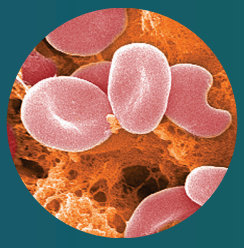

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›› Visit the Key Opinions website to see a video of Prof. Morie Gertz discussing cold agglutinin disease: https://keyopinions.info/downloads/cad-and-year-round-anemia

Abbreviations

aHR, adjusted hazard ratio; CI, confidence interval; DAT, direct antiglobulin test; HRU, health care resource utilization; LDH, lactate dehydrogenase; SD, standard deviation.

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PR. 2359

Chronic complement-mediated hemolysis in cold agglutinin disease drives year-round anemia regardless of the season

Morie Gertz

Introduction

Cold agglutinin disease (CAD) is a rare type of autoimmune hemolytic anemia characterized by chronic hemolysis.[1]

CAD usually affects people between the ages of 40 and 80 years. The median age at presentation is 67 years, but the disease has been diagnosed in people as young as 30 years old.[2] The disease is seen more often in women than men – around twice as many women are affected as men.[3,4]

As we shall see in the following article, CAD can have a variable and unpredictable course, occasionally with serious consequences.[1,5] And despite the name, evidence shows that people with CAD have a persistent risk of chronic hemolysis and thromboembolism regardless of the season.[6]

How is CAD diagnosed?

Generally, CAD is defined as an autoimmune hemolytic anemia with a monospecific C3d+ DAT and cold agglutinin titer >64 when tested at 4°C. In some cases there have been lower titers and/or DATs weakly positive for IgG and C3d.[7]

The term 'cold' is used because the autoantibodies – cold agglutinins (IgM antibodies) – causing hemolysis bind to their antigen on the surface of red blood cells at an optimal temperature of 0–4°C, unlike many other forms of autoimmune hemolytic anemia. However, depending on the thermal amplitude, they can also bind at higher temperatures. So the thermal amplitude may explain why in some patients the autoantibodies are pathogenic at higher temperatures.

That can then be followed by classical complement cascade activation binding C3b to the red blood cell surface, resulting in hemolysis.[8,9] Agglutination is not necessary for complement activation (Figure 1).

Hemolysis in people with CAD is driven entirely by the persistent activation of the classical complement pathway mediated by IgM antibodies,[10] which primarily target the I blood group system of carbohydrate antigens found on the surface of red blood cells. Extravascular destruction of red blood cells is the main mechanism of hemolysis in stable CAD. However, intravascular hemolysis can also occur in more severe cases when the full complement is activated.[8]

More than two-thirds of patients with CAD suffer from uncontrolled chronic

Figure 1. Adapted from: Patriquin CJ, Pavenski K. O, wind, if winter comes … will symptoms be far behind? Exploring the seasonality (or lack thereof) and management of cold agglutinin disease. Transfusion *2022;62(1):2–10.*[7]

