Getting personal: Individualizing therapy for cold agglutinin disease

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Optimizing the diagnostic workup for CAD: Clinical presentations and differential diagnoses

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What signs and symptoms should increase your clinical suspicion of cold agglutinin disease?

General and specific symptoms of CAD

- While AIHA conditions share common symptoms of anaemia and fatigue, misdiagnosis of CAD has therapeutic consequences because different types of AHIA should be treated differently[1]

General AIHA symptoms

Unexplained, chronic anaemia[2]

Fatigue[2,3]

Dyspnoea[3]

Palpitations[3]

CAD specific symptoms

Acrocyanosis (44% of patients)[2]

Cold-triggered symptoms (in 39–90% of patients)[1,2]

AIHA definitions

CAD[3]

- Monospecific DAT: C3d+, (IgG-/weakly +)
- CA titre ≥64 at 4°C

CAS[3]

- Clinical signs of CAD, where patients have an underlying condition

wAIHA[3]

- Monospecific DAT: IgG+, IgA+ (rarely), or C3d ± IgG
- No cold-reactive antibodies or no cold-associated symptoms

AIHA, autoimmune haemolytic anaemia; C, serum complement protein; CA, cold agglutinin; CAD, cold agglutinin disease; DAT, direct antiglobulin test; IgA, immunoglobulin A; IgG, immunoglobulin G; wAIHA, warm AIHA.

1. Berentsen S, et al. *J Blood Med*. 2019;10:93–103; 2. Swiecicki P, et al. *Blood*. 2013;122:1114–21; 3. Jäger U, et al. *Blood Rev*. 2020;41:100648.

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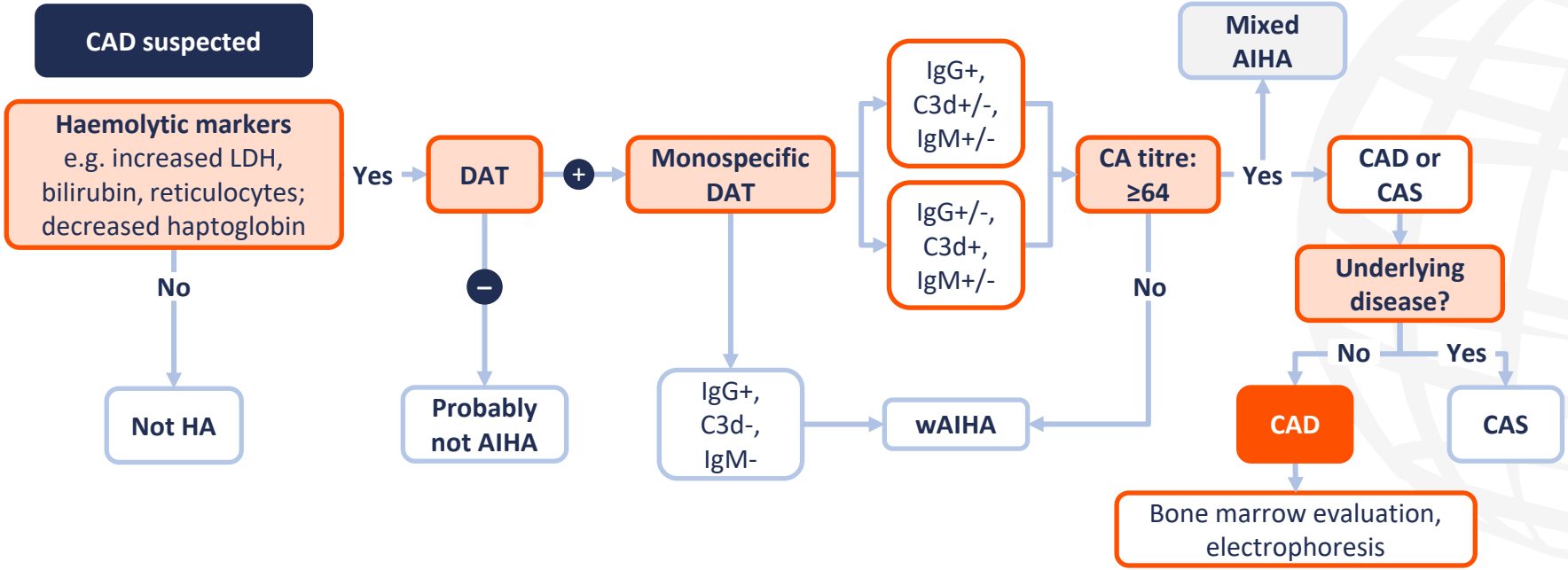
What tests, and in what order, are recommended to diagnose primary cold agglutinin disease?

