are drawn together in a process known as **agglutination**.
- Agglutination of red blood cells in small vessels in the periphery is responsible for circulatory symptoms in CAD.

1. Berentsen S, Brugnara C. Cold agglutinin disease. In: Post TW, ed. *UpToDate*. UpToDate; 2024.

Evaluation of suspected CAD

- Peripheral blood smear: polychromasia, anisocytosis, and spherocytes
- Direct antiglobulin test (DAT) is the pivotal test in evaluating CAD.
  - The DAT will be strongly positive for C3d and negative or weakly positive for IgG.
- If DAT is positive for C3d, then a **cold agglutinin titer** should be performed on a sample that has been kept warm (to avoid precipitation of cold agglutinin and a false-negative result).
  - The titer should be ≥64.[1]

Berentsen S, Tjønnfjord GE. *Blood Rev.* 2012;26(3):107-115.

Bone marrow evaluation

- Bone marrow evaluation is strongly advised in CAD at the time of diagnosis and/or prior to initiating therapy.[1]
- In CAD, the diagnostic bone marrow finding is clonal, low-grade lymphoproliferation.
  - Distinct from lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia) and marginal zone lymphoma, currently recognized in the World Health Organization (WHO) classification of hematolymphoid tumors.[2]
  - The *MYD88* L265P mutation, present in nearly all cases of lymphoplasmacytic lymphoma, is usually not found in CAD. By contrast, *KMT2D* and *CARD11* mutations are found frequently.[3]

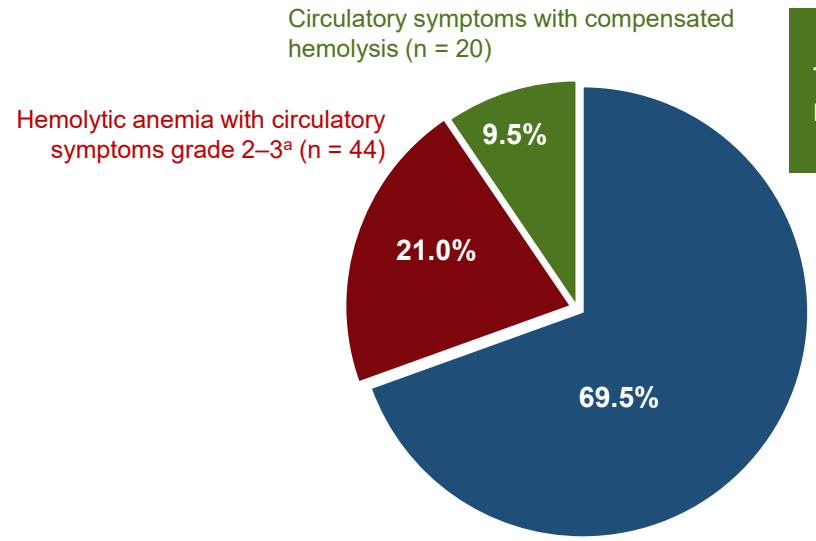
1. Berentsen S. *Blood*. 2021;137(10):1295-1303. 2. Campo E, et al. *Blood*. 2022;140(11):1229-1253. 3. Małecka A et al. *Br J Haematol*. 2018;183(5):838-842.

Diagnostic criteria for CAD

- Hemolytic anemia of variable severity (90% of cases) and peripheral circulatory symptoms (most cases)
- DAT strongly positive for complement (C3d)
- Cold agglutinin titer ≥64 at 4°C
- DAT negative or weakly positive for IgG
- Cold agglutinin is monoclonal (IgM kappa present in 90% of cases)
- Bone marrow evaluation shows primary CAD-associated lymphoproliferative B-cell disorder
- No overt clinical or radiological evidence of underlying disease (eg, acute infections; overt malignancy, typically B-cell lymphoma; other systemic autoimmune disorders)

Berentsen S, Tjønnfjord GE. *Blood Rev.* 2012;26(3):107-115.

Clinical phenotype of CAD in 210 patients



The majority of patients with CAD present with hemolytic anemia

[a] Grade 1: acrocyanosis only; Grade 2: Raynaud-like symptoms interfering with daily living; Grade 3: gangrene or ulcerations.
Berentsen S, et al. *Blood*. 2020;136(4):480-488.

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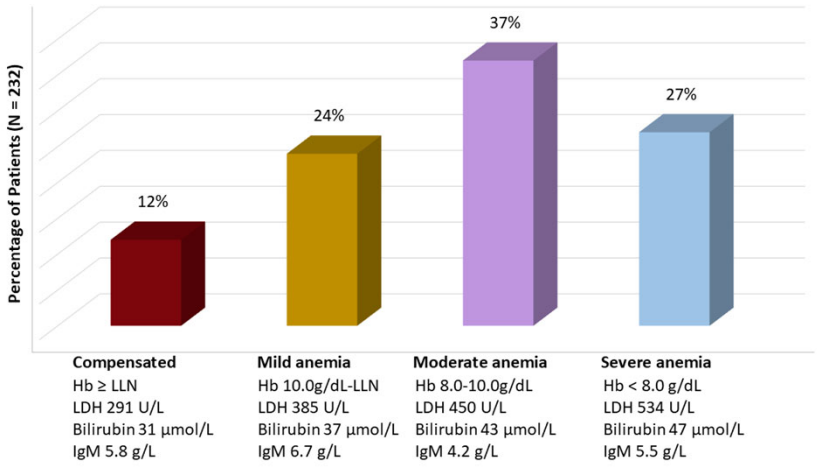
Anemia in CAD



64% of patients with CAD have baseline Hb < 10 g/dL (moderate or severe anemia).

