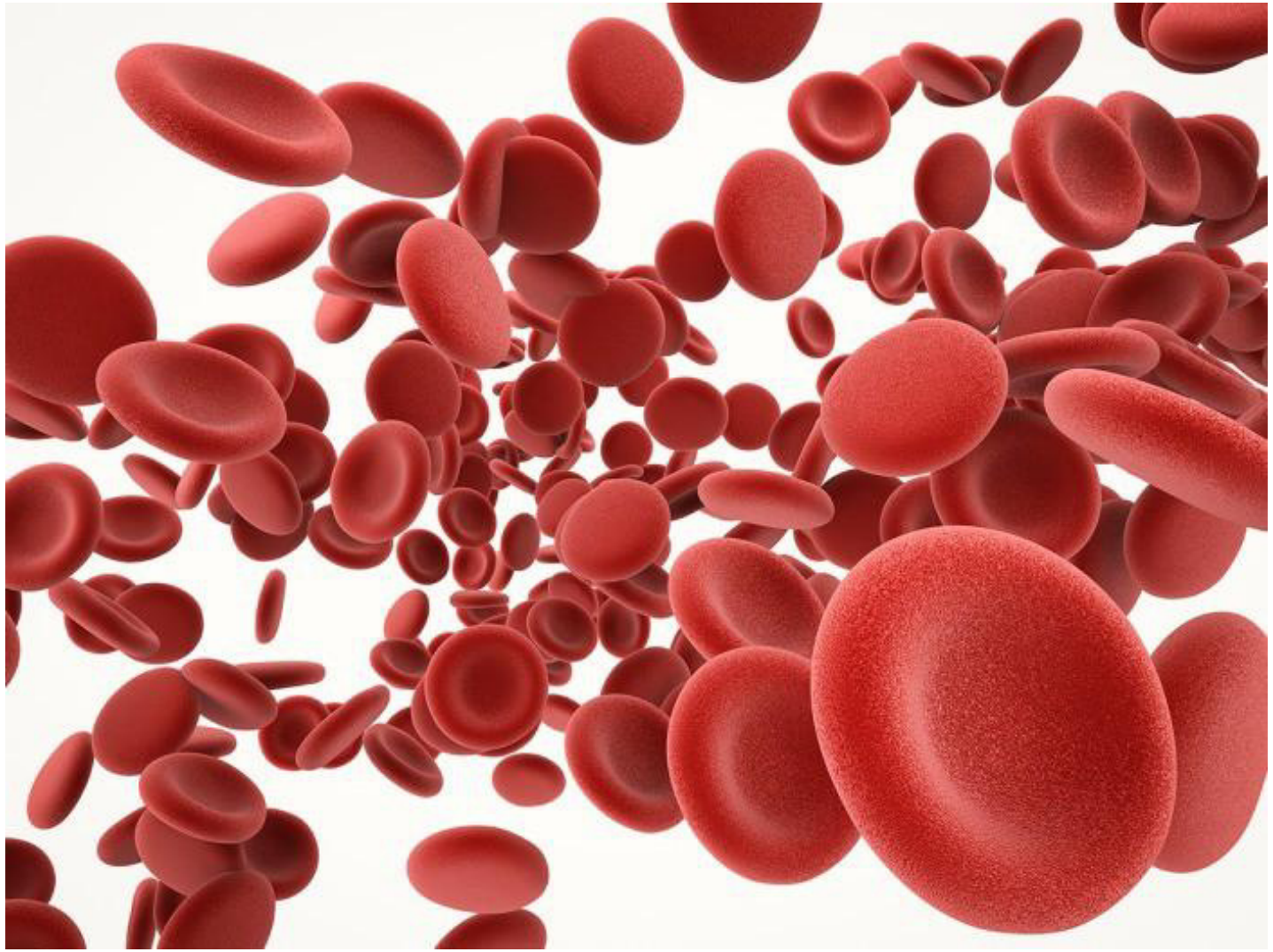
אנמיה המוליטית אוטואימונית



ד"ר אורלי זליג
מרכז רפואי הדסה

סדנת מתמחים
דצמבר31, 2025

Autoimmune Hemolytic Anemia - AIHA

- Autoimmune hemolytic anemia (AIHA) is a rare disease estimated incidence of 1–3 per 100,000/year
- AIHA is a greatly heterogeneous disease due to autoantibodies directed against erythrocytes, with or without complement activation.
- The clinical picture ranges from mild/compensated to life-threatening anemia, depending on the antibody's thermal amplitude, isotype and ability to fix complement, as well as on bone marrow compensation.
- Until few years ago, steroids, immunesuppressants and splenectomy have been the mainstay of treatment (in wAIHA)
- More recently, several target therapies are increasingly used in the clinical practice or are under development in clinical trial

