KPMG

Improving Quality of Care in Cold Agglutinin Disease

May 2023

Terms of reference

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Foreword

Foreword

Message from the Chair of the SteerCo

Cold Agglutinin Disease (CAD) is a rare hematological condition which can significantly impact the quality of life of patients. The nature of the disease and its symptoms can impede day-to-day life for patients, with substantial social and psychological impact.

CAD is a rare condition with limited awareness and prevailing unmet needs. Awareness and education amongst the general population and medical community, along with adherence to protocols by clinical teams can contribute to early diagnosis and prompt treatment. To progress and improve care delivery, diagnosis and treatment will need to continue to adapt.

The challenges that we face as providers of CAD care require us to collaborate with our peers, other specialists, community-based clinicians, and the wider medical community to share knowledge and continue to learn from one another.

We welcome the release of this report, in which KPMG has documented a number of examples of good practice in CAD care from centres around the world. The findings in this report demonstrate how dedicated care teams are tackling CAD-associated challenges in varied and innovative ways. We hope these examples can inspire readers to improve their own services and ultimately improve quality of life and treatment outcomes for patients living with CAD.

Dr Sigbjørn Berentsen, MD, PhD

02

Executive Summary

This Quality of Care report was developed to support the improvement of CAD patient care globally

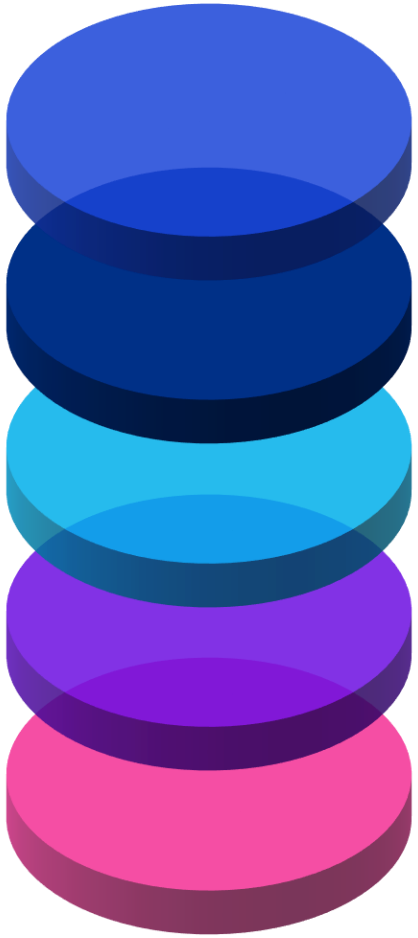
Raise awareness
of the current challenges faced in the treatment and management of CAD

Facilitate greater collaboration
between CAD specialists, community hematologists, primary care, and other HCPs

Support centers globally
in their pursuit of delivering standardised high-quality care

Develop CAD-specific interventions
to drive improvement in the quality of patient care

KPMG conducted a study on the current CAD care paradigm through a structured methodology



01

Conduct literature review

Academic/clinical publications, local/international guidelines

02

Conduct virtual interviews and visit sites

Multiple interviews with experts from 11 medical centers across the US, EU, and Asia

03

Document best practices

Key themes including symptom awareness, diagnosis, treatment, and follow-up

04

Review findings with CAD experts

Testing and validation of findings with world-leading experts in CAD care

05

Finalize report

Documentation of best practices and recommendations from participating centers and Steering Committee (SteerCo)

We have identified key CAD care challenges through literature review and our interviews and site visits

	Awareness and symptom identification	Diagnosis	Medical management	Non-medical management	Follow-up
Healthcare system	— Symptoms may not always be visible in the affected population. While CAD is generally witnessed in the elderly, symptoms can also manifest at a younger age [1]	— Testing challenges from blood agglutination in cold lab environments often lead to delayed results. Samples must be collected, transferred, stored, and processed quickly[2][5][6]	— Treatments often require continuous administration and may not always be effective for patients who have relapsed[5]	— CAD management protocols are established by well-resourced specialists and can be difficult to disseminate on a wider scale[8]	— Lacking established standard of care protocols for CAD can lead to high healthcare utilization post-treatment (e.g., patients can have an average of 7 ER visits per year)[9]
Healthcare professional	— Limited awareness and rarity of CAD (incidence of 1 per million) impacts physicians' recognition and interpretation of CAD symptoms[2][3] — The rare nature of CAD reduces interest and investment in training required to adequately educate the wider clinician community on CAD identification[12]	— Late diagnosis can be driven by delayed referrals from primary care and blood testing issues due to clumping in samples [2][3][7] — Lack of standardized protocols, and technician training due to CAD's rarity could lead to testing inefficiencies[12] — Diagnostic tests must be sensitive and specific in order to identify CAD with differential diagnoses[12]	— Treatment approaches can vary significantly, and HCPs must base proposed interventions on symptom severity and comorbidities or associated diseases[1] — Patients and blood products must be kept in a warm environment during transfusion to avoid agglutination and hemolysis[11]	— Lack of communication channels between specialists and primary care, which can impact efficient management of CAD patients across both care settings[1] — HCPs may not be aware of a patient's CAD diagnosis and haematologists considerations when they seek medical care for other health conditions or in emergency settings [12]	— Lack of coordination between specialists and primary care providers can lead to delays in data transfer, thereby impacting patient care[9][10]
Patient	— Limited CAD awareness in the general population can lead to increased patient stress and anxiety[4]	— Delayed diagnosis or misdiagnosis leads to disease progression, which can cause emotional distress for patients[4]	— Available treatments vary in their efficacy, side effect profile, and duration of response [1][2] — In some markets, CAD treatment can be expensive and inaccessible[12]	— There is a communication gap between specialists and patients regarding the impact of a chronic rare disease diagnosis on their physical and mental health[9]	— Patients with rare disease are more likely to suffer from psychological conditions[9], for which support is not always available

Sources: (1) CAD page, US Department of Health & Human Services - Genetic and Rare Diseases Information center, May 2016; (2) Diagnosis and Treatment of Cold Agglutinin Disease, Clinical Advances in Hematology & Oncology, (2019); (3) Cold Agglutinin Disease, Review article, Blood (2013); (4) Planning for the future when you have Cold Agglutinin Disease, Cold Agglutinin Disease news website, September 2020; (5) Cold Agglutinin Disease: current challenges and future prospects, Journal of Blood Medicine (2019); (6) Cold Agglutinin Disease; A Laboratory Challenge, Iranian Red Crescent Medical Journal, (2015); (7) Br J Gen Pract. Preventing gatekeeping delays in the diagnosis of rare diseases (2018); (8) Cold Agglutinin Disease, Hematology Am Soc Hematol Educ Program (2016); (9) National Gaucher Foundation. Tackling Mental Health Challenges Within the Gaucher Disease Community (2019); (10) Cold Agglutinin Disease burden: a longitudinal analysis of anemia, medications, transfusions, and health care utilization, Blood Advances (2017); (11) Cold Agglutinin Disease, UpToDate, October 2022 (12) KPMG primary research

Identified best practices were grouped thematically

Themes	Observed best practice interventions
Collaboration	— **Collaboration with affiliate hospitals:** Setting up local networks between hospitals in nearby regions can improve referrals[1], [7] — **Interdisciplinary collaboration:** Regular connection of hematology and transfusion teams to discuss and provide coordinated care[2], [6] — **Access to other specialists:** Established collaboration with other specialists can provide patients with cross-disciplinary care[2], [3] — **Coordinating physician assistants (PAs):** PAs support the hematologists in providing comprehensive care to patients[7]
Processes and protocols	— **Specialized transfusion departments:** Offering specialized transfusion capabilities including testing and transplant medicine[1], [5], [6], [7] — **Defined protocols:** Clinical team adherence to strict protocols for sample handling, diagnosis, treatment, and management of CAD[3], [4] — **Experienced lab professionals:** Ensure that an experienced team of technicians with advanced training manages care for CAD patients[3]
Patient education and support	— **Education for patients:** Focus patient education initiatives on long-term management of CAD including lifestyle changes and monitoring[1], [2] — **Patient focus groups:** Set up focus groups to bring CAD patients together and improve understanding of their needs[4] — **Access to support services:** Offer support services such as financial aid, psychological care, and financial guidance to CAD patients[5], [6]
Knowledge sharing	— **Education programs:** Have clinical teams participate in educational seminars and research meetings to foster knowledge-sharing[1], [5], 7] — **National MDT connect:** Set up an (inter)national MDT meeting among physicians from different centers through virtual channels[2] — **International seminars:** Organize regular educational seminars in collaboration with industry and medical societies[3]
Focus on clinical research	— **Commitment to clinical research:** Conduct basic & clinical research, aiming to develop novel CAD therapies[1], [2], [4], [5], [6]
Use of technology	— **Focus on digital innovation:** Aim to ease access to medical records and develop initiatives to improve patients' quality of life with digital solutions[4], [5]

Notes: Practices observed in the following centers: (1) Osaka University Hospital, Japan (2) Ospedale Maggiore di Novara, Italy; (3) Medical University of Vienna, Austria; (4) University College Hospital London, UK (5) Medstar Georgetown University Hospital, USA (6) University Of California – San Francisco, USA; (7) University of Southern California, US
This list is not exhaustive, and while we have documented these interventions in specific centers, they may resonate with other centers not explicitly mentioned

03

Context

CAD is a rare autoimmune hemolytic anemia, intensified by cold climatic conditions

Definition

CAD is a form of autoimmune hemolytic anemia (AIHA) in which cold agglutinins (IgM autoantibodies) are formed against red blood cell (RBC) antigens at temperatures (3-4°C). Clinical symptoms manifest primarily in the extremities due to the agglutination (clumping) or breakdown of RBCs

Symptoms

CAD signs and symptoms may vary from patient to patient and may worsen over time. These include:

- Anemia, with a median hemoglobin level of 8.9 g/dL
- Frequent episodes of fatigue and weakness
- Poor blood circulation leading to acrocyanosis or Raynaud syndrome
- Dyspnea (shortness of breath)

Disease types

CAD is subdivided into primary and secondary CAD

- Primary (idiopathic) CAD, refers to cold agglutinins that cause RBC agglutination and extravascular hemolysis without any underlying infection or malignancy. These individuals are characterized as having low-grade clonal bone marrow disorder
- Secondary CAD, also called Cold Agglutinin Syndrome (CAS), occurs as a result of an underlying disorder such as lymphoid malignancies, viral infections or autoimmune disorders[a][1, 2]

Diagnosis

Both physical and laboratory tests are required to confirm the diagnosis of CAD[1, 2]

Key diagnostic tests

Physical examination

Focuses on documentation of the signs and symptoms in each patient, including cold-induced circulatory effects (e.g. acrocyanosis or Raynaud syndrome)

Blood tests

Tests include complete blood cell count (CBC), a peripheral blood smear, a reticulocyte count, the Coombs test, a cold agglutinin (CA) titer, and serum protein electrophoresis and serum immuno-electrophoresis (immunofixation)

- Diagnostic criteria for CAD includes chronic hemolysis, a positive direct antiglobulin test (Coombs test), a cold agglutinin titer ≥64 at 4°C, and the absence of malignancy or relevant infections such as Epstein-Barr virus (EBV) or Mycoplasma
- A Coombs test detects the presence of specific antibodies attached to the membranes of erythrocytes and is positive for ~90% of individuals with CAD

Other associated tests

- Bone marrow aspiration or biopsy is only required to rule out malignancies. Flow cytometry studies of bone marrow may be performed to detect abnormal monoclonal lymphocytes
- Biochemical assays including bilirubin levels and haptoglobin protein levels are used to confirm the presence of hemolytic anemia in individuals with CAD