Testing sequence for CAD diagnosis



Adapted from Berentsen and Barcellini. 2021.

AIHA, autoimmune haemolytic anaemia; C, serum complement protein; CA, cold agglutinin; CAD, cold agglutinin disease; CAS, cold agglutinin syndrome; DAT, direct antiglobulin test; HA, haemolytic anaemia; IgG, immunoglobin G; IgM, immunoglobulin M; LDH, lactate dehydrogenase; wAIHA, warm AIHA.

Berentsen S, Barcellini W. *N Engl J Med.* 2021;385:1407–19.

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How important is timing of tests and proper sample handling in obtaining accurate results?

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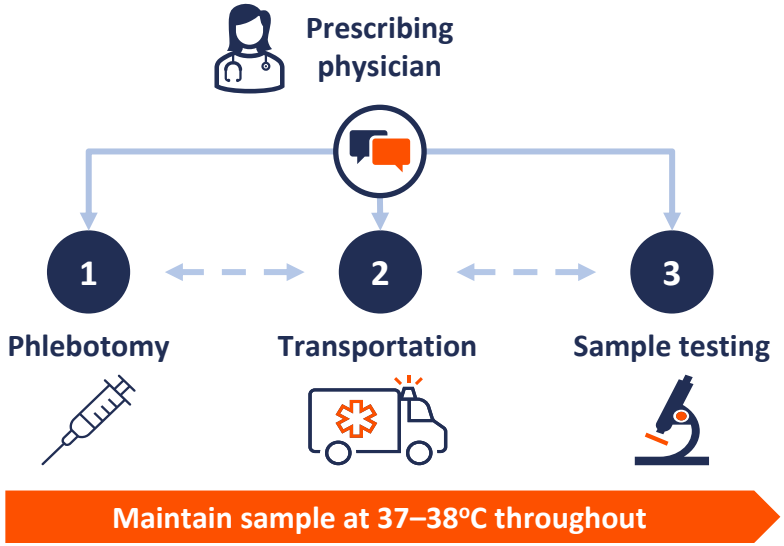
Proper handling of sample

- Proper handling of the sample is important to avoid false results or low sensitivity, requiring collaboration between teams[1,2]
- Incorrect sample handling may result in incorrect test results following CA titration, Ig quantification or electrophoresis[1]



Adapted from Berentsen, 2019; Agarwal et al. 2020.

Sample handling for testing:[3]

Hb, blood counts: Prewarm vacuum tube before drawing blood

CA titre, TA, Ig quantification, SPEP, IFX: maintain at 37–38°C until plasma removed

Flow cytometry: Prewarm bone marrow aspirate sample, wash cells at 37–38°C if needed

CA, cold agglutinin; Hb, haemoglobin; IFX, immunofixation; Ig, immunoglobulin; SPEP, serum protein electrophoresis; TA, thermal amplitude.

1. Berentsen S, et al. *J Blood Med.* 2019;10:93–103; 2. Agarwal S, et al. *Int J Sci Health Res.* 2020;5:95–9; 3. Berentsen S. *Blood*. 2021;137:1295–303.

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How do diagnostic delays impact treatment decisions and outcomes?

Meet the patient

69-year-old female

- Presented with dyspnoea in 2011, no diagnosis from PCP for several months
- Referred to haemologist after PCP noted anaemia

February 2012	Coombs positive HA CA titre positive	**Treatment** Rituximab* + steroids
May 2012	Partial response →	Weaned off steroids by June 2013
June 2013	Worsening fatigue, SOB, recurrent haemolysis	**Treatment** Rituximab* + high dose steroids (tapered off by January 2014)
October 2014	Recurrent haemolysis, SOB, fatigue	**Treatment** Steroids → no benefit Rituximab*
December 2016	Condition stable for 14 months prior Fatigue, SOB worsening	
January 2017	Rituximab* → no benefit	
April 2017	Anaemia, fatigue, SOB Lesions (ear and thumb) Pulmonary embolus	**Treatment** Started on plasma exchange
2018	Plasma exchange twice per week + cyclophosphamide for ~1 year Persistent fatigue; haemoglobin 9 g/dL	

*Rituximab dosing: 375 mg/m^2/week × 4 weeks
CA, cold agglutinin; HA, haemolytic anaemia; PCP, primary care physician; SOB, shortness of breath.
Patient case provided by Dr Broome

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Will longitudinal real-world data help to inform our understanding of the natural history of cold agglutinin disease?