תיאור מקרה 1

- בת 52
- ללא מחלות רקע
- התקבלה לבירור אנמיה שהתגלתה בעקבות תלונות של חולשה
- בבדיקה קוצר נשימה,חוורון, צהבת קלה בלחמיות פרט לכך ללא ממצא
- במעבדה: אנמיה 6ג%, MCV - 100 פ"ל 165,000 רטיקולוציטים/ממ"ק, שאר השורות תקינות, LDH X 1.5מהנורמה, בילירובין בלתי ישיר 2.7 מג/דל הפטוגלובין – לא נמדד

- Test blood counts and hemolytic markers (↑unconjugated bilirubin, ↑ LDH,↑ reticulocytes, ↓ haptoglobin)
- Perform blood smear morphology: possible spherocytes, agglutinates in CAD
- Consider confounding factors of hemolytic markers (Gilbert syndrome, hypo-haptoglobinemia, tissue necrosis or increased turnover, vitamin B12, folic or iron deficiency)

Diagnostic approach to suspected AIHA – 1. Hemolysis

Table 3
Markers of hemolysis

Type	Test	Expected/Comment	Intravascular	Extravascular
Direct	Haptoglobin	Low; most specific	More prominent	Less prominent
	LDH	High; not specific; isoenzyme 1 (RBC and heart)	Less prominent	More prominent
	Indirect bilirubin	High; not specific	Less prominent	More prominent
	AST	High; not specific	Present in both	Present in both
	Blood smear	Variable according to cause: Spherocytes, elliptocytes, schistocytes, sickle cell, etc.	Present in both	Present in both
Indirect	Reticulocyte count	>100 × 10^9/L; normal or low if hypoproliferative component	Present in both	Present in both
	Mean cell volume	High; from reticulocytosis; mostly normal though	Present in both	Present in both
	Soluble transferrin receptor	High (increased RBC turnover); iron deficiency	Present in both	Present in both
	Hemoglobin A1c	Unexpectedly low (limited time for RBC glycation)	Present in both	Present in both
	Carboxyhemoglobin	High (CO a breakdown product of heme metabolism)	Present in both	Present in both

Haptoglobin ↓ + LDH ↑ -
95% specific for hemolysis diag

N haptoglobin + N LDH
92% sensitive for absence of hemolysis

Reticulocytopenia in 20 -37%
Of pts at diagnosis

there may be confounding factors as these laboratory tests are not highly specific !

Low haptoglobin is also observed in liver disease, prior transfusion therapy, rigorous exercise, and, rarely, in ahaptoglobinemia, a genetic condition affecting 1:1000 whites and as many as 4% of African Americans

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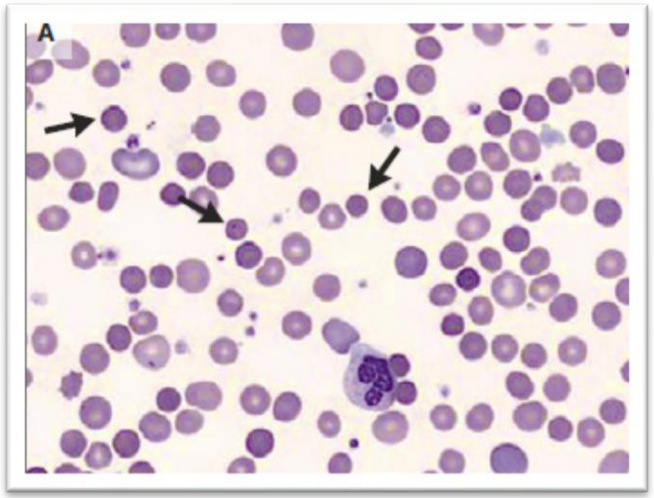