Notes: (a) Some of the causes for secondary CAD are malignancies including non-Hodgkin's lymphoma, chronic lymphocytic leukemia, or monoclonal gammopathy; and infections such as Mycoplasma pneumoniae, Epstein-Barr virus, mumps, or cytomegalovirus; or other autoimmune disorders such as rheumatoid arthritis or systemic lupus erythematosus

Sources: (1) Cold Agglutinin Disease, Rare Disease Advisor, 2021; (2) Cold Agglutinin Disease, Upto Date, 2023

CAD is a rare disease with heterogeneity of symptoms which can significantly impact patients' quality of life

CAD prevalence

CAD is a rare disease that accounts for ~15% of all AIHA diagnoses

- The incidence of CAD is 1 person per million globally, while in the US, the incidence is ~3.3 per million
- Given CAD's predisposition to temperature, prevalence in colder climates is nearly four times greater than in warmer climates. For instance, a study showed that CAD prevalence rates in were lower Northern Italy (~5 per million) compared to Norway (~20.5 per million)[(1)]

Severity of symptoms

- Patients with CAD may exhibit different symptoms depending on disease severity, which can be exacerbated during cold winter months
- Many CAD patients experience severe anemia and other relapsing symptoms, even after undergoing multiple therapies
- In the US, an average of 7 severe anemia events occur every year, and at least 65% of patients go through 11 transfusions per patient-year[(a)(2)]

Impact on quality of life

- CAD has a significant impact on patients' physical and emotional wellbeing, social life, and household finances
- In the US, nearly 90% of CAD patients experience fatigue on a daily basis, with episodes of increased intensity or sensitivity. Multiple transfusions and hospital visits and disrupted employment may further impact patients' psychological health[(3)]

Notes: (a) It is based on a study including 29 CAD patients treated at Stanford Health Care center in the US, from 2000 to 2016. Key findings included 7.1 severe anemia events per patient-year, and at least 65% of the patients went through transfusions with a mean of 11 transfusions per patient-year; (b) It is based on a survey of 50 CAD patients in the United States, conducted in 2020. Nearly 90% of the patients surveyed reported having experienced fatigue, on a daily basis, with episodes of increased intensity or sensitivity

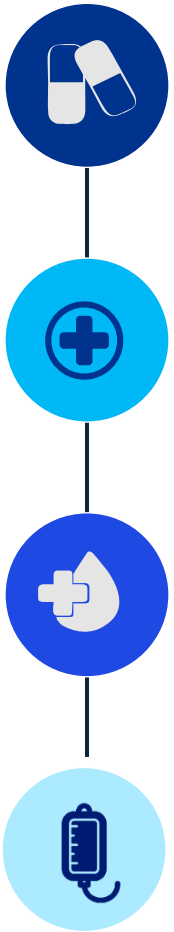
Sources: (1) Cold Agglutinin Disease, Rare Disease Advisor, 2023; (2) Mullins M. et.al. Cold Agglutinin Disease burden: a longitudinal analysis of anemia, medications, transfusions, and health care utilization, Blood Adv. 2017 May 23; 1(13): 839–848; (3) Joly F. et.al. The Burden of Cold Agglutinin Disease on Patients' Daily Life: Web-Based Cross-sectional Survey of 50 American Patients, JMIR Form Res. 2022 Jul; 6(7): e34248

CAD standard of care is reliant on the severity of symptoms

CAD treatment decisions are made depending on the severity of clinical symptoms

- **Mild symptoms** can be managed with lifestyle changes, including avoiding exposure to cold temperatures, avoiding cold food and water, using room heaters, and wearing warm clothing
- **Moderate or severe symptoms** require medical intervention and drug therapy

Response to treatment is primarily monitored by tracking symptom progression and measuring hemoglobin levels, markers of hemolysis (lactate dehydrogenase, bilirubin, haptoglobin, reticulocyte count), and IgM levels



Anti-B Cell therapies

- For patients with significant symptomatic hemolytic anemia or cold-induced ischemic symptoms. Anti-B Cell therapies target pathogenic B-cell clones in the bone marrow that produce monoclonal Cas. Some are used as a first-line treatment
- If patients do not respond to monoclonal antibodies (mAbs), then they can be treated with combination therapies including mAbs with alkylating agents

Therapies targeting complement proteins

- These therapies target the classical complement pathway responsible for extravascular and intravascular hemolysis in CAD. They reduce the need for transfusion and improve anemia and fatigue
- Some of the mAbs included in this therapy are Sutimlimab, Eculizumab, and Pegcetacoplan

Plasmapheresis

- Plasmapheresis removes CAs, primarily IgM autoantibodies from the plasma
- Plasmapheresis is only used as a temporary measure in emergency situations for patients with acute critical hemolysis, owing to its potential for long-term treatment effects

Blood transfusion

- Blood transfusions are utilized in emergency cases of severe hemolysis precipitated by infection or cold during winter months
- Patient samples are kept warm during pre-transfusion testing and cross-matching, and blood products are also warmed to body temperature prior to transfusion

Sources: (1) Cold Agglutinin Disease, Rare Disease Advisor, 2023; (2) Cold Agglutinin Disease, Upto Date, 2023; (3) Berentsen S. et.al. Cold Agglutinin Disease: Current challenges and future prospects, J Blood Med. 2019; 10: 93–103.

04

Methodology

KPMG conducted a study on the current CAD care paradigm through a structured methodology

01

Conduct literature review

Reviewed key published evidence on recommended good practice care and management e.g. local and international guidelines, academic/clinical publications

02

Conduct virtual interviews and visit sites

Conducted HCP interviews and onsite visits to understand the patient pathway, current practices, key challenges, and aspirations for improvements

03

Document best practices

Recorded interventions specific to each center. Findings were collated and organized by relevance across the patient pathway and identified common themes

04

Review findings with CAD experts

Formed a Steering Committee of CAD experts from around the world to test our findings. The SteerCo offered guidance and challenges to ensure global applicability and communication effectiveness

05

Finalize report

Collated the validated findings and expert recommendations for good practice in patient care and management in a final report

A literature review was initially conducted to identify evidenced challenges and good practices in CAD care

KPMG reviewed academic, peer-reviewed publications in addition to high-quality grey literature from a number of sources

International recommendations and research papers related to CAD were also included, such as JMIR[(a)] Formative Research, Journal of Blood Medicine, Blood Advances, Rare Disease Advisors, National Library of Medicine

KPMG consulted numerous publications by national governments and third-party databases detailing CAD good practices and future plans

Our robust literature review informed our site visit protocols. It helped us establish a comprehensive view of the care delivery in CAD landscape, with initial findings providing an insight into current challenges and common practices.

Notes: (a) JMIR represents Journal of Medical Internet Research

We interviewed various stakeholders to understand the care delivery pathway in CAD

Center overview (patient cohort size, facilities, funding)

Patient pathway (from awareness / symptom presentation to treatment and follow up)

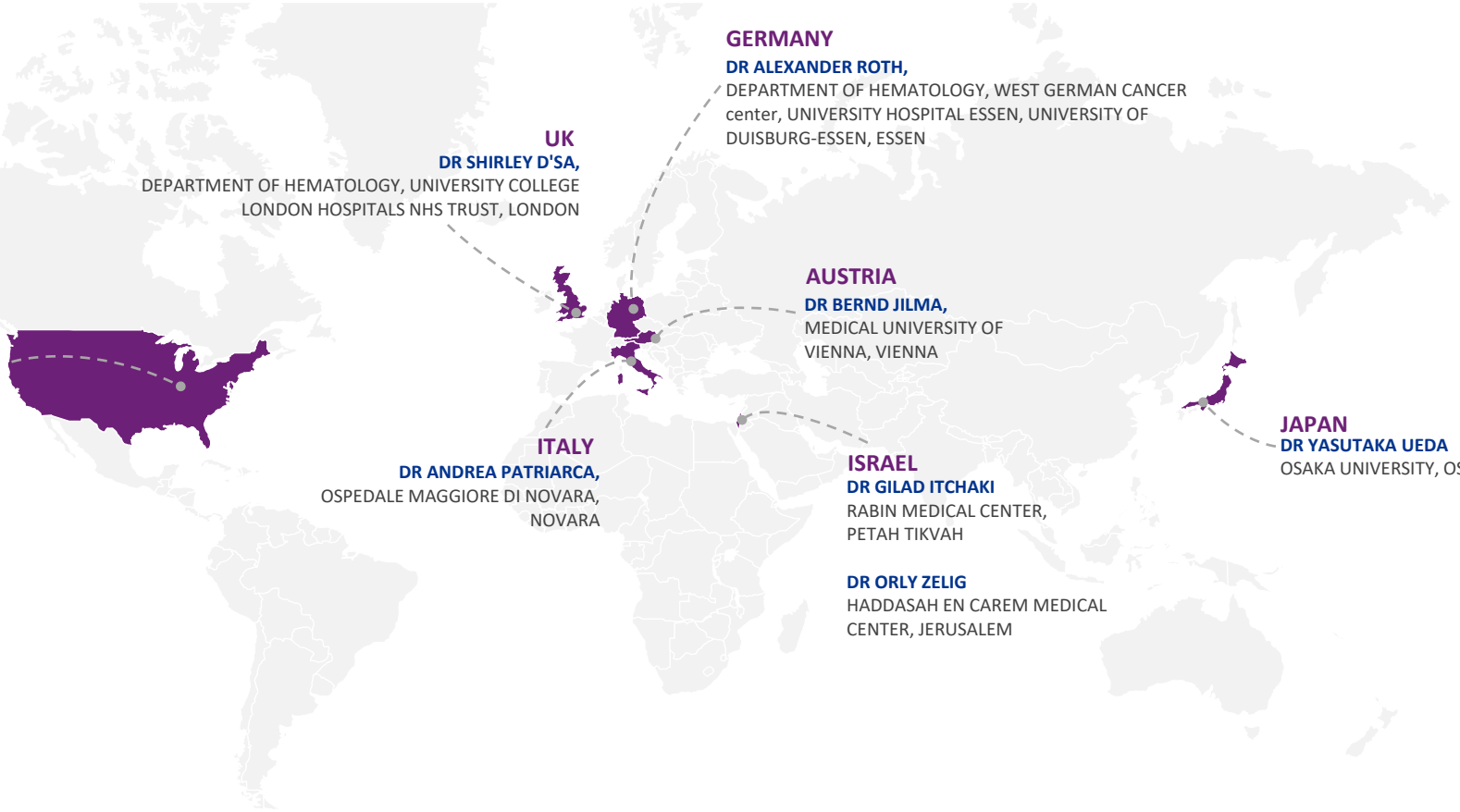
Measuring outcomes (how and when KPIs and outcomes are captured)

Challenges encountered by the care team and patients

Interventions (what is the initiative? what challenges does it address? what are the potential outcomes for patients and the healthcare system?)