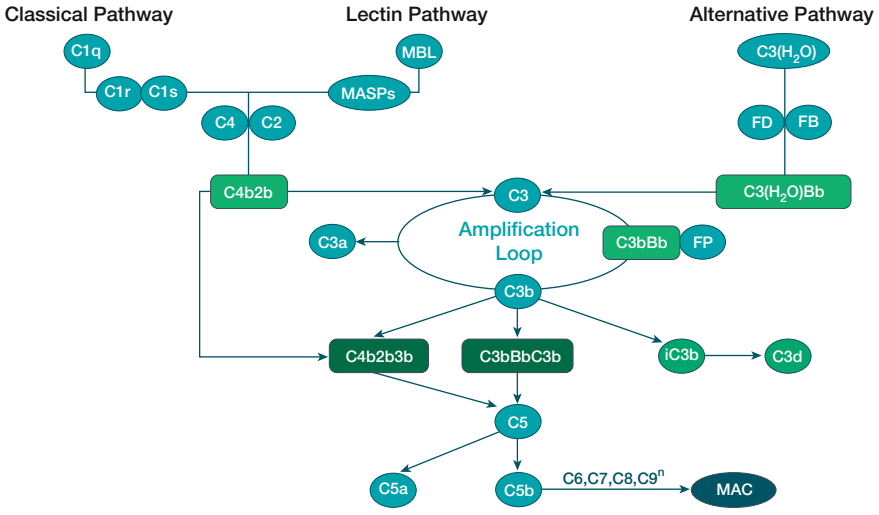
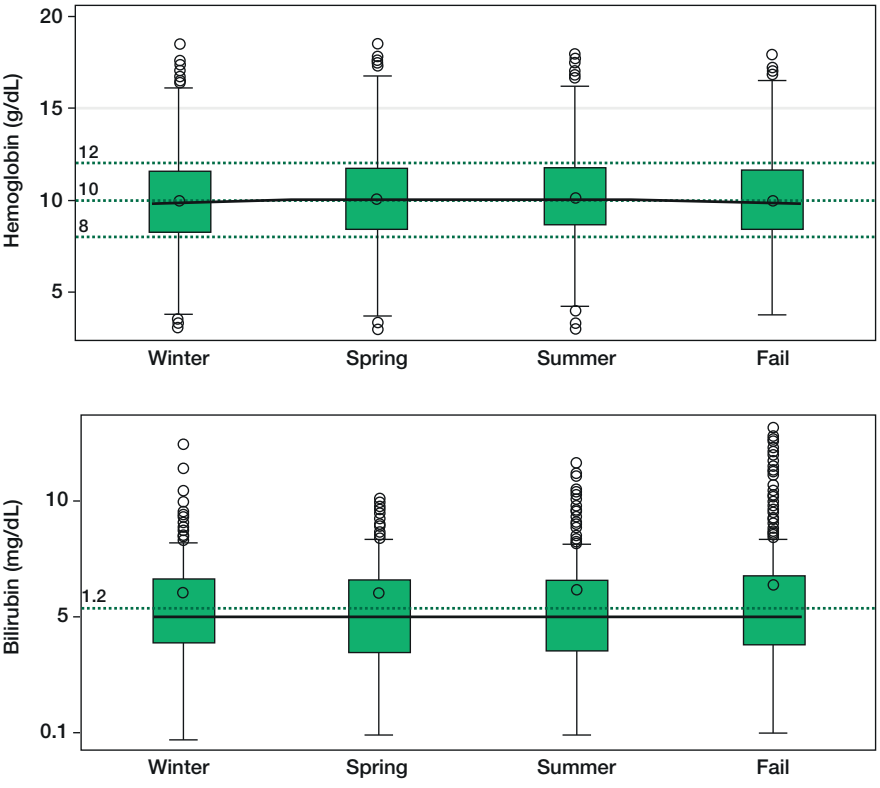


Figure 2. Source: Röth A, Fryzek J, Jiang X, et al. Complement-mediated hemolysis persists year round in patients with cold agglutinin disease. Transfusion *2022;62(1):51–9.*[6]



hemolysis with no or mild vascular symptoms.[1] Around 20% of the patients suffer from chronic hemolytic anemia with moderate-to-severe circulatory symptoms and only 10% may experience circulatory symptoms with compensated hemolysis. It is unlikely that complement is involved in circulatory symptoms.[7]

What is the effect of seasonal temperature on complement-mediated symptoms of CAD?

Persistent chronic hemolysis and thromboembolism risk may be evident all year in people with CAD. This has been demonstrated using the US database Optum, with which Roth *et al.* retrospectively identified individuals with terms relating to CAD in their notes. Among those with primary CAD anemia severity varied between patients no matter what the season and moderate anemia was present year-round (see Figure 2).[6]

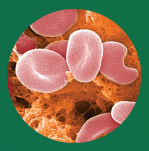
Further evidence of year-round presence of disease was evidenced in markers of hemolysis – bilirubin and LDH. Adjusted values for bilirubin were similar across all seasons and LDH figures indicate that hemolysis persisted year-round for the group of patients.[6]

Those laboratory data were reflected in health care resource utilization (HRU), transfusion days and thromboembolism through the seasons, which showed no significant variation across seasons except for a significantly higher number of outpatient visits in the Spring.[6]

What is the impact of CAD?