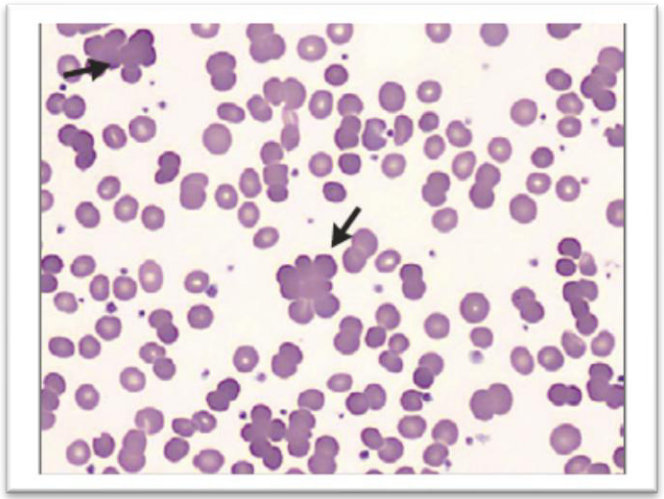

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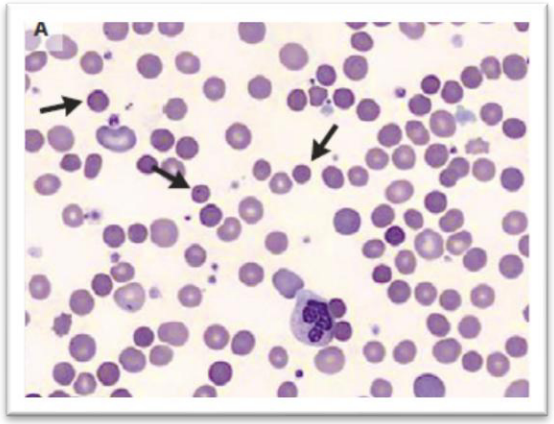
- אילו בדיקות נוספות?



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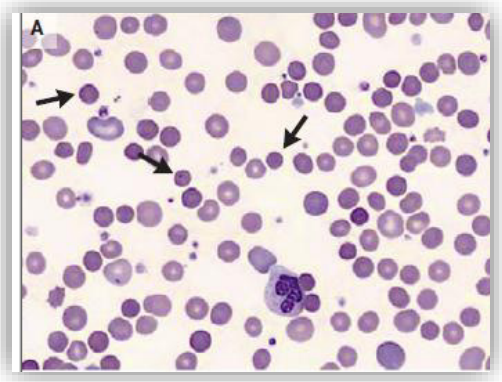

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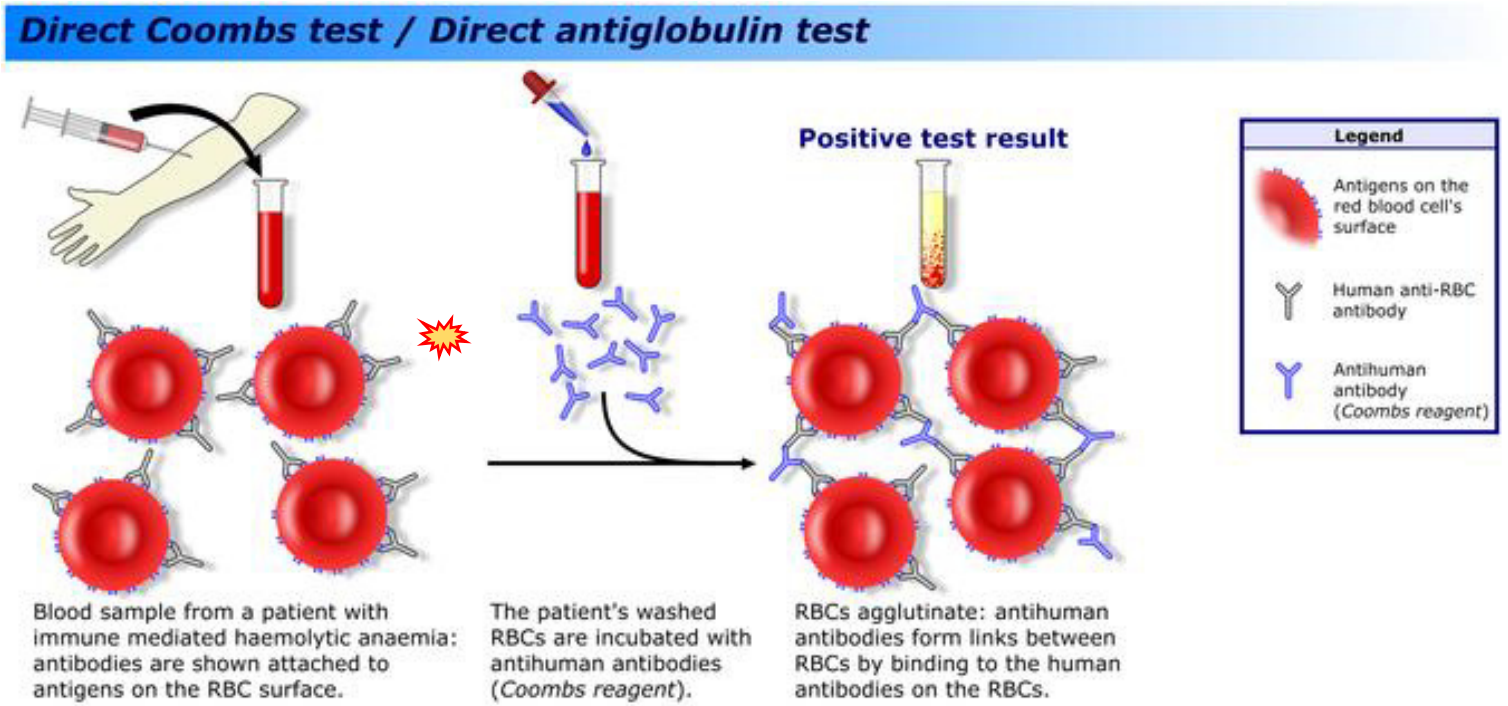
- DAT : IgG +3, C3d -