Findings from real-world evidence studies

In a matched cohort comparison study in patients with and without CAD over a 10-year period, TEs were reported in:[1]

Patients with CAD
(n=180/608)

Patients without CAD
(n=1,033/5,873)

HR 1.94
[95% CI 1.64–2.30]

Higher risk of a TE in patients with CAD vs patients without CAD

Patients with CAD have an increased risk of TEs when compared with a matched non-CAD population

In a retrospective analysis of CAD patients from a large US database:[2]

of patients had ≥1 severe anaemia event within the first year of follow-up

CADENCE Registry: Collecting real-world CAD data[3]

Observational, prospective, global registry following 725 patients with CAD

To collect data, including comorbidities, treatments and disease characteristics

New insights may help improve treatments for patients with CAD

CAD, cold agglutinin disease; CI, confidence interval; HR, hazard ratio; TE, thromboembolic event.

1. Broome C, et al. *Res Pract Thromb Haemost*. 2020;4:628–35; 2. Mullins M, et al. *Blood Adv.* 2017;1:839–48; 3. Röth A, et al. Presented at 25th EHA Congress. 11-21 June 2020. Abst EP1618.

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Current and emerging treatment options for CAD: Importance of individualizing therapy

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How are complement inhibitors changing the current treatment paradigm for cold agglutinin disease?

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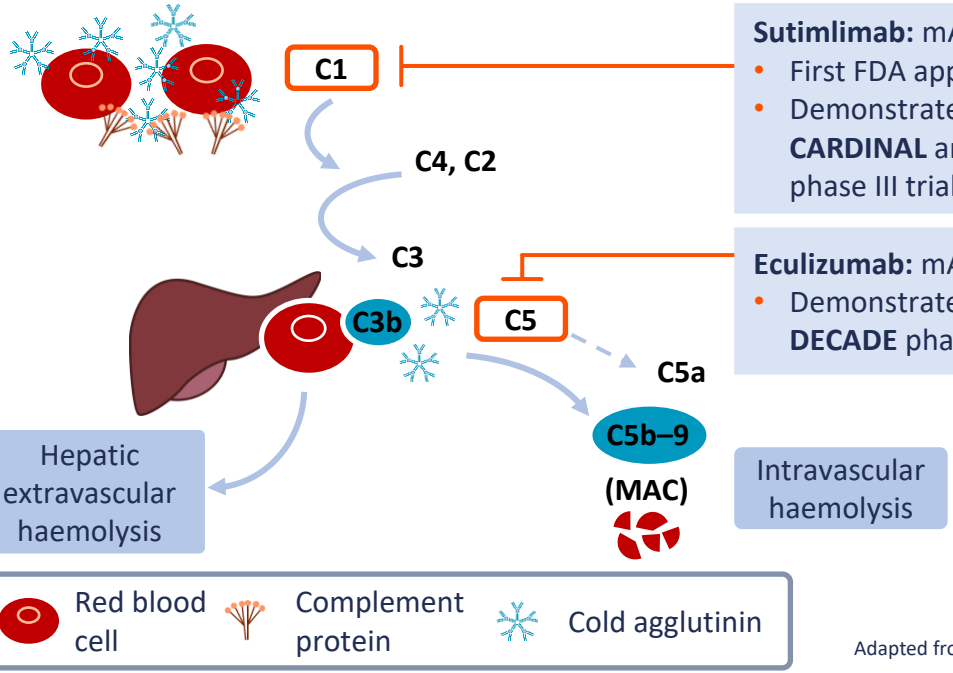
Complement targeting therapies in CAD



Sutimlimab: mAb C1s inhibitor
- First FDA approved treatment
- Demonstrated efficacy in **CARDINAL** and **CADENZA** phase III trials[1,2]

Eculizumab: mAb C5 inhibitor[3]
- Demonstrated efficacy in **DECADE** phase II trial[3]

Therapies under development:
- **Pegcetacoplan:** C3 inhibitor (trial ongoing: NCT05096403)[4]
- **Iptacopan:** Complement factor B inhibitor (trial ongoing: NCT05086744)[5]
- **BIVV020:** C1s inhibitor (trial completed: NCT04269551)[6]

Adapted from Berentsen. 2020.[7]

C, serum complement protein; CAD, cold agglutinin disease; FDA, Food and Drug Administration; mAb, monoclonal antibody; MAC, membrane attack complex; RBC, red blood cell.