Quality of life and symptom severity

Anemia is common among patients with CAD, and can be profound with hemoglobin levels as low as 4.5g/dl seen in some studies. For example, in a study of 232 patients from 24 centers in five countries (Norway,



Italy, UK, Finland and Denmark) with CAD – 9 out of 10 had anemia: the mean hemoglobin level was 9.3 g/dl (median, 9.2 g/dl; range 4.5–15.3 g/dl) and around a quarter (26.7%, *n* = 62) had hemoglobin levels <8.0 g/dl.[1]

The severity of anemia varies for each patient over time, with many patients remaining severely anemic despite receiving multiple therapies.[5] The severity of anemia in CAD correlates well with markers of hemolysis – LDH and bilirubin – but not IgM[8] (Figure 3).

In a population-based retrospective, multicenter, follow-up study conducted in Norway, 86 people with CAD found that over half needed a transfusion at some point during the study, and a large number who had not needed transfusions became dependent on them, while others for whom transfusions had been necessary no longer needed them. The authors comment that their findings demonstrate that CAD does not follow a progressive course, and point to a disease that is highly variable.[2]

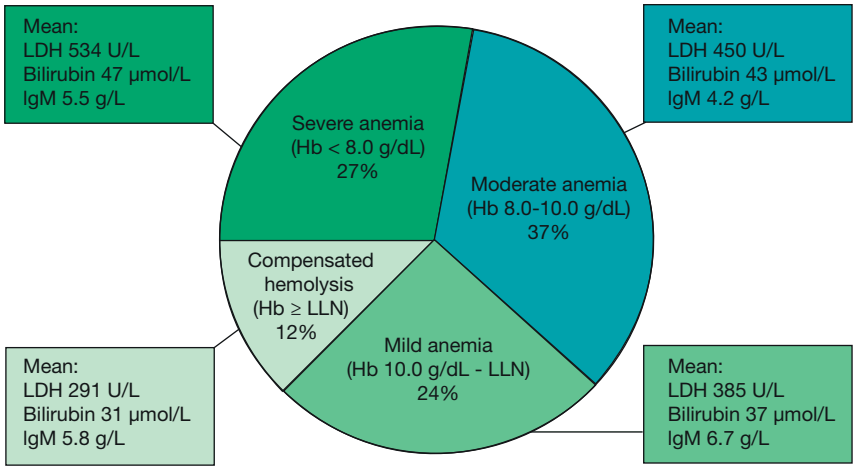
Variation in CAD severity throughout the course of the disease results in a range of symptoms – patients with mild symptoms can develop more severe symptoms at times requiring medical intervention, including red blood cell transfusions, and this fluctuation in symptoms can have a significant impact on quality of life. Most people with CAD are likely to have one episode of severe anemia during the course of their disease. For example, a retrospective analysis of 29 people with CAD identified from the Stanford Translational Research Integrated Database Environment from 2008 to 2016 found that 72% of patients had at least one severe anemia event within the first year of follow-up. And over the follow-up period, which averaged 5.6 years, there were 7.1 severe anemia events per patient-year. At least 65% (19/29) of the group received transfusions, with a mean of 11 transfusions per patient-year of follow-up (median 4.4; range 0.14–79), with an average 1.5 units (SD 1.3 units; range 1–15 units) of red blood cells given at each transfusion. Other studies have shown similar results with 48% to 80% of people with CAD having transfusions. The authors comment that their data demonstrate the volatile nature of CAD.[5]

People with CAD may be at higher risk of thromboembolic events and potentially at risk of associated mortality compared with those without the disease.[11]

For example, in a matched cohort comparison study comparing the risk of thrombotic events in people with and without CAD over a ten-year period Broome *et al.* found the risk almost twice as high in people with CAD (aHR, 1.94; 95% CI, 1.64–2.30). The researchers identified 608 patients with CAD from the Optum Claims-Clinical dataset between 2006 and 2016 and matched them with 5873 patients without CAD. For people with CAD compared with those without the disease the aHR for any venous event was 2.95 (95% CI, 2.28–3.82); for any cerebral event aHR was 1.26 (95% CI, 1.00–1.60), and for any arterial event aHR was 1.93 (95% CI, 1.37–2.72). Almost a third (29.6%; 180/608) of patients with CAD had at least one thrombotic event compared with 17.6% (1033/5873) of people without CAD. The authors acknowledge a number of limitations of the study, particularly that this analysis likely included patients with CAD and cold agglutinin syndrome, data on treatments in relation to thromboembolism development were not collected, and data on hereditary and acquired risk of thromboembolism were not collected.[11]