Diagnostic approach to suspected AIHA – 1. Hemolysis



Direct Antiglobulin (Coombs) Test
Detects the presence of immunoglobulins and/or complement (C3d) on tested RBCs

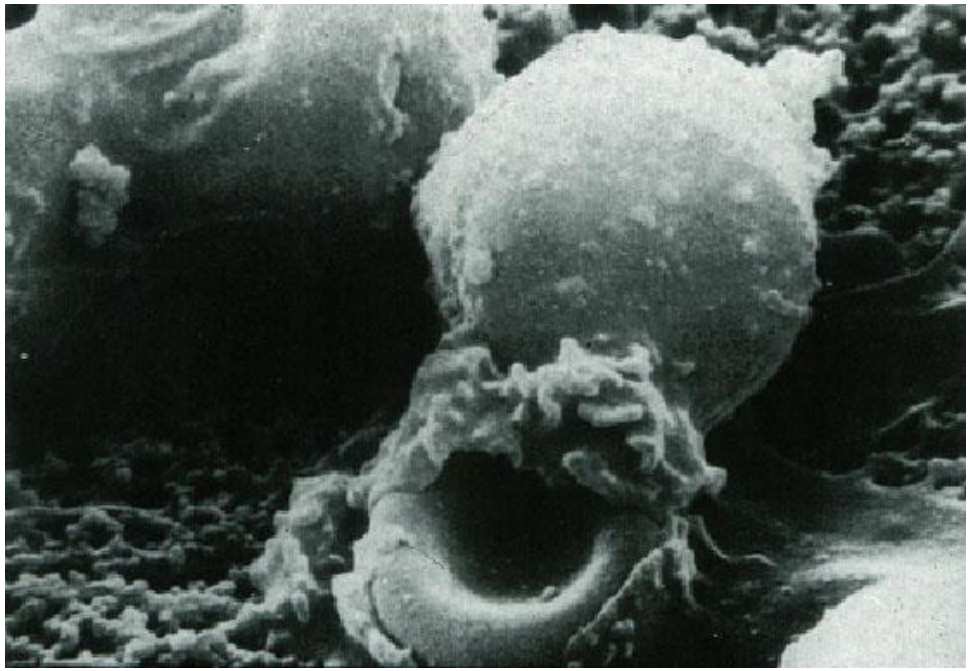
בדיקה אבחנתית ל AIHA – DAT

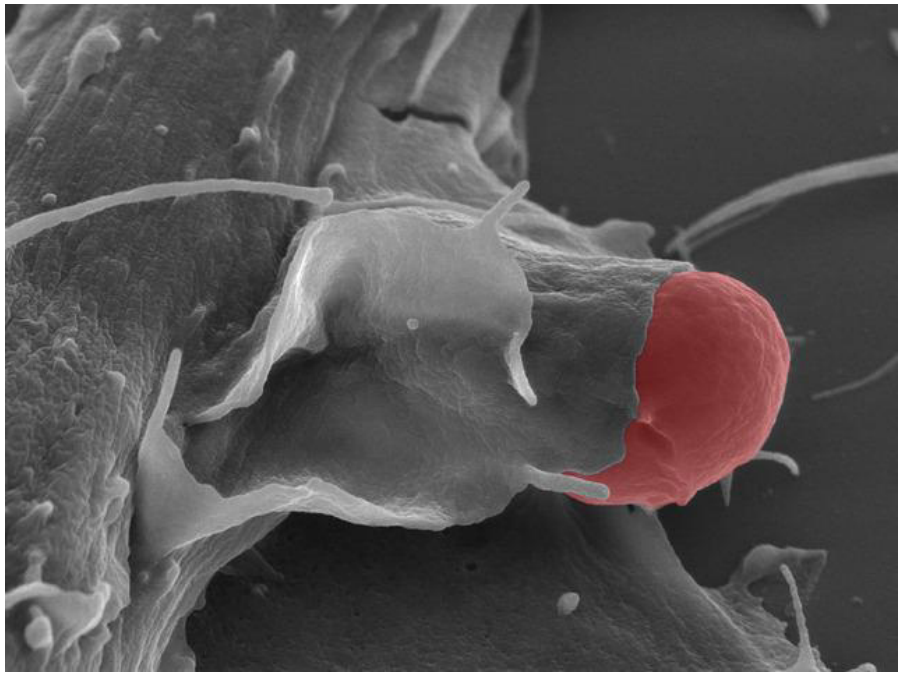
Warm type AIHA 60-70%	cold type AIHA (CAD) 20-25%	Mixed type AIHA 5-10%	Paroxysmal cold AIHA 1-5%	Atypical AIHA 1-5%
Primary (50%)	**Primary**	**Primary**	**Primary**	**IgA, DAT – Negative Warm-IgM**
Secondary (50%)	**Secondary (CAS)**	**Secondary**	**Secondary**	
Neoplasia (CLL, Lymphoma, Solid organ)	**Malignancy** (e.g. CLL, NHL, Solid organ)	**Infection** (e.g. Adenovirus, Influenza A, Syphilis, CMV, IM, VZV, Measles, Mumps, Mycoplasma pneumoniae, Haemophilus influenzae, E. coli)	Lymphoma, SLE	
Immune dysregulation	**Infection** (e.g. Mycoplasma, Viral infections, including IM)		Infection	
Connective tissue disorders (e.g. SLE, Sijogren syndrome, Scleroderma)	**Autoimmune disease**			
Ulcerative colitis, PBC, Sarcoidosis	Post-allogeneic HSCT			
Immune deficiency syndromes (e.g. CVID)				
Post transplantation				
Infection (e.g. Hepatitis C, HIV, CMV, VZV, Pneumococcal infection, Leishmaniasis, Tuberculosis)				
Drugs				

