Cold Agglutinin Disease: Natural History and Burden of Disease
Instructions

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Cold Agglutinin Disease Overview

- Cold agglutinins were identified more than 100 years ago
- The first monoclonal antibody ever identified was a cold agglutinin from a patient with cold agglutinin disease
- Primary cold agglutinin disease is responsible for approximately 15% of all autoimmune hemolytic anemias\(^1\)
- It is traditionally defined as AIHA mediated by cold agglutinins without any underlying condition, such as lymphoma, other malignancy, or infection

AIHA, autoimmune hemolytic anemia.

Autoimmune Hemolytic Anemia Consists of Warm, Cold, or Mixed Reactive Antibodies

- Cold agglutinins are autoantibodies that react optimally at cold temp. (3–4°C)\(^1\)
  - Can react at other temp. depending on the thermal amplitude
- If TA is >28–30°C, RBCs will agglutinate in acral parts of the circulatory system (even at mild ambient temp.), often leading to complement fixation and complement-mediated hemolysis\(^1\)
- Cold agglutinins almost exclusively interact with the "I" antigen on the RBC membrane present in almost all adults and children >18 months of age\(^1\)

<table>
<thead>
<tr>
<th>Form</th>
<th>Antibody</th>
<th>Temperature Reactivity</th>
<th>Cases, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm(^2)</td>
<td>IgG</td>
<td>37°C</td>
<td>75</td>
</tr>
<tr>
<td>Cold(^2)</td>
<td>IgM</td>
<td>Usually &lt;37°C</td>
<td>15</td>
</tr>
<tr>
<td>Mixed(^2)</td>
<td>IgG + IgM</td>
<td>Both 37°C and &lt;37°C</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

Ig, immunoglobulin; RBC, red blood cell; TA, thermal amplitude; temp., temperature.
Cold Agglutinin, the C1 Complex, and Activation of the Classical Complement Pathway

CA agglutinates RBCs at low temperatures and binds C1q

CA, cold agglutinin; C, complement protein; MBL, mannan-binding lectin; RBC, red blood cell.
Cold Agglutinin Disease Overview

- Few natural history studies exist
- Perceived as a relatively benign disease
- Patients often advised to “stay warm, move to warmer climate” as treatment for disease
Cold Agglutinin Disease in Norway: 86-Patient Cohort

- 16 cases per 1 million population
- Incidence: 1 case per 1 million per year
- Median age at onset: 67 years (range, 30–92 years)
- Male-to-female ratio: 0.55
- Median survival from onset: 12.5 years

- 91% cold-induced circulatory symptoms
- 74% exacerbation of anemia during febrile illness
- 51% received at least 1 RBC transfusion
- Mean initial hemoglobin 9.2 g/dL (range, 4.5–15.6 g/dL)

RBC, red blood cell.
Longitudinal Analysis of Cold Agglutinin Disease Burden

- The Stanford Translational Research Integrated Database Environment database was used to retrospectively identify patients with cold agglutinin disease diagnosed and treated at Stanford Health Care from 2000 to 2016.
- 29 patients were included in this analysis.
Stanford Cold Agglutinin Disease Cohort: Key Findings

- 79% of pts had severe/moderate (45%/34%) anemia at disease onset
- Mean (8.3 g/dL) and median (8.2 g/dL) hemoglobin were similar
- 72% of pts had at least 1 severe anemia event in first year of follow up
- 5 pts had a thrombotic event, 3 pts had a portal vein thrombosis, and 2 pts had an acute venous embolism and thrombosis of deep vessels

Pts, patients; PY, patient-years; RBC, red blood cell; SD, standard deviation.
Stanford Cold Agglutinin Disease Cohort: Key Findings

- The severity of anemia varied for each patient over time
- 7.1 severe anemia events per PY (787 events/110.5 PY)
- 10.8 moderate anemia events per PY (1196 events/110.5 PY)
- 8.0 mild anemia events per PY (888 events/110.5 PY)
Stanford Cold Agglutinin Disease Cohort: Key Findings

- **65%** of patients had at least one transfusion
- Mean transfusions per PY: **11.0** (median, 4.4; range, 0.14–79)
- Mean units of RBCs per transfusion: **1.5** (SD, 1.3; range 1–15 units)
Stanford Cold Agglutinin Disease Cohort: Key Findings

- Mean number of therapies per patient: 3.5
- Many patients remained severely anemic despite multiple therapies
- 67% of patients had a severe anemia event within 6 months of initial therapy

Pts, patients; PY, patient-years; RBC, red blood cell; SD, standard deviation.
Retrospective Analysis of the Largest Cold Agglutinin Disease Cohort to Date

- Optum’s de-identified Integrated Claims-Clinical dataset
  - Links EMR data with adjudicated claims data
  - Provides de-identified information on medications, laboratory results, vital signs, body measurements, diagnoses, procedures, and clinical notes distilled with Natural Language Processing for approximately 55 million patients in the United States
- 814 patients with cold agglutinin disease and 7960 comparison patients were identified from 2006 to 2016
- The average number of comparisons per patient with cold agglutinin disease was 9.8, with only 4% of patients having fewer than 10 matched comparators