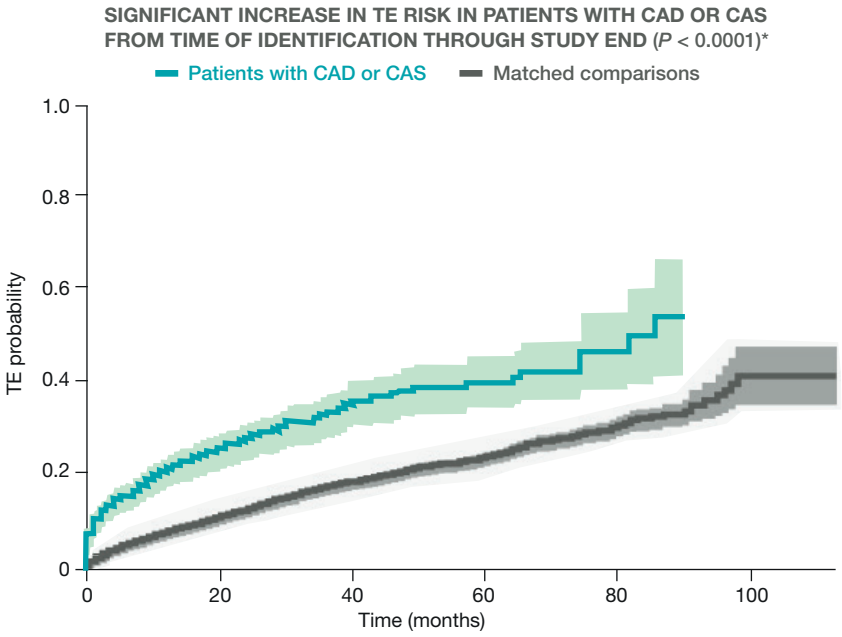
The cause of thrombosis in CAD has not yet been elucidated. However, the complement system is known to be an inflammatory mediator and has been shown to be associated with thrombotic and atherosclerotic disease.[12,13] Additional studies are needed to further understand the thromboembolic risk associated with CAD.

Figure 3. Severity of anemia in cold agglutinin disease (percentages of patients). Severity of anemia correlates nicely with markers of hemolysis (LDH and bilirubin levels), but not with IgM levels, which may be associated with complement-independent RBC agglutinating activity as well as complement-mediated hemolysis. Hb, hemoglobin level; LDH, lactate dehydrogenase; LLN, lower limit of normal (Hb 11.5 g/dL in women and 12.5 g/dL in men).



Source: Berentsen S. New Insights in the Pathogenesis and Therapy of Cold Agglutinin-Mediated Autoimmune Hemolytic Anemia. *Front Immunol* 2020;11:590.[8]

Figure 4.



- The increased incidence of TEs in patients with CAD or CAS was noted from the time of identification through the entire 10-year follow-up period
- The adjusted absolute risk difference calculation revealed a significant excess risk of TEs for patients with CAD or CAS vs patients without CAD or CAS at 1 year (11.9 per 100 patients, 95% CI: 11.7-12.1 per 100 patients) and 5 years (11.9 per 100 patients; 95% CI: 11.6-12.2 per 100 patients) after the index date

Source: Broome CM, Cunningham JM, Mullins M, *et al.* Increased risk of thrombotic events in cold agglutinin disease: a 10-year retrospective analysis. *Res Pract Thromb Haemost* 2020;4(4):628-635. doi:10.1002/rth2.12333.