wAIHA pathogenesis

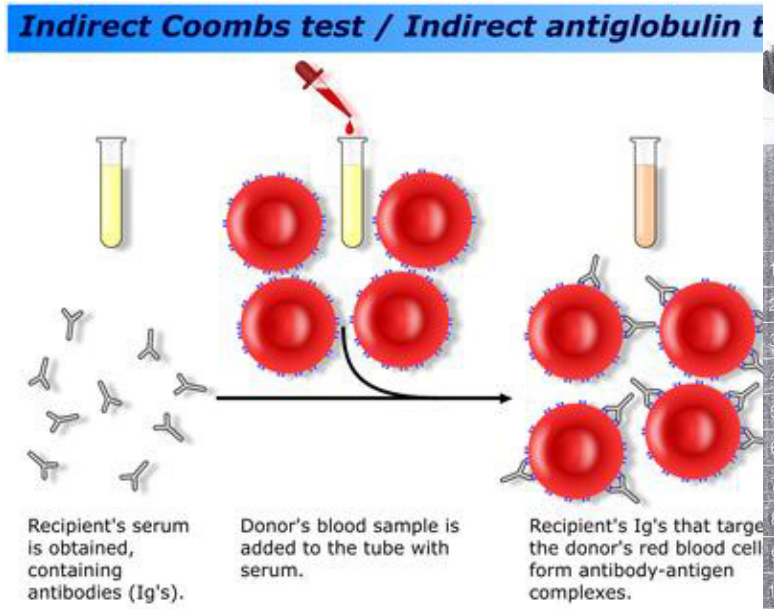
- **נוגדן חום – אופטימום הפעילות ב – 37^0C**
- **ברב המכריע של המקרים IgG פוליקלונלי (IgA -5%)**
  - **בעיקר IgG1 ו - IgG3**
  - **יכול לקשור משלים אך ביעילות נמוכה**
- **Panagglutinin – מגיב עם כל התאים האדומים, כולל תאים עצמיים**
  - **לא ספציפי, אם כי ב 70% מהמקרים מכוון לחלבוני קבוצת הדם band 3 /Rh (לאפיטופ לא פולימורפי)**
- **ההמוליזה – אקסטרה-וסקולרית, בכל המערכת הרטיקולואנדותליאלית אבל בעיקר בטחול**
- **התמונה הקלינית: אנמיה**