1. Röth A, et al. *N Engl J Med.* 2021;384:1323–34; 2. Röth A, et al. *Blood.* 2022;140:980–91; 3. Röth A, et al. *Blood Adv*. 2018;2:2543–49; 4. ClinicalTrials.gov. NCT05096403; 5. ClinicalTrials.gov. NCT05086744; 6. ClinicalTrials.gov. NCT04269551. All trial data can be found at: https://clinicaltrials.gov/ct2/ (accessed 15 September 2022); 7. Berentsen S. *Front Immunol*. 2020;11:590

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In terms of the evolving treatment landscape for cold agglutinin disease, when should clinicians consider the use of rituximab or sutimlimab?

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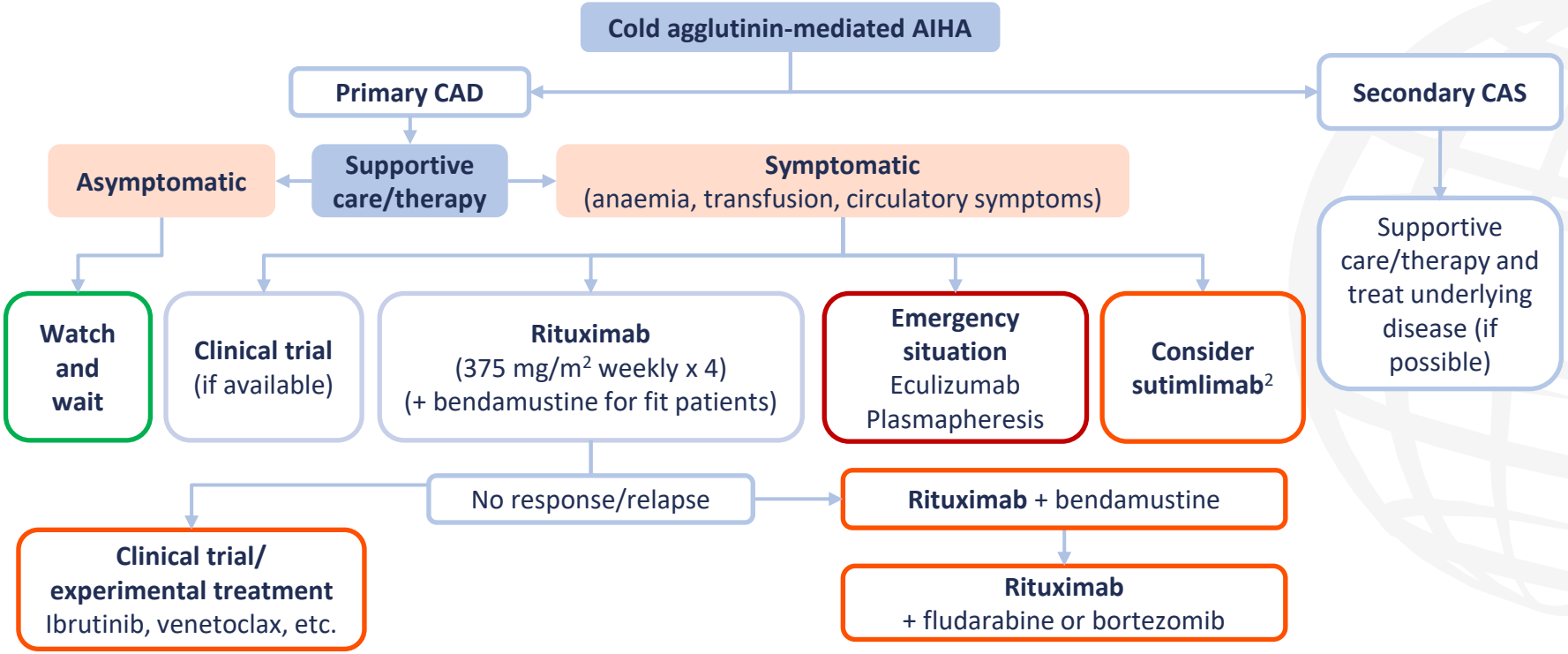
Treatment algorithm for CAD[1,2]



Adapted from Jäger, et al. 2020.