Patient survey data reveal some of the realities of the impact of CAD on daily lives of people with the disease. An internet-based survey of patients conducted by Sanofi and the Cold Agglutinin Disease Foundation in September 2020 found that 90% (45/50) of the respondents said they had felt fatigued. Participants in the study were aged 18 years or older, self-reported a diagnosis of CAD and living in the US. Average age at diagnosis of CAD was 59.2 years. Most patients (44/50, 88%) had had symptoms before their diagnosis, including: fatigue (tiredness, lack of stamina, or weakness; 37/50, 74%); shortness of breath (19/50, 38%), and acrocyanosis (18/50, 36%). Twenty-one thought their CAD had become worse since diagnosis and 10 thought it had become better.[14]

In terms of impact on daily life, respondents said that physical wellbeing (40), emotional wellbeing (31) and social life (28) were most impacted.[14]

Respondents cited CAD-related symptoms such as fatigue (45/50), shortness of breath (29/50) as well as joint pain, headaches or acrocyanosis (22/50) as having the greatest impact on their daily life.[14]

Healthcare resource utilization

Inpatient hospitalizations, outpatient visits, and emergency room visits were analyzed for 410 patients with CAD identified from the Optum-Humedica database between 2006 and 2016. Patients with CAD required extensive healthcare resources compared with matched controls.[4]

HRU was also significantly higher among patients with CAD than those without CAD in the 12 months after the index date, for example:[4]

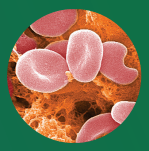
- 2.5X more patients with CAD used hospital inpatient services compared with matched comparisons: 36.3% (n = 149) vs 14.5% (n = 491) ($p < 0.0001$)
- 17.3 visits: the average number of outpatient visits compared with 6.7 visits for matched comparisons ($p < 0.0001$)
- 1.5X more patients with CAD required emergency room visits compared with matched comparisons: 25.9% (n = 106) vs 17.2% (n = 583) (p = 0.0005)

However, rates of HRU or number of transfusion days were not impacted by the changes in season.[15]

How is CAD managed?

The rarity of CAD makes clinical investigation of therapies challenging and comparative randomized controlled trial evidence is lacking.[16]

Treatment of CAD has traditionally been guided by disease severity. However, the strategy of cold avoidance has been found to be of variable efficacy in mild cases. Indeed, cold avoidance will not address complement-mediated symptoms.



Transfusions are given when indicated. However, many patients have been using off-label pharmacotherapies to manage CAD.[17]

In terms of pharmacotherapy, B-cell-directed therapies are available with overall response rates of 54% to 76%.[18]

The variable efficacy of treatments for CAD means that patients with the disease often relapse and therefore require further interventions. For example, Mullins *et al.* found that hemoglobin levels fell below 8g/dl in 67% (n=10) of patients within six months of initial treatment, and half with at least six months of follow-up had severe anemia after their last course of treatment.[5]

More recently treatment with monoclonal antibodies targeting the complement that triggers hemolysis is showing some promise, particularly for patients with symptoms driven predominantly by activation of the classical complement pathway.[8]

Conclusion

Cold agglutinin disease is a rare[1] chronic subtype of autoimmune hemolytic anemia. The disease has a variable and unpredictable course and is occasionally associated with serious consequences.[5]

The term 'cold' refers to the pathogenesis of the disease rather than its clinical manifestation and could be regarded as potentially misleading as symptoms can occur year-round and at different latitudes and climates.[6,11]

People with CAD may be at higher risk of thromboembolic events and potentially at risk of associated mortality compared with those without the disease.[11] Anemia is common among patients with CAD and can be profound with hemoglobin levels as low as 4.5g/dl seen in some studies.[1]

Cold avoidance is not effective for all patients at managing symptoms and off-label therapies have inherent limitations. The variable results of treatment mean that people with CAD often relapse and require further interventions.[5]

Year-round vigilance for monitoring and potential management of CAD is essential, and drugs that target the complement pathway – the source of risk in some patients – are needed.