Extra- Vascular Hemolysis

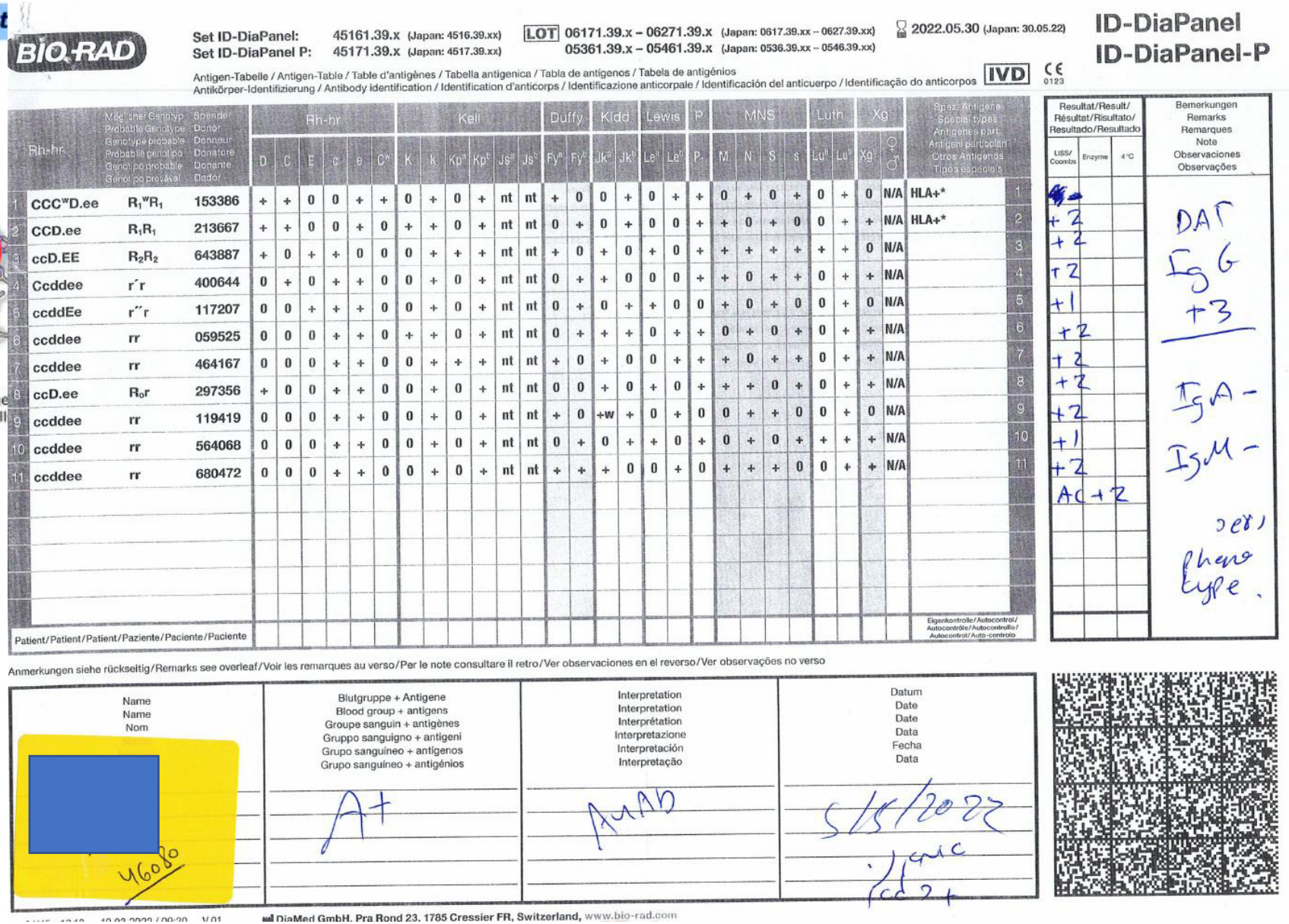




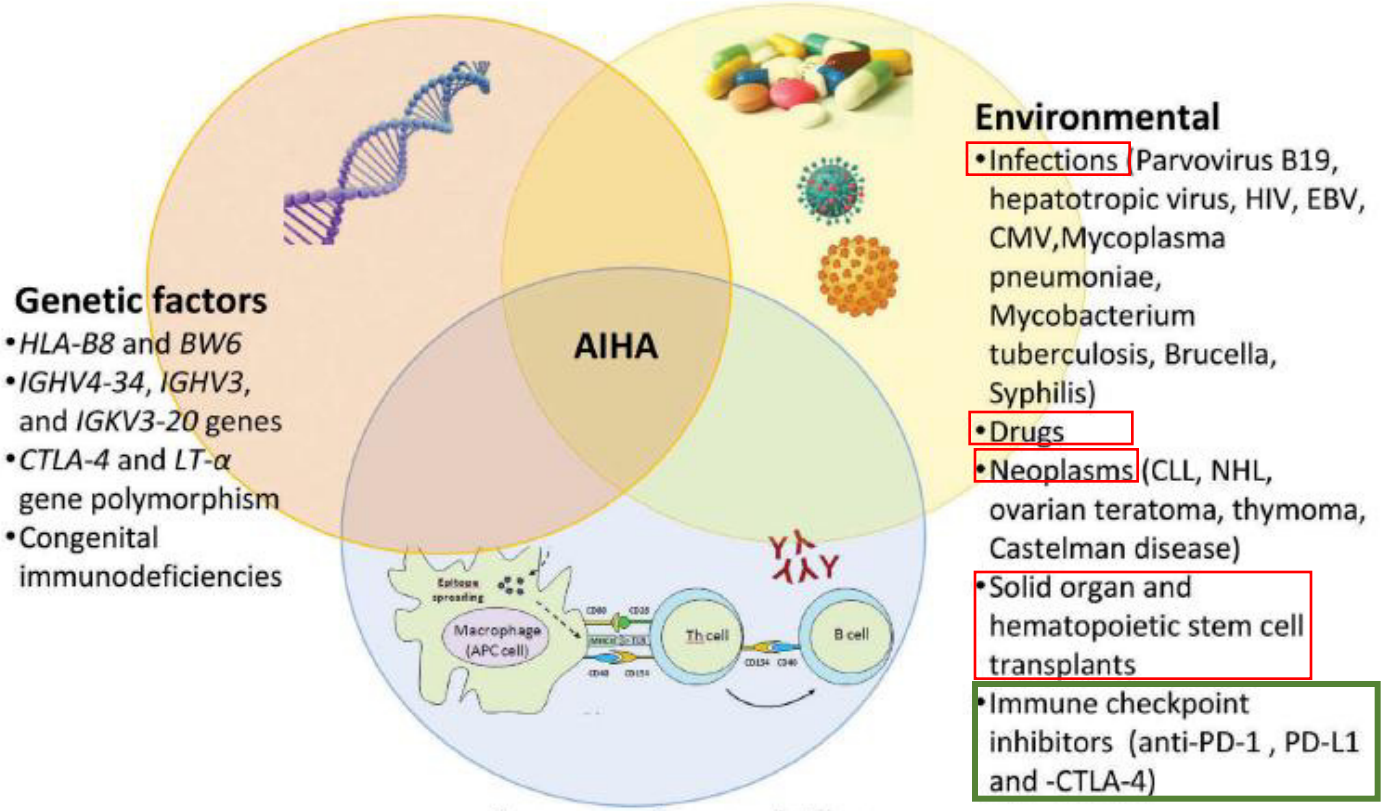
Indirect antiglobulin test



Panagglutinin



wAIHA pathogenesis

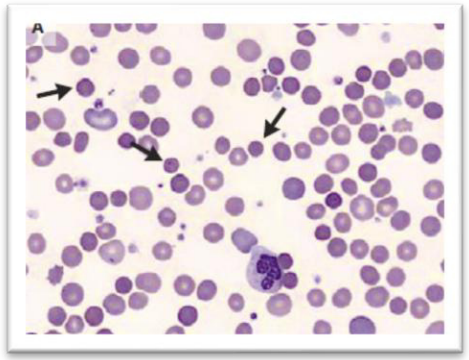


Multifactorial

ure 1. Genetic, immunologic, and environmental factors involved in the pathogenesis of autoimmune hemolytic anemia (AIHA).
: chronic lymphocytic leukemia, NHL: non-Hodgkin lymphoma, PD1/-L: programmed death 1 and its ligand, CTLA-4: cytotoxic T-lymphocyte-associated protein 4.

W. BARCELLINI ET AL. EXPERT REVIEW OF HEMATOLOGY 2020, VOL. 13, NO. 6, 585–597

תיאור מקרה 1



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Perform the direct antiglobulin test (DAT) with monospecific antisera anti-IgG, -IgA, -IgM, -C (C3d)

IgG+ → **wAIHA** (60-70% of cases)

IgG+ plus C+ → Cold agglutinin titer ≥ 1/ 64 → **Mixed AIHA** (5-10% of cases)

C+ → Cold agglutinin titer ≥ 1/ 64 → **CAD** (20-25% of cases)

negative

If AIHA is still suspected perform more sensitive methods in reference labs (washes with cold or LISS, eluate, flow cytometry, ELISA, Dual-DAT, MS-DAT, Donath-Landsteiner test, drug-dependent AIHA