AIHA, autoimmune haemolytic anaemia; CAD, cold agglutinin disease; CAS, cold agglutinin syndrome.

1. Jäger U, et al. *Blood Rev*. 2020;41:100648;
2. FDA. Sutimlimab PI. 2022. Available at: www.accessdata.fda.gov/drugsatfda_docs/label/2022/761164s000lbl.pdf (accessed 15 September 2022).

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Are there any biomarkers or other factors to help tailor treatment to the individual patient?

Specific markers for CAD identification

- Primary CAD is characterised by chronic haemolysis and an absence of underlying disease[1]
- A monospecific DAT strongly positive for C3d and a CA titre ≥64 at 4° are currently needed for diagnosis[1]

Assessing immunoglobulin classes:

- Ig class quantification must be performed for all types of AIHA[2]
- SPE and immunofixation allow antibody identification[1]
- CAs in CAD are mostly monoclonal IgMκ[3]

Haemolytic markers offer insights to the disease state[4]

- **Bilirubin:** extravascular haemolysis; reduction may indicate treatment response
- **LDH:** intravascular haemolysis; decreases as haemolysis slows
- **Haptoglobin:** intravascular and extravascular haemolysis
- **Reticulocytes:** usually elevated in haemolysis until haemoglobin levels restored

AIHA, autoimmune haemolytic anaemia; C, serum complement protein; CA, cold agglutinin; CAD, cold agglutinin disease; DAT, direct antiglobulin test; Ig, immunoglobulin; IgM, immunoglobulin M; LDH, lactate dehydrogenase; SPE, serum protein electrophoresis.

1. Jäger U, et al. *Blood Rev*. 2020;41:100648; 2. Berentsen S, Barcellini W. *N Engl J Med.* 2021;385:1407-19; 3. Berentsen S. *Front Immunol*. 2020;11:590;
4. Barcellini W, Fattizzo B. *Dis Markers*. 2015;2015:635670.

What indicators can be used to measure treatment response and how can we measure the impact of cold agglutinin disease from a patient perspective?

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Indicators for measuring treatment response

Treatment goals

- Resolve underlying haemolysis[1]
- Reduce fatigue (resolve anaemia, decrease complement-driven cytokines)[2]
- Improve laboratory data[1]
- Improve quality of life[1]
- Improve or resolve cold-induced circulatory symptoms[1]

Assessing treatment efficacy

A multifocal approach considers symptoms and laboratory findings[3]

Complete response[3]

Absence of:

- Anaemia
- Signs of haemolysis
- Clinical symptoms of CAD
- Monoclonal serum protein
- Bone marrow lymphoproliferation

Partial response[3]

- Hb increase (≥2 g/dL or normal range)
- IgM decrease (≥50% initial value or normal range)
- Symptom improvement
- Transfusion independence

Assessing the patient experience

PROs help clinicians make effective treatment decisions[4]

- CAD regularly causes fatigue, and impacts on accumulated comorbidities[5,6]
- PROs offer insight into patients' perception of their disease state [4,6]
- **PRO outcomes include:[6]**
  - FACIT-Fatigue
  - SF-12
  - EQ-5D-5L
  - PGIC

CAD, cold agglutinin disease; EQ-5D-5L, EuroQol 5-dimension 5-level questionnaire; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, haemoglobin; IgM, immunoglobulin M; PGIC, Patient Global Impression of Change; PRO, patient-reported outcome; SF-12, 12-Item Short Form Health Survey.

1. Jäger U, et al. *Blood Rev*. 2020;41:100648; 2. Weitz IC. Presented at: ASH Annual Meeting 2020. Abstr 759; 3. Gabbard AP, Booth GS, et al. *Clin Hematol Int*. 2020;2:95–100; 4. Ciani O, Federici C. *Clin Ther*. 2020;42:25–33; 5. Joly F, et al. *JMIR Form Res*. 2022;6:34248; 6. Röth A, et al. *Ann Hematol*. 2022;101:2169-77.

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