Implementation of interventions (who/what/how)

KPMG interviewed specialists from 11 leading global centers to identify and document examples of good practice in CAD care



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Findings were reviewed by each center's lead expert and the SteerCo in developing the final report

Document good practice in CAD care

Center review of findings

- Following each center visit, KPMG documented the findings in a center-specific report identifying roles and responsibilities of team members, key challenges faced, and 'good practice' interventions
- Each report was shared with the center for review and approval (to validate the findings). These center-specific reports are included in the appendix section of this comprehensive report

Review findings with CAD experts

Review of findings (SteerCo discussion)

- Four leading hematologists formed the main SteerCo to help validate our initial findings from center visits
- This collaboration enabled the development of globally-relevant good practice interventions for the management of CAD

Finalize report

Report finalization

- We have outlined key challenges in CAD care and good practice initiatives that enable leading centers to deliver high-quality care to CAD patients
- The final report has been reviewed and signed off by members of the SteerCo

05

Findings

We have identified key CAD care challenges through literature review and primary research

	Awareness and symptom identification	Diagnosis	Medical management	Non-medical management	Follow-up
Healthcare system	— Symptoms may not always be visible in the affected population. While CAD is generally witnessed in the elderly, symptoms can also manifest at younger ages [1]	— Testing challenges from blood agglutination in cold lab environments often lead to delayed results. Samples must be collected, transferred, stored, and processed quickly[2][5][6]	— Treatments often require continuous administration and may not always be effective for patients who have relapsed[5]	— CAD management protocols are established by well-resourced specialists and can be difficult to disseminate on a wider scale[8]	— Lacking established standard of care protocols for CAD can lead to high healthcare utilization post-treatment (e.g., patients can have an average of 7 ER visits per year)[9]
Healthcare professional	— Limited awareness and rarity of CAD (incidence of 1 per million) impacts physicians' recognition and interpretation of CAD symptoms[2][3] — The rare nature of CAD reduces interest and investment in training required to adequately educate the wider clinician community on CAD identification[12]	— Late diagnosis can be driven by delayed referrals from primary care and blood testing issues due to clumping in samples[2][3][7] — Lacking standardized protocols, and technician training due to CAD's rarity could lead to testing inefficiencies[12] — Diagnostic tests must be sensitive and specific in order to identify CAD amongst differential diagnoses[12]	— Treatment approaches can vary significantly, and HCPs must base proposed interventions on symptom severity and comorbidities or associated diseases[1] — Patients and blood products must be kept in a warm environment during transfusion to avoid agglutination and hemolysis[11]	— Lacking communication channels between specialists and primary care which can impact efficient management of secondary CAD patients[1] — HCPs may not be aware of a patient's CAD diagnosis and the attendant considerations when they seek medical care for other health conditions or in emergency settings [12]	— Lack of coordination between specialists and primary care providers can lead to delays in data transfer, thereby impacting patient care[9][10]
Patient	— Lacking CAD awareness in the general population can lead to increased patient stress and anxiety[4]	— Delayed diagnosis or misdiagnosis leads to disease progression, which can cause emotional distress for patients[4]	— Available treatments vary in their efficacy, side effect profile, and duration of response [1][2] — In some markets, CAD treatment can be expensive and inaccessible[12]	— There is a gap in communication between specialists and patients regarding the impact of a chronic rare disease diagnosis on their physical and mental health[9]	— Patients with rare disease are more likely to suffer from psychological conditions[9], for which support is not always available

Sources: (1) CAD page, US Department of Health & Human Services - Genetic and Rare Diseases Information center, May 2016; (2) Diagnosis and Treatment of Cold Agglutinin Disease, Clinical Advances in Hematology & Oncology, (2019); (3) Cold Agglutinin Disease, Review article, Blood (2013); (3) CAD page, US Department of Health & Human Services - Genetic and Rare Diseases Information center, May 2016; (4) Planning for the future when you have Cold Agglutinin Disease, Cold Agglutinin Disease news website, September 2020; (5) Cold Agglutinin Disease: current challenges and future prospects, Journal of Blood Medicine (2019); (6) Cold Agglutinin Disease; A Laboratory Challenge, Iranian Red Crescent Medical Journal, (2015); (7) Br J Gen Pract. Preventing gatekeeping delays in the diagnosis of rare diseases (2018); (8) Cold Agglutinin Disease, Hematology Am Soc Hematol Educ Program (2016); (9) National Gaucher Foundation. Tackling Mental Health Challenges Within the Gaucher Disease Community (2019); (10) Cold Agglutinin Disease burden: a longitudinal analysis of anemia, medications, transfusions, and health care utilization, Blood Advances (2017); (11) Cold Agglutinin Disease, UpToDate, October 2022 (12) KPMG primary research

Identified and categorized good practice interventions by themes

Interventions focused on collaboration

Collaboration with affiliate hospitals

What is it?

- A referral network is set up comprising multiple affiliate hospitals from nearby regions
- The team proactively coordinates with these centers by describing patient cases, providing a second opinion, and ensuring timely referrals

What are potential outcomes?

- Increased CAD awareness
- Smoother referral process and follow-up care
- Improved knowledge-sharing

Where was it observed?

Osaka University Hospital, Japan; University of Southern California, USA

Interdisciplinary collaboration

What is it?

- Establish regular team connects among hematology, lab and transfusion departments
- Facilitate discussions on CAD (or AIHA), developments in testing and treatment, and delivery of coordinated care for patients

What are potential outcomes?

- Timely diagnosis and treatment initiation
- Increased CAD awareness

Where was it observed?

Ospedale Maggiore di Novara, Italy; University of California, San Francisco, USA

Access to other specialists

What is it?

- Establish connections with other specialists (e.g., psychologists and cardiologists)
- Care of patients with comorbidities are coordinated other specialists (e.g., cardiologists, diabetologists, gastroenterologists)

What are potential outcomes?

- Easier referral to other specialists
- Improved quality of life
- Improved patient outcomes

Where was it observed?

Ospedale Maggiore di Novara, Italy; Medical University of Vienna, Austria

Coordinating physician assistants (PA)

What is it?

- PAs support hematologists in providing comprehensive care to the patients through coordination with other HCPs
- PAs stay informed about treatment regimens, educate patients, and collaborate with pharmacists and nurses (in county hospitals) to maintain follow-up

What are potential outcomes?

- Improved patient outcomes
- Efficient follow-up
- Reduced workload for hematologists

Where was it observed?

University of Southern California, USA

Interventions focused on processes and protocols

Specialized laboratory/ transfusion department

What is it?

- Centers offer specialized transfusion capabilities through an experienced team and advanced tools. Samples are handled appropriately with temperature maintenance
- Support is offered to the hematology dept. with blood testing across cardiovascular, liver, heart transplantation, post-operative management, and other critical areas

What are potential outcomes?

- Timely diagnosis and treatment initiation
- Efficient management of patients

Where was it observed?

Osaka University Hospital, Japan; Georgetown MedStar Hospital, USA; University of Southern California, USA; University of California, San Francisco, USA

Experienced lab professionals

What is it?

- A highly experienced team of biomedical technicians with advanced training in hematology sample handling provides care to patients with CAD
- All new technicians are required to undergo six months of training with experienced technicians, before they can work independently

What are potential outcomes?

- Easier access to other specialists
- Improved quality of life

Where was it observed?

Medical University of Vienna, Austria

Defined protocols

What is it?

- The clinical team adheres to strict protocols for handling samples, diagnosis, treatment, and management of CAD patients
- Awareness about sample handling protocols among HCPs (across departments) is created by hematologists

What are potential outcomes?

- Timely diagnosis and treatment initiation
- Efficient management of patients

Where was it observed?

University College Hospital London, UK; Medical University of Vienna, Austria

"In the sample order form itself, it is mentioned that the samples have to be kept warm and immediately analyzed. However, there is limited availability of device to maintain optimum temperature" - *Hematologist*

"The ten hematologists in the team, connect twice every week to discuss cases and plan treatment. The team maintains close collaboration with the in-house blood bank team, through regular communication to ensure that blood products are supplied and administered appropriately" - *Hematologist*

Interventions focused on patient education and support

Education for patients

What is it?

- The clinical team provides education to patients about long-term management of CAD including symptom recognition, prevention with lifestyle changes, and regular monitoring
- This can help patients identify the need for ancillary treatment

What are potential outcomes?

- Increased CAD awareness
- Improved quality of life and long-term management

Where was it observed?

Ospedale Maggiore di Novara, Italy; Osaka University Hospital, Japan

Access to support services

What is it?

- The hematology department provides patients access to support services , such as social care, psychological support, finance guidance, transportation facilities etc.
- The department provides patients education materials and help link patients to patient association groups

What are potential outcomes?

- Improved patient outcomes
- Enhanced quality of life

Where was it observed?

Georgetown MedStar Hospital, US; University of California, San Francisco, USA

Patient focus groups

What is it?

- Hematology teams at hospitals set up a focus group to bring together patients with CAD, with the aim of understanding CAD patients' needs, educating patients, and co-developing tailored patient assistance tools

What are potential outcomes?

- Increased CAD awareness
- Improved quality of life

Where was it observed?

University College Hospital London, UK

"Patient education is highly important. Elderly patients may face challenges in seeking information through Internet. Patient centered educational seminars could be helpful for patients to connect and share information"
- *Hematologist*

"Patients can seek guidance from a social worker to access social programs with financial grants for reimbursement for healthcare associated costs. Additionally, consultations over telephones are also offered to patients with mobility challenges"
- *Hematologist*

Interventions focused on knowledge sharing

Education programs

What is it?

- The hematologist shares information about CAD with clinical team and other departments, with focus on symptom recognition and sample handling
- The clinical team contributes to educational conferences, academic papers and foster knowledge sharing amongst the HCPs

What are potential outcomes?

- Increased awareness about CAD
- Enhanced collaboration among HCPs
- Improved patient outcomes

Where was it observed?

Osaka University Hospital, Japan; Georgetown MedStar Hospital, USA; University of Southern California, USA

International seminars

What is it?

- The clinical team organises seminars in collaboration with professional training vendors and National Society of Serology, four to five times a year
- Aimed at sharing knowledge and information on CAD amongst physicians and biochemists across the country

What are potential outcomes?

- Increased awareness about CAD
- Enhanced collaboration among HCPs

Where was it observed?

Medical university of Vienna, Austria

National MDT connect

What is it?

- The hematologist aims to conduct regular National MDT meetings through virtual channels to facilitate discussion and knowledge sharing among physicians from different centers

What are potential outcomes?

- Increased awareness about CAD
- Enhanced collaboration among HCPs
- Improved patient outcomes

Where was it observed?

Ospedale Maggiore di Novara, Italy

"Symptom recognition is always challenging; hence I have been sharing knowledge with my colleagues at the center to identify leading symptoms such as hemolytic anemia, blue nose/ears. Additionally, we give presentations to community doctors / primary physicians"
- *Hematologist*

Interventions focused on research & use of technology

Commitment to clinical research

What is it?

- Dedication to clinical research (focused on CAD or AIHA), and improved access to innovative therapies
- One center has an established trials team, who manage all research participants including data collection, arranging research/grant funding, and offering access to support services such as counselling or financial guidance

What are potential outcomes?

- Development of new therapies
- Improved patient outcomes

Where was it observed?

University College Hospital London, UK; Ospedale Maggiore di Novara, Italy; Osaka University Hospital, Japan; Georgetown MedStar Hospital, USA; University of Southern California, USA

"Clinical trials are essential to get access to latest treatments. Additionally, we need to focus on educating the HCP community about the latest research as well"
- *Hematologist*

Focus on digital innovation

What is it?

- Leverage digital technology (e.g. devices and software platforms) to monitor patients and enable more accurate symptom tracking
- Provide access to a platform for sharing medical records with physicians and patients

What are potential outcomes?

- Easier data sharing
- Long term management of CAD patients

Where was it observed?