Key points

- Cold agglutinin disease is a rare[1] type of chronic autoimmune hemolytic anemia.[5]
- The disease has a variable and unpredictable course and is occasionally associated with serious consequences.[5]
- Hemolysis is driven entirely by the persistent activation of the classical complement pathway.[10]
- A database study involving 594 people with CAD found that moderate anemia was present no matter what the season, and persistent chronic hemolysis and thromboembolism risk were evident all year-round.[6]
- People with CAD may be at higher risk of thromboembolic events and potentially at risk of associated mortality compared with those without the disease.[11]
- Anemia is common among patients with CAD, and can be profound with hemoglobin levels as low as 4.5 g/dl seen in some studies.[1]
- Cold avoidance is not effective for managing symptoms in all patients and off-label therapies have inherent limitations.[5]
- Recent treatments targeting the complement pathway are showing some promise, particularly for patients with symptoms driven predominantly by activation of the classical complement pathway.[8]

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References

1. Berentsen S, Barcellini W, D'Sa S, *et al*. Cold agglutinin disease revisited: a multinational, observational study of 232 patients. *Blood* 2020;136(4):480–8.

2. Berentsen S, Ulvestad E, Langholm R, *et al*. Primary chronic cold agglutinin disease: a population based clinical study of 86 patients. *Haematologica* 2006;91(4):460–6.

3. National Organization for Rare Disorders (NORD). Cold Agglutinin Disease (https://rarediseases.org/rare-diseases/cold-agglutinin-disease; accessed 12 September 2021)

4. Su J, Bylsma LC, Jiang X, *et al*. Healthcare resource utilization among commercially insured patients with cold agglutinin disease in the United States. *J Med Econ* 2020;23(8):902–

5. Mullins M, Jiang X, Bylsma LC, *et al*. Cold agglutinin disease burden: a longitudinal analysis of anemia, medications, transfusions, and health care utilization. *Blood Adv* 2017;1(13):839–48.

6. Röth A, Fryzek J, Jiang X, *et al*. Complement-mediated hemolysis persists year round in patients with cold agglutinin disease. *Transfusion* 2022;62(1):51–9.

7. Patriquin CJ, Pavenski K. O, wind, if winter comes … will symptoms be far behind? Exploring the seasonality (or lack thereof) and management of cold agglutinin disease. *Transfusion* 2022;62(1):2–10.

8. Berentsen S. New Insights in the Pathogenesis and Therapy of Cold Agglutinin-Mediated Autoimmune Hemolytic Anemia. *Front Immunol* 2020;11:590.

9. Swiecicki PL, Hegerova LT, Gertz MA. Cold agglutinin disease. *Blood* 2013;122(7):1114–21.

10. Shi J, Rose EL, Singh A, *et al*. TNT003, an inhibitor of the serine protease C1s, prevents complement activation induced by cold agglutinins. *Blood* 2014;123(26):4015-22.

11. Broome CM, Cunningham JM, Mullins M, *et al*. Increased risk of thrombotic events in cold agglutinin disease: a 10-year retrospective analysis. Res Pract Thromb Haemost 2020;4(4):628–35.

12. Conway EM. Reincarnation of ancient links between coagulation and complement. *J Thromb Haemost* 2015;13(Suppl 1):S121–32.

13. Ricklin D, Reis ES, Lambris JD. Complement in disease: a defence system turning offensive. *Nat Rev Nephrol* 2016;12(7):383–401.

14. Joly F, Schmitt LA, Watson PAM, *et al*. The Burden of Cold Agglutinin Disease on Patients' Daily Life: Web-Based Cross-sectional Survey of 50 American Patients. *JMIR Form Res* 2022;6(7):e34248.

15. Fryzek j, Hooda N, Esen B, *et al*. Seasonality of healthcare resource utilization among cold agglutinin disease patients in Denmark: a retrospective analysis. Poster presented at European Hematology Association Annual Meeting 2022.

16. Berentsen S. How I treat cold agglutinin disease. *Blood* 2021;137(10):1295–1303.

17. Berentsen S, Röth A, Randen U, *et al*. Cold agglutinin disease: current challenges and future prospects. *J Blood Med* 2019;10:93–103.

18. Berentsen S, Randen U, Vågan AM, *et al*. High response rate and durable remissions following fludarabine and rituximab combination therapy for chronic cold agglutinin disease. *Blood* 2010;116(17):3180–4.