EMR, electronic medical record.
Broome C, et al. ASH 2017; Poster 928.
Retrospective Analysis of the Largest Cold Agglutinin Disease Cohort to Date

Age

70% ≥65 years of age at diagnosis

Broome C, et al. ASH 2017; Poster 928.
Retrospective Analysis of the Largest Cold Agglutinin Disease Cohort to Date

Gender

62% Female

Broome C, et al. ASH 2017; Poster 928.
Retrospective Analysis of the Largest Cold Agglutinin Disease Cohort to Date

Race

- 83.8% Caucasian
- 8.8% Unknown
- 2.3% Asian
- 5% African American

Broome C, et al. ASH 2017; Poster 928.
Retrospective Analysis of the Largest Cold Agglutinin Disease Cohort to Date

Geography

- 43.6% Midwest
- 28.9% South
- 12.9% Northeast
- 12.4% West
- 2.2% Unknown

Broome C, et al. ASH 2017; Poster 928.
Retrospective Analysis of the Largest Cold Agglutinin Disease Cohort to Date

Mean follow up: 75.6 months (range: 0–125 months)

<table>
<thead>
<tr>
<th>Cold agglutinin disease (N = 814)</th>
<th>Matched comparison (N = 7960)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in 2016 or age at death</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;25 years</td>
<td>21 (3)</td>
</tr>
<tr>
<td>25–64 years</td>
<td>225 (28)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>568 (70)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>307 (38)</td>
</tr>
<tr>
<td>Female</td>
<td>507 (62)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>682 (84)</td>
</tr>
<tr>
<td>African American</td>
<td>41 (5)</td>
</tr>
<tr>
<td>Asian</td>
<td>19 (2)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>72 (9)</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
</tr>
<tr>
<td>Northeast</td>
<td>105 (13)</td>
</tr>
<tr>
<td>South</td>
<td>235 (29)</td>
</tr>
<tr>
<td>Midwest</td>
<td>355 (44)</td>
</tr>
<tr>
<td>West</td>
<td>101 (12)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>18 (2)</td>
</tr>
<tr>
<td><strong>Follow-up month</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>75.6 (38)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>81 (0–125)</td>
</tr>
</tbody>
</table>

SD, standard deviation.
Broome C, et al. ASH 2017; Poster 928.
Retrospective Analysis of the Largest Cold Agglutinin Disease Cohort to Date: Thromboembolic Events

- 395 TEs were recorded among 255 patients with cold agglutinin disease
- 31.3% of patients with cold agglutinin disease developed a TE compared with 20.2% of comparison patients ($P<0.0001$)

TE, thrombotic event.
Broome C, et al. ASH 2017; Poster 928.
Retrospective Analysis of the Largest Cold Agglutinin Disease Cohort to Date: Thromboembolic Events

- 18% of patients with cold agglutinin disease had 1 type of TE compared with 14% of the comparisons ($P<0.0001$)
- 13% of patients with cold agglutinin disease and 6% of comparisons had 2 or more types of TE ($P<0.0001$)

TE, thrombotic events.
Broome C, et al. ASH 2017; Poster 928.
Number, Percentage, OR, and 95% CI for TEs in Patients Compared With Matched Patients: 2006–2016

<table>
<thead>
<tr>
<th>Number of TEs</th>
<th>Cold agglutinin disease, n (%)</th>
<th>Comparisons, n (%)</th>
<th>OR (95% CI)</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>559 (68.7)</td>
<td>6355 (79.8)</td>
<td>1.85</td>
<td>(1.52–2.24)</td>
</tr>
<tr>
<td>1+</td>
<td>255 (31.3)</td>
<td>1605 (20.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio; TE, thrombotic event.
<sup>a</sup>Conditional logistic regression.
Broome C, et al. ASH 2017; Poster 928.
## Number and Percentage of Patients With Cold Agglutinin Disease and Matched Comparisons With TEs in the Optum Database: 2006–2016

<table>
<thead>
<tr>
<th>Disease</th>
<th>TEs in patients with cold agglutinin disease, n (%)</th>
<th>TEs in comparisons, n (%)</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any venous events</td>
<td>86 (10.6)</td>
<td>282 (3.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Portal vein obstruction</td>
<td>6 (0.7)</td>
<td>2 (0.03)</td>
<td>N/A&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>37 (4.5)</td>
<td>148 (1.9)</td>
<td>0.003</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>40 (4.9)</td>
<td>135 (1.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mesenteric</td>
<td>10 (1.2)</td>
<td>20 (0.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any cerebral events</td>
<td>201 (24.7)</td>
<td>1276 (16.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cerebral infarction, occlusion, and stenosis of cerebral and precerebral arteries</td>
<td>184 (22.6)</td>
<td>1112 (14.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vascular syndromes of brain in cerebrovascular diseases,</td>
<td>47 (5.8)</td>
<td>365 (4.6)</td>
<td>0.041</td>
</tr>
<tr>
<td>Transient cerebral ischemic attacks, and related syndromes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any arterial events</td>
<td>68 (8.4)</td>
<td>373 (4.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Arterial embolism and thrombosis</td>
<td>16 (2.0)</td>
<td>60 (0.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>55 (6.8)</td>
<td>329 (4.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>255 (31.3)</td>
<td>1605 (20.2)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

N/A, not applicable; TE, thrombotic events. <sup>a</sup>Conditional logistic regression, adjusted for age, gender, race, region, active time in the system, and follow-up months; <sup>b</sup>The P-value is not reliable owing to too few cases.