University College Hospital London, UK; Georgetown MedStar Hospital, USA

"To ensure efficient sample handling, patients can be electronically marked (in records) to show that their samples need to be warm"
- *Hematologist*

06

Appendix

Center report – Ospedale Maggiore di Novara, Italy

Executive summary

This report features Ospedale Maggiore di Novara, a public tertiary center involved in CAD research and providing CAD care delivery in the North-Eastern region of Italy

Key Strengths

01

Interdisciplinary Collaboration

The hematology and transfusion medical departments meet quarterly to discuss stem cell collection and immuno- hematology test procedures. This facilitates collaboration between team members and coordinated care for patients

02

Education for Patients

The clinical team coordinates with education programs to help patients learn about long-term CAD management through symptom recognition, regular monitoring, lifestyle changes, and awareness about need for ancillary treatment

03

Clinical Research

The center's hematologist collaborates with other leading experts in various clinical trials for CAD and other related autoimmune diseases

Key Challenges

01

Maintenance of Specimen Temperature

Samples are collected as well as processed in the hematology laboratory. Other departments may be unaware of the process and protocol for maintaining the right temperature of CAD samples, which can result in mishandling

02

Misdiagnosis of CAD

Acute patients who present to the Emergency Room (ER) do not always receive a timely CAD diagnosis. The symptoms of anemia can be generic, and often blood samples agglutinate by the time they reach the lab. Both of these factors can delay accurate diagnosis and CAD treatment initiation

03

Limited access to CAD treatment in local centres

Patients' treatment options are often limited to hub CAD centres within Italy, with local centres unable to provide all available CAD therapies

Sources : (1) Maggioreospnovara

CAD in Italy

Healthcare system and structure	The national health service (Servizio Sanitario Nazionale; SSN) is responsible for universal coverage of healthcare benefits and providing budget guidance to 19 regions and two autonomous provinces in Italy[1]
Insurance and Funding	The national healthcare system is funded mainly by national and regional taxes, supplemented by private expenditure and insurance schemes. Regions and provinces are responsible for management of primary care, hospital care, outpatient specialist care, public health care and social care. Primary care is provided by self-employed and contracted GPs and pediatricians whereas outpatient specialist care is provided by local health units or public and private accredited hospitals[1]
CAD prevalence and incidence	The incidence of CAD is around 9 people per million in North Italy, and prevalence is 50 per million people every year in Italy. The higher value of prevalence and incidence of CAD in Italy is contributed by cold climatic conditions[2]
Care provision	Patients presenting mild symptoms of anemia are managed at local clinics by general physicians, if patients present moderate to severe symptoms of anemia (hemoglobin less than or equal to 7 g/dL) are treated at the center. Around 40-50% of CAD patients are treated in the outpatient unit; they are only admitted to the hospital if their overall physical presentation deteriorates due to severe anemia
Guidelines and societies	**Guidelines:** British Society of Haematology guidelines for the diagnosis and management of primary autoimmune haemolytic anaemia **Medical societies:** GIMEMA Foundation[9], Società Italiana di Ematologia[7] **Patient association groups (PAGs):** Associazione Patologie Autoimmuni Internazionale[8]

CAD Statistics

	Italy	World
% GDP spent on healthcare [4],[5]	**9.5**	**10**
Patient: physician ratio[6]	**125**	**556**
Public healthcare spend (% of all health expenditure)[5]	**76**	**60**
CAD Incidence[2],[3]	**9***	**1***

Sources : (1) The Commonwealth fund (2) NORD (3) National Library of medicine (4) Statista (5) Country Economy (6) The World Bank Databank (7) MDS Europe (8) Orphanet (9) GIMEMA

*1,000,000 individuals

The Center and CAD division

Center

Center Type	**Public hospital**
Size	**842 total beds in the center, with 24 beds dedicated to hematology**
Setting	**Inpatient and outpatient units**
Catchment area	**The center is located in north-eastern quadrant of Piedmont region and provides care to patients coming from provinces of Novara, Vercelli, Verbano-Cusio-Ossola**
Accreditations & affiliations	**Accredited by Joint Accreditation committee- ISCT[a] and EBMT[b] and National Center of transplants for execution of autologous transplantation of hematopoietic stem cells[1]**

CAD division

Patient Cohort

10 CAD patients in the year 2021 due to the COVID pandemic, this year there were 24 patients

Services Offered

Diagnosis, treatment, transfusion, psychological support, and clinical research

Guidelines used

British Society of Haematology guidelines for the diagnosis and management of primary autoimmune haemolytic anaemia

Facilities on site

Hematology, blood transfusion services, laboratory services, and clinical studies

CAD Core Team

- Hematologist
- Transfusion medicine physician (2)
- Blood lab technician (2)

Governance and processes

- **Team meetings:** The hematology department and transfusion medicine department meet quarterly to discuss potential improvements to the quality of care in hematology
- **Electronic patient records:** Outpatient records are electronic, and patients receive printed copies of their detailed letters after every appointment. Records are not yet shared across different hospitals on one shared system

Sources: (1) Maggioreospnovara

Notes: (a) ISCT- International Society for Cell and Gene Therapy, (b) EBMT- European Society for Blood and Marrow Transplantation

Roles and Responsibilities of the team

01

Hematologist

- Conducts initial diagnosis of CAD in collaboration with the transfusion physician and lab specialist
- Establishes treatment plans for the CAD and other hematology patients
- Participates or leads clinical research for hematological diseases (including CAD and other autoimmune diseases)

02

Transfusion medicine physician

- Collaborates with the hematologist and lab technicians to establish CAD diagnosis
- Manages selection of donors, transfusion medicine, productive and therapeutic apheresis, stem cell collection and immuno-hematology tests

03

Blood lab technician

- Assists transfusion physicians with initial screening to process and analyze the blood samples
- Manages processing and production of blood components and transfusion medicine
- Educates patients about long-term CAD management by symptom recognition, regular monitoring and lifestyle changes

Overview of CAD patient pathway

Awareness and symptom recognition

- The clinical team provides education to patients about CAD including symptom recognition, lifestyle changes, and regular monitoring
- Information on clinical trials and contact information for the hematology clinical trial team are published on the center's website for patients who are interested in CAD trials

Referrals and Diagnosis

- Patients with moderate to severe symptoms of anemia (with a hemoglobin less than or equal to 7 g/dL) are referred to the center by primary care or via the emergency room
- Hematologists at the center perform routine blood tests to observe CAD characteristics
- To establish diagnosis, the laboratory performs Cold Agglutinin titer to check for the presence of CAD specific proteins (turnaround time of ~24 hours)
- The center has also started bone marrow flow cytometry for confirmation of CAD diagnosis

Treatment

- Treatment is planned based on the severity of the anemia, founded on the results of CT scan and biopsy
- Patients with mild anemia are initiated on steroid treatment, which takes ~3-4 hours to complete. Following this, patients are given antibody therapy infusions (if needed)
- For severe cases, patients are infused with antibody therapy. The entire procedure may include four or more infusions, depending upon the response
- ~10-20% of CAD patients require transfusion, and this is performed in the transfusion medicine department when necessary

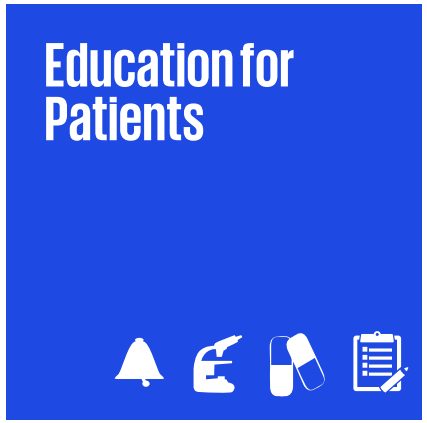
Non-Medical Treatment

- The clinical team educates patients about long-term management of CAD by identifying symptoms and lifestyle changes
- Psychological support is offered to the patients if needed

Follow-Up

- Follow-up protocol for severe cases is once every two weeks, while for mild cases it is once a month

Interventions and good practices across the CAD patient pathway



Education for Patients

- The clinical team **provides education to patients about long-term management of CAD** including symptom recognition, prevention with lifestyle changes, and regular monitoring
- This can help patients identify the need for ancillary treatment

Interdisciplinary Collaborations

- The **hematology department and transfusion medical department connect once every three months** to discuss stem cell collection and immunohematology test procedures
- This facilitates collaboration between team members and coordinated care for patients

Access to Other Specialists

- A **psychologist is associated** with the hematology department
- All the hematology patients can access psychological support whenever needed

Clinical Research

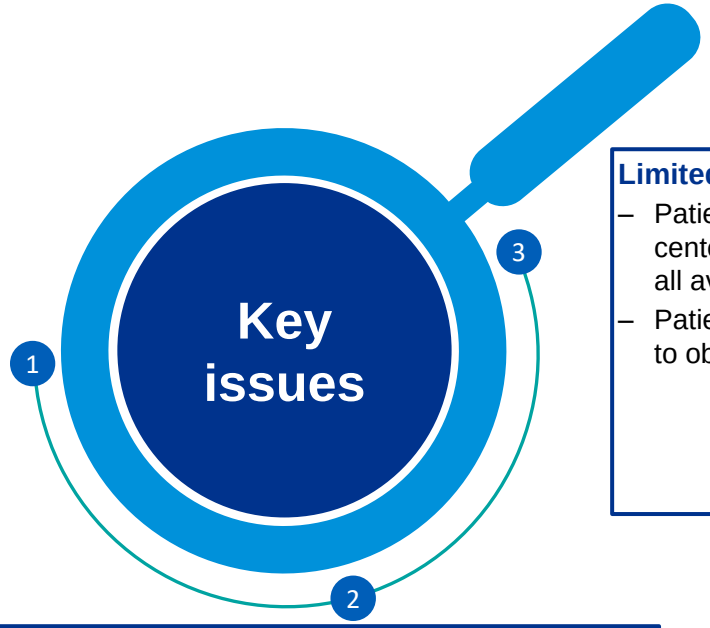
- The center **hematologist acts as the principal investigator** and runs various clinical trials for CAD and other autoimmune diseases

Key: Awareness and symptom recognition | Referral and diagnosis | Treatment | Non-medical treatment | Follow-up

Challenges faced in CAD care delivery

Misdiagnosis of CAD

- Acute patients who present to the emergency room do not always receive a timely CAD diagnosis. The symptoms of anemia can be generic, and often blood samples agglutinate by the time they reach the lab
- Misdiagnosis leads to delayed testing, diagnosis and initiation of CAD treatment, and some of the patients are required to be reanimated and undergo plasmapheresis in order to confirm the diagnosis



Limited access to CAD treatment in local centers

- Patients' treatment options are often limited to hub CAD centers within Italy, with local centers unable to provide all available CAD therapies
- Patients may need to travel long distances to the center to obtain treatment

Maintenance of specimen temperature

- Test samples are collected in the hematology department and processed in the hematology laboratory
- Departments other than hematology may be unaware of the process and protocol for maintaining the right temperature (37 degrees Celsius), making it difficult to handle the samples during transit, which can lead to delay precise diagnosis

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Center report – University College Hospital London, UK

Executive summary

This report highlights University College Hospital London, a public tertiary CAD research & care delivery center in central London in the UK

Key Strengths

01

Defined protocols

The Hematology department has developed and implemented standard protocols for sample processing and diagnosis and treatment procedures for CAD patients

02

Focus on digital innovation

The center has partnered with a company that enables collection of patient-reported outcome data from an approved, clinically validated, FDA-cleared and CE-marked wearable device. It records real-time biometric markers linked to sleep quality, physical activity, and cardiac and lung function

03

Commitment to clinical research

The center has a dedicated clinical trials team who streamline research contracting, manage research funding, and coordinate with enrolled patients. Patients have access to support services including counselling, financial guidance and inpatient referrals through Macmillan Cancer Center