If DAT still negative, reconsider other causes of hemolysis (congenital, toxic, mechanical, drugs, infections, PNH).

If all negative

DAT-negative AIHA (5-10% of cases)

Diagnostic test if secondary forms are suspected: chest x-rays, abdomen ultrasound or TC scan, bone marrow evaluation (morphology, cytometry, cytogenetics, and biopsy), serum and urine electrophoresis, serum IgG, IgA and IgM levels, lymphocyte subpopulations by cytometry, autoimmune screening (ANA, anti-DNA, anti-ENA, LAC, ACA, anti-beta2 glycoprotein 1), infectious screening (parvovirus B19, mycoplasma pneumonia, mycobacterium tuberculosis, brucellosis, syphilis, EBV, CMV, hepatotropic virus, HIV, SARS-CoV-2)

Consider DAT positive for alloantibodies in recently transfused patients

Consider a false positive DAT (hypergamma-globulinemia, paraproteins. therapy with Ivlg or daratumumab)

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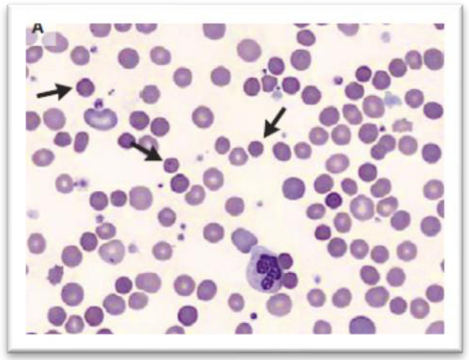