Even patients with normal Hb have evidence of ongoing hemolysis.

The level of IgM (cold agglutinin) does not correlate linearly with the degree of anemia.

Hb: hemoglobin; LDH: lactate dehydrogenase; LLN: lower limit of normal. LDH, bilirubin, and IgM values represent means.

Berentsen S. *Blood*. 2021;137(10):1295-1303

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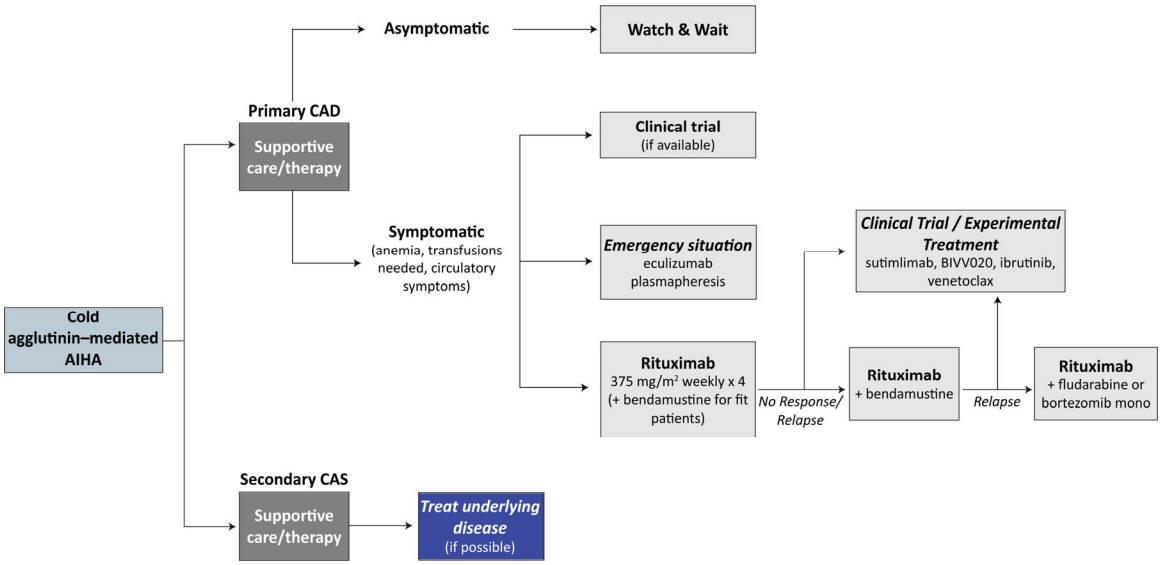
Possible consequences of CAD

Transfusions required	50% of patients considered transfusion dependent for short or long periods[1]
Elevated thromboembolic threat[2,3]	• Increased risk of venous thromboembolism or other thromboembolic events • 68% higher incidence of thromboembolic events[2]
Reduced quality of life[4]	• 90% of patients report fatigue; ~25% of patients report fatigue that lasts throughout the day • Patients report that CAD has major impacts on their physical and emotional well-being, social life, and household finances.
Higher mortality rate[3,5]	Multiple studies show patients diagnosed with CAD have a significantly higher mortality rate than a matched population without CAD.

1. Berentsen S. *Br J Haematol.* 2018;181(3):320-330. 2. Broome CM, et al. *Res Pract Thromb Haemost*. 2020;4(4):628-635. 3. Bylsma LC, et al. *Blood Adv.* 2019;3(20):2980-2985. 4. Joly F, et al. *JMIR Form Res*. 2022;6(7):e34248. 5. Hill QA, et al. *Blood.* 2019;134:4790.

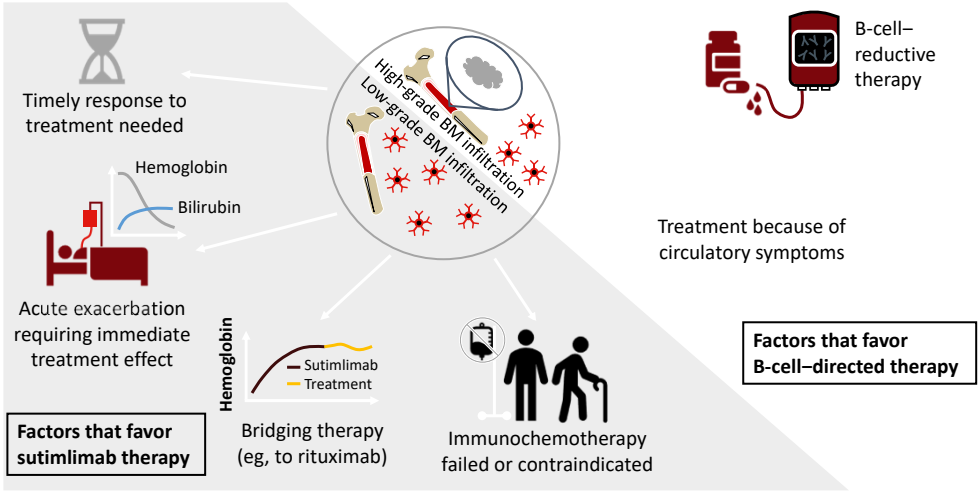
Treatment for cold agglutinin-mediated autoimmune hemolytic anemia (AIHA)



1. Jäger U, et al. *Blood Rev*. 2020;41:100648. 2. Röth A. *Blood*. 2020;136(4):380-381.

Considerations when choosing therapy for CAD

Potential indications for sutimlimab in cold agglutinin disease



BM: bone marrow.

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