Key Challenges

01

Complexity in sample processing

Processing CAD patient samples and maintaining their optimal temperature can be challenging in a referral center with a large lab and staff. Clinical and laboratory teams collaborate to ensure that protocols are followed

02

Limited information on CAD

The center may benefit from utilizing more forums including webinars, podcasts, and patient information leaflets to raise awareness amongst patients and HCPs

03

Patient travel burden

Frequent therapy administration requires patients to regularly travel from distant locations. This can become burdensome as patients continue treatment during relapse or over a prolonged period

CAD in UK

Healthcare system and structure	The Department of Health and Social care provides stewardship to the National Health Service (NHS) and guides national healthcare strategy, while the NHS manages resource allocation. Healthcare is devolved regionally with NHS divisions in England, Northern Ireland, Scotland and Wales controlling individual budgets[1],[2]
Insurance and Funding	The UK healthcare system is publicly funded and based on the principle of being free at the point of use for all British citizens. Services are mostly owned and provided by the NHS, which is primarily financed by general taxation[1] General Practitioners (GPs) are self-employed but reimbursed by the public healthcare system, and generally operate in group practices of four to six. An important function of primary care is to act as "gatekeepers" to other NHS services including specialist outpatient appointments, which are accessible through GP referral[1],[2]
CAD prevalence and incidence	The incidence of CAD is around 1 person per million, and the prevalence is 16 people per million every year in Northern European countries. The higher value of prevalence and incidence of CAD in the region is attributed to colder climatic conditions[3]
Care provision	Patients presenting initial symptoms of anemia or infection are managed at local clinics or hospitals by GPs. If these patients do not respond well to multiple lines of initial treatment, they are referred to tertiary centers for further opinion or treatment
Guidelines and societies	**Guidelines:** National Institute for Health and Care Excellence (NICE) guidelines on autoimmune hemolytic anemia[7] **Medical society:** British Society for Haematology[8]

CAD Statistics

	UK	World
% GDP spent on healthcare[4],[5]	**9.9**	**10**
Patient: physician ratio[6]	**167**	**556**
Public healthcare spend (% of all health expenditure)[5]	**82**	**60**

Sources : (1) Expatica UK; (2) The Commonwealth fund (3) NORD; (4) World Bank; (5), Country Economy; (6) The World Bank Databank; (7) NICE; (8) BSH.UK; (9) Aplastic anaemia and MDS international foundation

*1,000,000 individuals

The Center and CAD division

Center

Center Type	**Public, specialist teaching hospital**
Size	**~100 hematology beds in the center**
Setting	**In- and out-patient units**
Catchment area	**The center is located in London and provides care to patients across the whole of the UK**
Accreditations & affiliations	**Accredited by care quality commission (CQC)[1]**

CAD division

Patient Cohort

50 CAD patients across all age groups and gender seen annually

Services Offered

Diagnosis, treatment, transfusion, counselling, and clinical research

Guidelines used

NICE guidelines on autoimmune hemolytic anemia[3]

Facilities on site

Hematology, blood transfusion services, laboratory services, and clinical studies

Core Team

- Consultant hematologist
- Clinical research fellow
- Physician associate
- Clinical nurse specialists
- Research nurses
- Clinical trials practitioners
- Data managers

Governance and processes

– **Team meetings:** Hematology team conducts weekly multidisciplinary team meetings (MDT) comprising hematologists, pathologists, and radiologists to discuss and align on treatment protocol for CAD patients

Sources: (1) UCLH; (2) 2021/2022 Annual report, UCLH, (3) NICE

Roles and responsibilities of the core team

01

Consultant hematologist

- Treats various hematology patients with IgM-related diseases and other autoimmune conditions, including CAD
- Plans the treatment protocol for CAD patients in collaboration with clinical and transfusion teams
- Contributes to the development of international protocols and guidelines for the treatment of CAD including hemolytic anemia in collaboration with other international HCPs
- Liaises with lab professionals and phlebotomists to ensure appropriate sample processing and testing

02

Clinical research fellow and physician associate

- Collaborate with hematologists, research nurses, and data managers to facilitate paperwork for enrollment in clinical research
- Conduct weekly meeting with hematologist and sub-investigator to discuss the data of all patients enrolled in clinical research
- Propose the feasibility and practicalities of running potential clinical research studies

03

Research nurse, clinical trials practitioner, and clinical nurse specialist

- Play an integral role in care delivery for hematology patients enrolled in clinical trials and are involved in advocating for patients during enrollment
- Administer treatment to CAD patients hospitalized in the center
- Facilitate clinical research studies, and manage CRO contracts
- The team of nurses is specialized in hematology, and manages hematology patients enrolled in clinical trials as well as those under active treatment

Overview of CAD patient pathway

Awareness and symptom recognition

- There is not a specific program in place for CAD awareness, however the center is looking to develop this in the form of written information, podcasts, and webinars in partnership with charitable organizations

Referrals and Diagnosis

- Patients presenting CAD symptoms (e.g., anemia or infection) are referred to the center by GPs[(a)] and local hospitals. Patients with severe anemia may also come through emergency care at the center
- Nurses and phlebotomists, follow a defined sample processing protocol to ensure an efficient and timely diagnosis
- Trained phlebotomists in the lab collect samples in pre-heated blocks for blood tests
- To confirm a diagnosis, the clinical laboratory assesses the level of cold agglutinin titer in the blood

Treatment

- Treatment is planned based on the severity of anemia and presence of infection
- Patients presenting acute infection, hemolysis, and low Hb undergo transfusion at the center. Subsequent lines of treatment include anti-CD20 mAb[(b)] therapy which may be combined with chemotherapy agents
- In emergency situations, anti-complement C5 therapy may be used following application for compassionate access
- Patients who do not respond to available treatments are enrolled in clinical trials. Research participants are offered counselling, financial guidance, emotional support and inpatient care, if needed

Non-Medical Treatment

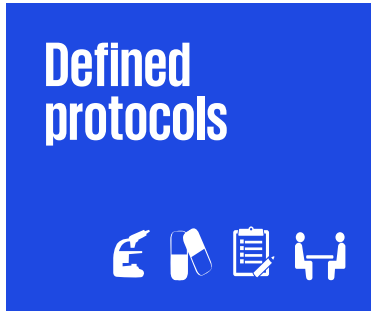
- The clinical team uses telehealth to monitor patients (including phone calls), and directs them to consult in-person, if required

Follow-Up

- Patients undergoing active treatment visit the center for monthly follow-ups, whereas patients in remission follow-up every three months
- Patients enrolled in clinical research are followed-up as defined by the clinical research protocol, which may vary across studies

Notes: (a) GPs are general practitioners; (b) mAbs represent molecular antibody drugs used in the treatment of CAD

Interventions and good practices across the CAD patient pathway



Defined protocols

- Hematologists have developed protocols for nurses and lab specialists for CAD patient management
- Hematologists liaise with allied HCPs across departments to reiterate the significance of temperature control while handling CAD samples
- Nurses are trained to administer blood transfusions and IV fluids through a warming device, and keep patients warm during admissions or in theatre

Focus on digital innovation

- The center has partnered with a company that enables collection of patient-reported outcome data from an approved, clinically validated, FDA-cleared and CE-marked wearable device. It records real-time biometric markers linked to sleep quality, physical activity, and cardiac and lung function
- A telehealth platform is utilized by physicians and patients to access medical records

Patient focus groups

- The Hematology team is setting up a focus group to bring together CAD patients to understand their needs, educate them, and help co-develop patient assistance tools

National MDT connect

- The Hematology department is in the process of setting up a schedule for the National MDT meeting through virtual channels. The aim is to bring together physicians from different centers to foster knowledge sharing (through case discussions) and improve outcomes

Commitment to clinical research

- A dedicated clinical trials team streamlines the CRO contracting process, manages research funding, and coordinates with enrolled patients
- An associated cancer center offers support services including counselling and financial guidance
- Hematologists and allied HCPs actively participate in clinical trials

Collaboration with local hospitals

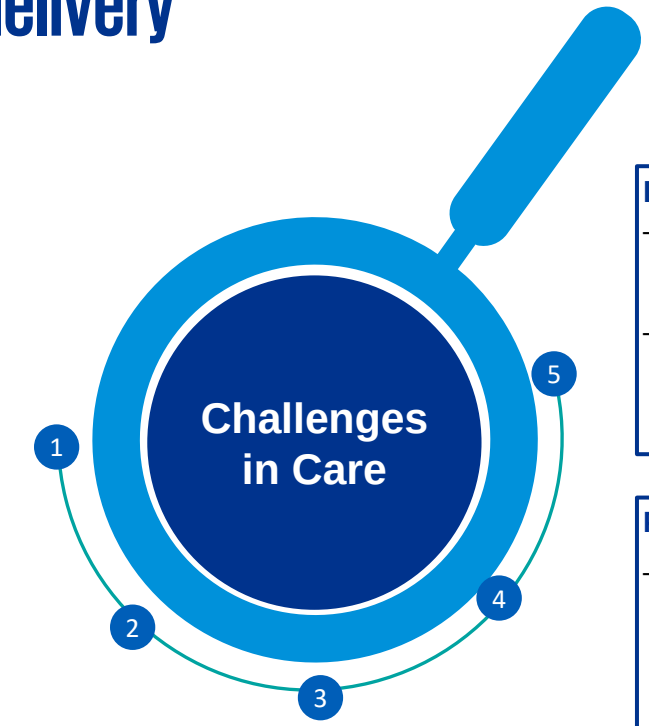
- The hematology department is continuously developing clinical partnerships with local hospitals to share care of patients, and highlight the opportunity to participate in clinical trials when relevant, as well as pursue appropriate therapies and avoid inappropriate therapies

Key: Awareness and symptom recognition; Referral and diagnosis; Treatment; Non-medical treatment; Follow-up

Challenges faced in CAD care delivery

Complexity in sample processing
- Processing CAD patient samples and maintaining them at the optimal temperature can be challenging in a sizable referral center with a large lab and staff
- Handling temperature-sensitive blood samples may be improved with a streamlined communication plan between clinical and lab teams

Lacking patient support groups
- Currently, there are no dedicated CAD patient support groups
- Patients managing CAD and/or enrolled in the same research studies could benefit from such groups to connect, share knowledge, and discuss their concerns



Limited CAD awareness among other departments
- Clinical teams within other departments, including nurses and phlebotomists, may not be aware of the specific needs of CAD patients if they are admitted for another condition
- Mishandling of patient samples and drugs in cold temperature may delay diagnosis or reduce treatment effectiveness

Patient travel burden
- Frequent therapy administration requires that patients regularly travel from distant locations. This can become burdensome, as patients continue with treatment during relapse or over prolonged periods

Limited availability of CAD management information
- HCPs' busy schedules can preclude them from having the capacity to spread knowledge on rare diseases
- The center may find opportunities to utilize various forums, including webinars, podcasts, and patient information leaflets, to educate patients and HCPs about CAD

KPMG

Center report – Osaka University Hospital, Japan

Executive summary

This report features Osaka University Hospital, a public tertiary center involved in CAD research and providing CAD care delivery in one of Japan's largest metropolitan areas

Key Strengths

01 Depth of experience in CAD management

The clinical team at Osaka University has experience in diagnosing and managing CAD. Lab technicians are able to appropriately handle and process CAD patient samples, and hematologists collaborate with pathologists to facilitate precise diagnosis and treatment plans

02 Collaboration with affiliate hospitals

Osaka University Hospital has set up a referral network of 20 affiliate hospitals in the Osaka and Hyogo region. This facilitates knowledge sharing and a smooth referral process for CAD patients