Broome C, et al. ASH 2017; Poster 926.
Percentages of Patients With Cold Agglutinin Disease by Anemia Severity Prior to a TE in the Optum Database: 2006–2016

**Minimum Hgb Severity Within 1 Month Prior to TE**

- Severe (Hb ≤8 g/dL): 23.1%
- Moderate (Hb 8.1–10 g/dL): 47.4%
- Mild (Hb >10 g/dL): 29.5%

Hgb, hemoglobin; TE, thrombotic event.
Broome C, et al. ASH 2017; Poster 928.
Percentages of Patients With Cold Agglutinin Disease by Bilirubin and LDH Abnormality Prior to a Thrombotic Event in the Optum Database: 2006–2016

90.5%

9.5%

Abnormal bilirubin or LDH
Normal bilirubin and LDH

LDH, lactate dehydrogenase.
Broome C, et al. ASH 2017; Poster 928.
Hemoglobin Levels Within 12 Months of Treatment With at Least 12 Months’ Follow-up After Treatment (Excluding the Patients With Transfusion Within 1 Month Before and 12 Months After Treatment)

<table>
<thead>
<tr>
<th>Patients had Hgb value within 12 months of treatment, a n</th>
<th>Maximum Hgb increase, mean (SD) b</th>
<th>Patients who had response, c n (%)</th>
<th>Average number of days to respond c (among responders)</th>
<th>Average number of days to reach maximum Hb (among responders)</th>
<th>Proportion of patients with Hgb decrease at least 1.5 g/dL after response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>35</td>
<td>1.8 (1.5)</td>
<td>19 (54.3)</td>
<td>84.1</td>
<td>181.9</td>
</tr>
<tr>
<td>Rituximab/bendamustine</td>
<td>5</td>
<td>1.0 (1.4)</td>
<td>2 (40.0)</td>
<td>160.5</td>
<td>262.0</td>
</tr>
</tbody>
</table>

Hgb, hemoglobin; SD, standard deviation. aIf patient did not have Hgb value on the day of treatment, the most recent Hgb value within 1 month before treatment is the treatment value; b0 if no hemoglobin increase after treatment; cHgb change of at least 1.5 g/dL after treatment.

Broome C, et al. ASH 2017; Poster 928.
Bilirubin or LDH Levels After Treatment for Patients With at Least 12 Months’ Follow-up After Treatment (Excluding Patients With Transfusion Within 1 Month Before and 12 Months After Treatment)

<table>
<thead>
<tr>
<th></th>
<th>Patients with cold agglutinin disease with bilirubin or LDH values within 12 months after treatment, N</th>
<th>Elevated bilirubin within 12 months after treatment, n (%)</th>
<th>Elevated LDH within 12 months after treatment, n (%)</th>
<th>Elevated bilirubin or LDH within 12 months after treatment, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>28</td>
<td>18 (64.3)</td>
<td>18 (64.3)</td>
<td>22 (78.6)</td>
</tr>
<tr>
<td>Rituximab/bendamustine</td>
<td>2</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
<td>2 (100.0)</td>
</tr>
</tbody>
</table>

LDH, lactate dehydrogenase.
Broome C, et al. ASH 2017; Poster 928.
Summary

- The prevailing treatment paradigm for cold agglutinin disease has traditionally been based on hemoglobin levels and RBC transfusion requirements.
- This retrospective analysis, using the Optum Integrated Claims-Clinical dataset, is the first to demonstrate that cold agglutinin disease is associated with a statistically significant increased risk of venous, arterial, and cerebral TEs and that patients with cold agglutinin disease are more likely to have more than 1 type of TE.
- The severity of anemia does not appear to predict TE risk, whereas markers of hemolysis (LDH and/or bilirubin) may.

LDH, lactate dehydrogenase; RBC, red blood cell; TE, thromboembolic event.
Summary

- Standard therapy with rituximab in this cohort of patients did not result in sustained control of hemolysis, as demonstrated by elevated bilirubin and LDH values in 90% of patients within 12 months of last dose.
- The potential morbidity and possible mortality associated with thrombotic events in patients with cold agglutinin disease should not be underestimated.
- Future studies should evaluate not only Hb response but also evidence of ongoing hemolysis/complement activity. Prevention of thrombotic events in cold agglutinin disease may require an alternative treatment approach that targets complement.

Hgb, hemoglobin; LDH, lactate dehydrogenase.