03 Specialized transfusion department

The hospital specializes in blood transfusion testing and transplant medicine. The center is ranked amongst the top 5 hospitals in Japan for blood transfusion related tests and procedures, and has technicians who are experienced in processing CAD patient samples

Key Challenges

01 Early detection and treatment

There may be existing CAD cases in community hospitals that are not detected, diagnosed and/or treated by general physicians due to a lack of experience with the rare disease. These cases are usually referred to the specialists at Osaka University by community hospitals only after patients' symptoms worsen

02 Patient quality of life

Clinical test results do not always correspond to the impact that symptoms can have on a patient and their quality of life. Establishing the diverse and unique needs of each patient, and aligning treatment plans to these needs, can be challenging in practice

03 Lack of efficient diagnostic procedures

Protocols to establish differential diagnosis between CAD and Secondary Cold Agglutinin Syndrome (CAS) are undefined. Pathologists are required to adopt a trial-and-error approach and conduct multiple tests (using various markers) to confirm the diagnosis

CAD in Japan

Structure	The statutory health insurance system (SHIS) in Japan provides universal health care coverage. All residents must enroll, either through employment or residence-based schemes. Residents pay a 10-30% co-payment for all health services and pharmaceuticals with the benefit from the cap on co-payment burden(1)
Insurance and Funding	Statutory Health Insurance covers ~98% of its population. The remaining ~2% is covered by the separate public Social Assistance Program for low-income population. Primary services are offered through privately run medical clinics, with a limited number of clinics being owned by public entities, the government, and non-profit organizations. In the past, there has not been a distinct division between primary and specialist care settings The government has put in place nationwide initiatives to incentivize healthcare professionals and promote optimal referral and coordination between primary and specialty care(1)
CAD prevalence and incidence	Globally, the prevalence of CAD is around 16 people per million and incidence is 1 person per million every year(2) In Japan, The prevalence is estimated to be between 3-10 people per million, and the incidence is estimated to be 1-5 people per million every year(7)
Care provision	Mild cases of anemia are managed at local hospitals; if patients present severe symptoms of anemia and require further medical intervention are treated at tertiary centers. Most CAD patients are treated in the outpatient department; they are only admitted to the hospital if their overall physical condition deteriorates due to severe anemia or side effects of treatment
Guidelines and societies	**Medical societies:** Japanese Society of hematology (JSH), Japan Society of Transfusion **Patient advocacy groups:** Patient group for paroxysmal nocturnal hemoglobinuria (PNH)

Healthcare Statistics

	Japan	World
Public Health Spend (% of all health expenditure)(3)	**83.4**	**60**
Patient: Physician ratio(4)	**400**	**556**
%GDP spend on healthcare(5)(6)	**11.1**	**10**

Sources : (1) The Commonwealth fund; (2)NORD, 2020; (3) Country Economy; (4) The World Bank Databank; (5) Statista; (6) WHO, global spending on health; (7) Yoshiyuki Ohno. 1999 Report (Survey Research Group for Understanding the Epidemiological Image of Diseases Not Targeted by the Specified Disease Treatment Research Project) (2000): 31-88

The Center and CAD division

Center

Center Type	**Public - teaching hospital (national university corporation), tertiary**
Size	**1086 beds in total, 40 beds in the Hematology department**
Setting	**Inpatient and outpatient**
Catchment area	**Primarily provides care to patients from Northern part of Osaka (Settsu and Umeda)**
Accreditations & affiliations	**Certified by the International Organization of Standardization (ISO 15189), recipient of the highest standard certification in 3rdG:Ver.2.0 from the Japan Council for Quality Healthcare, and certified under Japan Medical Service Accreditation for International Patients (JMIP)**

CAD division

Patient Cohort

10-20 CAD patients total in the outpatient department

Services Offered

Diagnosis, treatment, transfusion, pathology, clinical research

Guidelines used

Japan Transfusion guidelines (not CAD specific)

Facilities on site

Hematology, pathology, clinical research services, blood transfusion services, and laboratory services

CAD Core Team

- Hematologist
- Pathologist
- Clinical technician
- Transfusion technician
- Outpatient nurse

Governance and processes

- **Collaboration:** Once the diagnosis is confirmed for the suspected cases of CAD, HCPs (hematologists and pathologists) collaborate to discuss individual patient cases and outline the treatment plan
- **Referral system:** Osaka University Hospital has established a referral network of 20 hospitals in Osaka and Hyogo region, with suspected CAD cases referred to the center as needed

Roles and Responsibilities of the team

01

Hematologist

- Conducts the initial diagnosis of CAD and collaborates with laboratory and transfusion teams to coordinate activities in patient care
- Provides patient guidance and education on blood transfusions and the associated risks

02

Pathologist

- Supports the hematologist in the differential diagnosis process, and uses biopsy to identify primary or secondary CAD based on the underlying cause

03

Clinical technician

- Assists physicians with initial screening through blood testing, bone-marrow biopsy, and flags any indicators of CAD
- Performs clinical tests based on the requests received from the outpatient department by hematologists

04

Transfusion technician

- Collaborates with hematologists to determine suitability for transfusion using the Coombs test and Cold Agglutinin titer
- The transfusion team works independently and specializes in blood transfusion testing and transplant medicine

05

Outpatient nurse

- Works jointly with clinical technicians to administer blood transfusions and follow-up care
- Provides patients with guidance and education on lifestyle changes and activities of daily living

Overview of CAD patient pathway

Awareness and symptom recognition

- The center has set up a referral network of affiliate hospitals which facilitates knowledge sharing about hematological conditions (including CAD)
- HCPs from the center also participate in academic conferences

Referrals and Diagnosis

- Patients with symptoms of anemia undergo a complete blood count test. Mild cases are managed at local hospitals
- If patients present **with severe anemia or related symptoms**, they are referred to Osaka University or other tertiary hospitals for care
- The hematologist at the center repeats blood tests to observe CAD characteristics
- To confirm the diagnosis, transfusion department performs a **Coombs test** and the **Cold Agglutinin titer**
- Post diagnosis, the team conducts tests to identify the underlying causes(1) , using **a bone marrow biopsy**

Treatment

- Treatment is outlined based on **biopsy results and hemoglobin levels** (Hb levels of less than 9 g/dL indicate severe anemia)
- Patients begin with standard treatment and blood transfusion. For further intervention, therapies usually used in oncology may be used as well as the anti-complement drug
- Remission therapy (combination of chemotherapy and antibody therapies) is given based on the patient's health status and tolerance
- Hospitalization is advised for patients with high-risk comorbidities including renal failure, thrombosis, or hypertension, which are better managed at the center

Non-Medical Treatment

- A team of physicians and nurses is involved in decision making throughout the patient journey, with **a focus on lifestyle changes, activities of daily living**, and education on identifying signs of CAD

Follow-Up

- Follow-up appointments in the outpatient department are conducted **every two months** during the summer
- From September onwards, the frequency of follow-up appointments is determined by the grade of anemia based on set **KPIs for monitoring** (symptomatic improvement of anemia, hemolysis, reticulocytes, LDH level, and indirect bilirubin level)
- Comorbidity management is a core strength of tertiary centers, with access to a range of departments and specialists
- Patients on anti-complement drugs are subject to vigilant monitoring every fortnight at the outpatient clinic

Sources : (1) Małecka A. et.al. Cold agglutinin–associated B-cell lymphoproliferative disease shows highly recurrent gains of chromosome 3 and 12 or 18, Blood Adv (2020) 4 (6): 993–996

Notes : (1) Primary Cold agglutinin disease is a rare autoimmune hemolytic anemia caused by a distinct type of B-cell associated lymphoproliferative disease of the bone marrow.

Interventions and good practices across the CAD patient pathway

Collaboration with affiliate hospitals

- Osaka University has set up a **referral network including 20 affiliate hospitals** in the Osaka and Hyogo region
- Collaboration helps physicians with the referral process for CAD patients, ensuring early initiation of treatment and long-term follow-up care
- These initiatives facilitate knowledge sharing and aim to increase awareness

Clinical research

- The center **conducts CAD research in collaboration with other centers** by collecting patient data (capturing the target end points) including hemoglobin levels, level of hemolysis, LDH, indirect bilirubin level, reticulocyte score and others

Specialized transfusion department

- Osaka University Hospital is **among the top 5 hospitals in Japan for blood transfusion tests**, with a focus on blood transfusion testing and transplant medicine
- The transfusion team supports the hematology department with blood testing across cardiovascular, liver, heart transplantation, post-operative management, and other critical areas
- Coombs test and the Cold Agglutinin titer are performed to confirm the CAD diagnosis

Education programs

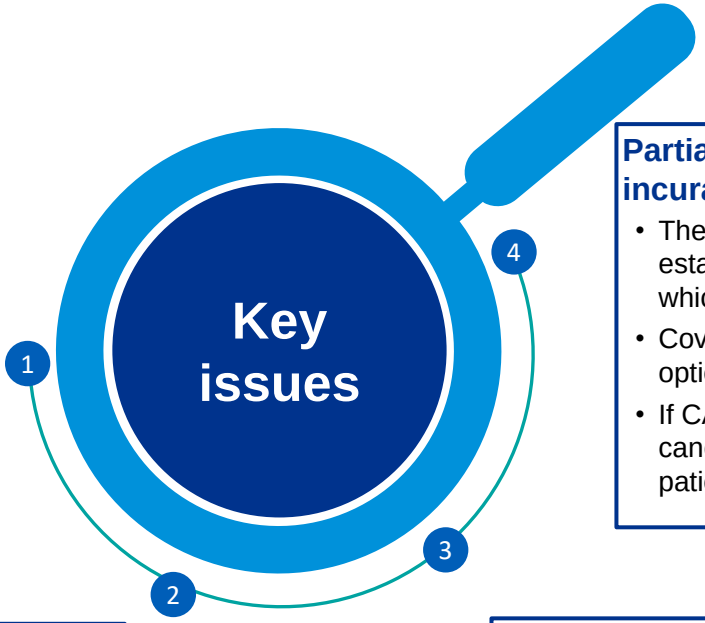
- The **physicians and nurses work closely with patients to educate them** about CAD, with a focus on lifestyle changes, and activities of daily living to help improve their quality of life
- The clinical lab team attends educational conferences and research meetings (academic and industrial). The aim is to contribute to conference presentations and academic paper submissions, and to foster knowledge sharing amongst the professionals

Key: Awareness and symptom recognition | Referral and diagnosis | Treatment | Non-medical treatment | Follow-up

Challenges faced in CAD care delivery

Early detection and treatment:

- There is a reference guideline for the treatment of autoimmune hemolytic anemias, including CAD, which summarizes the knowledge of experts in Japan and covers a wide range of content including diagnosis
- Despite these guidelines, there may be existing CAD cases in community hospitals that are not detected, diagnosed and/or treated by general physicians due to a lack of experience with the rare disease
- These cases are usually referred to the specialists at Osaka University by community hospitals only after patients' symptoms worsen



Partial coverage for CAD under the scheme incurable disease:

- The Ministry of Labor, Health, and Welfare of Japan has established a subsidy scheme for incurable diseases, which covers AIHA and CAD
- Coverage for diagnostic tests as well as treatment options for CAD are not always covered
- If CAD patients experience symptoms derived from cancer, anticancer drugs may increase cost burden on patients

Patient quality of life:

- Clinical test results do not always correspond to the impact that symptoms can have on a patient and their quality of life. Establishing the needs of each patient and aligning treatment plans to these needs can be challenging in practice
- Long-term remission is difficult to achieve, and patients often experience recurring symptoms 6-12 months after treatment. Treatment options that can be tolerated by elderly patients can also be limited

Lack of efficient diagnostic procedures:

- Differential diagnosis of CAD and Secondary Cold Agglutinin Syndrome (CAS) is not always straightforward, as there are no specific immunostaining markers to differentiate
- Pathologists at national centers work to establish a precise diagnosis by using various markers to rule out other possibilities, and these tests can be time and resource intensive

KPMG

Center report – Medical University of Vienna, Austria

Executive summary

This report features the Medical University of Wien, a public tertiary center in CAD research and care delivery in Vienna and surrounding regions of Austria

Key Strengths

01

Experienced lab professionals

The center has a team of biomedical technicians who are highly experienced and trained to deliver enhanced care and management of CAD patients. The onboarding of biomedical technicians includes six months of apprenticeship with experienced technicians before they start operating independently

02

Protocol for sample handling

The center follows a specific sample handling protocol that involves preheating blood samples along with usage of molecular tests (e.g. PCR test) to minimize serologic challenges and identify suitable transfusion products for CAD patients

03

Seminars and symposia

Hematologists and transfusion medicine specialists participate in various conferences and seminars in both academic and industry settings to help facilitate knowledge sharing in hematology, including CAD

Key Challenges

01

Variance in lab results

Low temperature during sample-handling and testing may interfere with serology results and increase the risk of transfusion reactions. Serology tests in CAD may produce false positives, and have a reduced yield of cells in the blood sample as a result of agglutination

02

Limited treatment options

Number of available and reimbursed treatment options for CAD is limited and primarily focused on steroids. Some patients can become unresponsive to treatment shortly after they are put on therapy, underscoring the need to explore other emerging therapies to improve treatment outcomes and patient experience

03

Limited training for HCPs

Given CAD's rare occurrence, the medical community may benefit from regular training of HCPs and lab staff to enhance sample handling and diagnosis

CAD in Austria

Healthcare system and structure	The Ministry of Social Affairs, Healthcare and Consumer Protection provides access to healthcare for each Austrian citizen through the public healthcare system. The public healthcare system provides access to primary and specialist healthcare services which can be supplemented with a private health insurance to access other ancillary services (e.g. dentistry, gym membership, travel insurance etc.)[1],[2]
Insurance and Funding	The Austrian healthcare system is publicly funded through the health insurance tax deducted from each citizen's paycheck. Equal portions of employee and employer contributions are paid to contribute 7.65% of the employee's monthly wage towards health insurance tax[1],[2] Unemployed people, including pensioners, spouses of workers, and citizens out of work for extenuating reasons are entitled to free healthcare at the point of service to ensure affordability[1],[2]
CAD prevalence and incidence	The incidence of CAD is nearly one in 150,000 people, and affects between 40 and 50 people in Austria[3]
Care provision	Patients presenting initial symptoms of anemia or infection are managed by HCPs at local clinics or community hospitals. If these patients exhibit severe symptoms, they are referred to tertiary centers for a further opinion or treatment
Guidelines and societies	**Medical society:** Medical University of Vienna (MUV)[7] **Patient association group (PAG):** Austrian Pro Rare Austria – Alliance for Rare Diseases[8]

CAD Statistics

	Austria	World
% GDP spent on healthcare[4],[5]	**11.5%**	**9.8%**
Patient: physician ratio[6]	**183**	**556**
Public healthcare spend (% of all health expenditure)[5]	**79**	**60**

Sources: (1) Expatica (2) Internations,(3) Medical University of Vienna (4) World Bank, (5), Country Economy; (6) The Global Economy, (7) MUV Austria, (8) Alliance for rare disease

The Center and CAD division

Center

Center type	**Public hospital**
Size	**200 bed capacity at the center**
Setting	**Inpatient and outpatient units**
Catchment area	**The center is located in Vienna, and provides care to patients from the surrounding area**
Accreditations & affiliations	**Accredited by the Agency in Health and Social Sciences (AHPGS), and ISO certification according to 9001:2015(1)**

CAD division

Patient Cohort

Currently managing 10-20 CAD patients, with diagnosis of ~1-2 new patients every year across all age groups and genders

Services offered

Diagnosis, treatment, transfusion, psychological support, and clinical research

Guidelines used

Facilities on site

Hematology, blood transfusion services, laboratory services, and clinical studies

CAD core team

- Hematologist
- Serologist

Governance and processes

– **Medical records:** The center stores/maintains patient medical records for ~20 years. These including lab results as well as information regarding response to treatment

Sources: (1) Medical University of Wien

Roles and responsibilities of the core team

01

Hematologist

- Manages CAD patients in collaboration with the transfusion physician and lab specialist
- Conducts lectures and visits in primary care communities to increase awareness around CAD
- Treats and manages CAD patients enrolled in clinical research

02

Serologist

- Performs both routine diagnostic and clinical workup for CAD patients
- Processes 300+ cold agglutinin and direct antiglobulin tests annually
- Performs a number of pre-transfusion screening tests including blood group, antibody typing, Rh factor, and compatibility testing
- Performs tests for domestic and international CAD patients

Overview of CAD patient pathway

Awareness and symptom recognition

- Hematologists play an integral role in dissemination of knowledge and information on CAD amongst other HCPs through lectures

Referrals and Diagnosis

- Patients presenting CAD symptoms (e.g. anemia, pulmonary embolism etc.) either come through PCP referral or self-referral
- Diagnosis is made based on multiple indicators, including erythrocyte and hemoglobin levels
- Antiglobulin test (e.g. Coombs test) is performed to confirm the type of anemia (e.g. autoimmune hemolytic anemia)
- Pre-transfusion testing including blood type, RH factor typing, and antibody tests are performed for patients planning to undergo transfusion

Treatment

- Treatment is outlined based on the severity of anemia, the patients' age, and the grade of bone marrow infiltration
- Treatment primarily involves steroids. Novel therapies (e.g. mAbs, immunochemotherapy) are gradually being considered as other treatment options
- Patients with low infiltration of bone marrow are put on mAbs, and the rest of the patient cohort is initiated on immunochemotherapy
- The hemoglobin levels for patients on mAbs are monitored for the first week after initiating mAb therapy

Non-Medical Treatment

- Patients who need psychological support are directed to the relevant healthcare professionals to access support services, such as counselling sessions

Follow-Up

- Patient follow-up is scheduled based on the severity of anemia
- Patients with severe anemia follow up weekly whereas patients with mild anemia follow-up annually. Typically, patients fall in between and require follow-up every three to six months

Interventions and good practices across the CAD patient pathway

Protocol for sample handling

- The center adheres to the protocol of preheating blood samples and uses molecular tests (e.g. PCR test). The protocol is in place to minimize challenges in serology testing and identify suitable transfusion products for CAD patients

Access to other specialists

- Patients with comorbidities are often referred to other specialists (e.g. cardiologist, diabetologist, and gastroenterologist) to manage complications and enhance treatment outcome
- Referral to psychology department is offered when psychological support is needed

Seminars and symposia

- The serology team organises seminars in collaboration with pharmaceutical manufacturers and the Austrian Society of Serology four to five times a year. The seminars are aimed at encouraging knowledge and information sharing in hematology, which can include CAD, among physicians and biochemists across Austria

Experienced lab professionals

- The center has a team of biomedical technicians who are experienced and trained in managing CAD patient investigations
- Newly hired biomedical technicians are required to undergo six months of training with experienced technicians before they start operating independently

Key: Awareness and symptom recognition | Referral and diagnosis | Treatment | Non-medical treatment | Follow-up

Challenges faced in CAD care delivery

Variance in lab results

- Low temperature in transit or lab environment may impact patient samples, causing agglutination and interfering with serology test results, and may increase risk of transfusion reactions
- Blood samples taken from CAD patients often contain agglutinated cells, which may obscure results for blood tests for other diagnoses

Limited treatment options

- There is a limited number of treatment options available for CAD. Steroids remains the main line of treatment for the disease
- Some of the patients tend to become unresponsive to steroids treatment, shortly after the treatment initiation. There is an opportunity to explore other emerging therapies (e.g. immunotherapies) to improve outcomes

Limited training for HCPs

- Differentiation between types of anemia (warm vs. cold hemolytic anemia; intravascular vs. extra vascular hemolysis) may be challenging even for experienced hematologists
- Given CAD's rare occurrence, the medical community may benefit from regular refresher training of HCPs and lab staff or standard protocol to enhance sample handling and diagnosis

KPMG

Country report – US centers

Executive summary

This report features expert perspectives from two tertiary centers – Georgetown University and University of Southern California (USC) - and one community hospital, the University of California San Francisco (UCSF) – Fresno Campus

Key Strengths

01

Specialized lab/transfusion department

The centers have well-equipped lab and transfusion department to carry out blood tests and other diagnostic procedures; with the teams adhering to a defined sample handling protocol. Additionally, the laboratory in USC utilizes molecular typing and high sensitivity assays to ensure accurate diagnosis

02

Knowledge sharing among HCPs

The hematologists organize trainings on symptom recognition for CAD to help increase timely referrals and coordinated patient care. Weekly conferences are held at USC and UCSF to discuss non-malignant hematology cases including CAD and AIHA[(a)] to foster knowledge sharing among HCPs

03

Access to support services

Patients are offered reading materials to provide education on CAD and access to Patient Associations (PAGs), and other support services, including psychological care, social care, financial guidance, and transportation facilities

Key Challenges

01

Limited awareness about CAD

There is limited awareness about CAD and its impact on patient's mental and physical health. There is a need to organise educational programs for HCPs with focus on symptom recognition to help increase early diagnosis and treatment initiation

02

Absence of uniform CAD specific guidelines

Treatment and management of CAD is primarily driven by physician's experience as there are limited established clinical guidelines that are specific to CAD

03

Partial coverage for test and treatment associated with CAD

Diagnostic tests and treatment options for CAD are not always covered by public health insurance. The cost burden for patients with malignancy is further increased due to the cost of the prescription of anticancer drugs

Notes: (a) AIHA is autoimmune hemolytic anemia

CAD in US

Healthcare system and structure	The US healthcare system is composed of both public and private healthcare providers, and various for-profit and non-profit payors that provide access to care for 92% of the population. The federal government outlines legislation, national strategies, ensures administration and funding of national insurance programs, and regulates the approval of pharmaceutical and medical device products[1]
Insurance and Funding	The US healthcare system provides access to care through different public insurance programs (e.g. Medicare and Medicaid), employer sponsored programs, and private health insurance. Medicare and Medicaid insurance programs are funded through federal, state, and local tax revenues which provides universal access to care for all adults aged 65+, and people with disabilities and low-income families, respectively. Additionally, there are safety funds to enable care for uninsured, low-income, and vulnerable people, regardless of their ability to pay [1] Primary care physicians (PCPs) generally operate in physician owned practices and are reimbursed through various methods including negotiated fees for privately insured individuals, and administrative fees for public healthcare system[1]
CAD prevalence and incidence	The incidence of CAD is around 1 person per 300,000, and the prevalence is 16 people per million every year in The United States[2],[3]
Care provision	Patients presenting mild symptoms of anemia or infection are managed at local clinics or hospitals by PCPs. Patients with severe symptoms of anemia (hemoglobin less than or equal to 6 g/dL) are referred to the specialist centers for further intervention
Guidelines and societies	**Guidelines:** American Society of Hematology[7], Recommendations for the treatment of AIHA[6] **Medical society:** American Society of Hematology[7] **Patient association groups (PAGs):** Cold agglutinin disease foundation (CAD foundation), National organization for rare disorder (NORD)[8]

CAD Statistics

	US	World
% GDP spent on healthcare[1],[3]	**8**	**10**
Patient: physician ratio[4]	**384**	**588**
Public healthcare spend (% of all health expenditure)[1]	**45**	**60**

Sources: (1) The Commonwealth fund; (2) Rare Disease Advisor; (3) Journal of medical economics; (4) World Bank; (5) The World Bank Databank; (6) International Consensus Meeting; 7) MDPI; (8) NORD and CAD foundation

The Centers and CAD divisions

	Georgetown MedStar Hospital	University of Southern California	University of California, San Francisco (Fresno)
Centers			
Center Type	Not for profit, teaching and research hospital[1]	Private, research university[3] with access to patients from LA Country hospital	Academic medical center[5]
Size (no. of beds)	609[1]	411[4]	626[6]
Setting	Inpatient and outpatient units	Inpatient and outpatient units	Inpatient and outpatient units[7]
Catchment area	Located in Northwest Washington D.C[1]	Located in Los Angeles, South California	Provides care to patients in the Bay area of Northern California
Accreditations & affiliations	Recognized for excellence in blood management by the Joint Commission and Association for Advancement of Blood & Biotherapies[2]	Accredited by Joint Commission on Accreditation of Healthcare Organization (JCAHO)[8]	Fully accredited by the Joint Commission
CAD divisions			
Patient cohort	Approximately 10 CAD patients	2-4 CAD patients per year at the center	1-2 CAD patients per year
Services offered	Diagnosis, treatment, transfusion, counselling support, and clinical research	Diagnosis, treatment, transfusion, counselling support, and home-care	Diagnosis, treatment, transfusion, and counselling support
Guidelines used	American Society of Hematology[9], Recommendations for the treatment of AIHA[10]	American Society of Hematology[9]	American Society of Hematology[9]
Facilities onsite	Hematology, blood transfusion services, laboratory services, and clinical studies	Hematology, blood transfusion services, laboratory services, and clinical studies	Hematology, blood transfusion services, laboratory services
Core team	Hematologist, Pathologist, Clinical Nurse	Hematologist, Physician Assistant, Clinical Lab Technician, Pharmacist, Outpatient Nurse	Hematologist, Clinical Research Practitioner, Research Nurse
Governance and processes	**Team meetings:** The hematologist conducts seminars within the hospital with a focus on symptom recognition for timely referrals and treatment	**Collaboration:** The hematology team collaborates with community physicians to offer second opinions, referral guidance and treatment plans	**Team meetings**: Weekly hematology departmental conferences are conducted to discuss and learn about hematological conditions such as CAD and AIHA

Sources: (1) Georgetown; (2) Georgetown awards and recognition, (3) USC, (4) Keck Medicine of USC, (5) Department of medicine, (6) UCSC Fresno website, (7) UCSF website, (8) USC Accreditation (9) ASH, (10) International Consensus Meeting

Roles and responsibilities of the core team

These are key roles observed supporting the hematology department across centers in the US[(a)]

01

Hematologist

- Conducts the initial diagnosis of CAD and collaborates with the pathologist and transfusion teams to plan the treatment protocol
- Promotes knowledge sharing among HCPs
- Participates in clinical research on hematological conditions including CAD

02

Pathologist

- Collaborates with the hematologist to establish differential diagnosis
- Uses a bone marrow biopsy to identify primary or secondary CAD based on the underlying cause

03

Physician Assistant

- Supports the hematologist in the management of CAD through collaboration with other HCPs
- Provides patient education
- Supports patient follow-up through coordination with HCPs in community centers

04

Clinical Nurse

- Provides integrated care to the patients in collaboration with other HCPs
- Administers blood transfusions, inpatient support, and follow-up care
- Supports clinical research through data collection

05

Clinical lab technician

- Conducts blood tests, bone marrow biopsy and other testing procedures
- Assists the hematologist in establishing the diagnosis

06

Pharmacist

- Collaborates with specialists or other HCPs to support medication adherence
- Supports data collection and follow-up care

Notes: (a) Some of these roles might not be present in all the centers

Overview of CAD patient pathway (Georgetown MedStar Center)

Awareness and symptom recognition

– Internal trainings and seminars to improve CAD awareness and symptom recognition

Referrals and Diagnosis

– Patients presenting moderate to severe anemia are referred to the center by primary care and local hospitals

– The hematologist orders blood tests to check for CAD characteristics (turnaround time is ~3 days). Samples are handled using blood warmers to ensure temperature control

– To establish the underlying cause of the disease bone marrow aspiration is used

– Hematologist follows guidelines (International Consensus of Hemolytic Anemia) to differentiate CAD and CAS

Treatment

– Treatment plan is based on the results of the blood tests, as patients can exhibit variability in clinical phenotypes

– Patients begin with standard treatment including mAbs and blood transfusions, as needed. For further intervention, complement therapies are used

– The center participates in clinical research and its patients are currently enrolled in two clinical trials on CAD, and three trials focused on AIHA

Non-Medical Treatment

– CAD patients can access psychological and social support, if needed

– Additionally, patients are directed to relevant CAD patient advocacy groups (PAGs)

Follow-Up

• Patients' follow-up procedures are variable, driven by physician's experience

Notes: (a) mAbs represent molecular antibody drugs used in the treatment of CAD

Overview of CAD patient pathway (University of California, San Francisco)

Awareness and symptom recognition

- The clinical team conducts weekly meetings to share knowledge on CAD and AIHA, focused on symptom recognition
- Education is offered to patients through access to patient support groups and educational materials, during initial consultations

Referrals and Diagnosis

- Patients presenting severe symptoms of anemia are referred to the center by primary care physicians or via the emergency room
- Hematologists at the center orders for blood tests along with a Coombs test to observe CAD characteristics. The lab team follows set protocols for conducting investigations for all diseases (including CAD)
- To confirm the diagnosis and identify the underlying causes the hematologist assesses the patients' history, performs a CAT scan and bone marrow biopsy

Treatment

- Treatment is planned based on the severity of anemia and the presence of infection
- Patients presenting low Hb undergo transfusion at the center. For further intervention, mAbs are used
- The FACIT-Fatigue questionnaire may be used to monitor patients

Non-Medical Treatment

- CAD patients can access oncology support services, including psychological support, social care, financial guidance, and transportation, as needed

Follow-Up

- The hematologist shares a detailed summary with the oncologist at the local community center to ensure smooth transition of care
- Complete details about treatment protocols are shared and the patients are encouraged to visit the center, as needed

Notes: (a) mAbs represent molecular antibody drugs used in the treatment of CAD

Overview of CAD patient pathway (University of Southern California)

Awareness and symptom recognition

– The internal medicine physician from the center conducts educational sessions on CAD, locally as well as nationally

Referrals and Diagnosis

– Patients presenting symptoms of anemia are referred to the center by primary care physicians, local hospitals, and the emergency care department at the center

– Hematologists at the center perform blood tests to observe CAD characteristics

– To establish the diagnosis, the laboratory performs Cold Agglutinin titer (turnaround time of ~48-72 hours)

– The center also performs bone marrow biopsy to help detect underlying causes

Treatment

– There are treatment protocols in place at the center for CAD, warm AIHA, ITP and other hematological disorders

– CAD treatment is planned based on the severity of the anemia and biopsy results

– Patients begin with standard treatment including use of mAbs and blood transfusions, as needed. For further intervention, complement therapies may be used

– There is a clinical trials unit at the center, and eligible patients may be enrolled in studies when available

Non-Medical Treatment

– CAD patients can access support services such as social care and home-based care

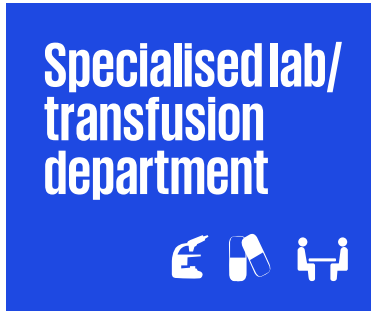
Follow-Up

– Patients undergoing infusion treatment initially visit once a month, and then follow-up every four months

– Patients treated with PD-1 inhibitors are monitored once a month

Notes: (a) mAbs represent molecular antibody drugs used in the treatment of CAD

Interventions and good practices across the CAD patient pathway

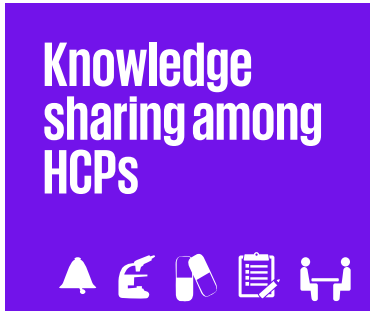


Specialised lab/transfusion department

- The centers have access to specialized labs equipped with tools to conduct all types of blood tests and procedures, and the teams follow defined protocols for sample handling
- The team at blood banks associated with USC have experience with CAD, and uses molecular typing and high-sensitivity assays to conduct accurate diagnosis

Access to support services

- During initial consultations, patients are given access to patient associations and reading material to provide education on CAD
- Patients are also offered access to support services such as social care, psychological support, transportation facilities, and financial guidance



Knowledge sharing among HCPs

- The hematologist conducts training in the other departments, about CAD, with a focus on symptom recognition to help increase timely referral and treatment
- Weekly meetings are conducted at USC and UCSF, to discuss non-malignant hematology cases including CAD and AIHA

Coordinating physician assistants

- The physician assistants (PAs) support the hematologists in providing comprehensive care to the patients through coordination with other HCPs
- PAs are aware of the treatment regimen. They educate patients, as well as collaborate with pharmacists and nurses (in county hospitals) to maintain follow-up

Collaboration with affiliate hospitals

- USC team proactively coordinates with different county services (local prisons, sheltered housing, etc.) by regularly reviewing and providing second opinions to community physicians
- Collaboration aims to increase awareness, facilitate knowledge sharing and improve referral process

Committed to clinical research

- Georgetown center regularly participates in clinical research, and is currently involved in two CAD and three AIHA specific clinical trails (enrolling multiple CAD patients across trials)
- There is a clinical trials unit at the University of Southern California, and eligible patients may be enrolled in studies when available

Key: Awareness and symptom recognition; Referral and diagnosis; Treatment; Non-medical treatment; Follow-up

Challenges faced in CAD care delivery

Limited awareness about CAD

- CAD's rare occurrence may result in limited awareness of symptoms and its impact on patients physical and mental health
- HCPs may benefit from trainings to improve symptom recognition, initiate appropriate referrals and help increase timely diagnosis and treatment

Partial coverage for tests and treatment associated with CAD

- The coverage for diagnostic tests as well as treatment options for CAD is often limited under existing insurance programs
- If CAD patients experience symptoms derived from cancer, anticancer drugs may increase the cost burden on patients
- Financial assistance programs may benefit patients, but are not universal

Limited availability of information on CAD management

- There is a need for HCPs to undertake initiatives to learn as well as spread information about CAD
- Cross department collaboration (including pathologists, blood banks, clinical laboratories, and nurses) may help in disseminating information about CAD

Absence of uniform CAD specific clinical guidelines:

- With no international standard guidelines for treatment and management of CAD, physicians are required to provide care based on their experience
- The symptoms presented by patients can vary significantly in intensity and may require multiple tests to confirm the diagnosis

Glossary

Glossary

Abbreviation	Definition
AIHA	Autoimmune hemolytic anemia
CAD	Cold agglutinin disease
CAS	Cold agglutinin syndrome
ER	Emergency room
HCP	Healthcare provider
MDT	Multidisciplinary team
PA	Physician assistant

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