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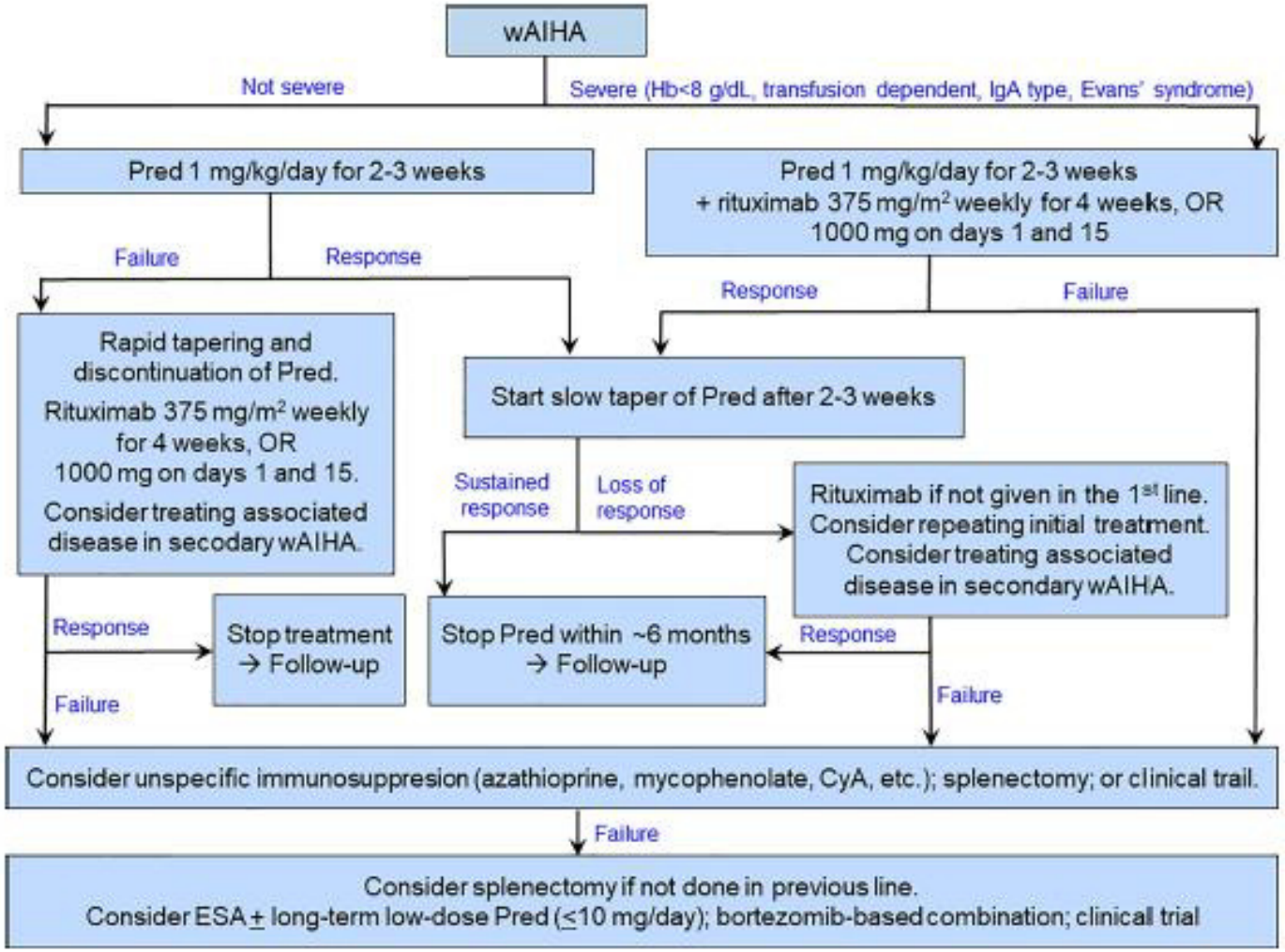
- **טיפול?**

סטרואידים:

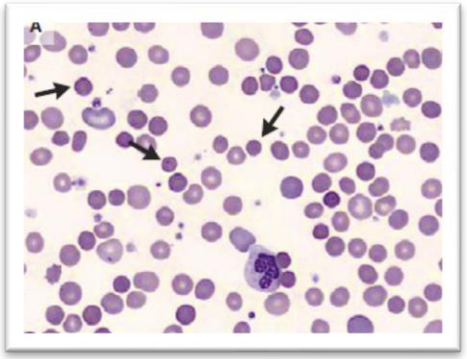
- עדיין הטיפול קו ראשון המיידי (עם או בלי ריטוקסימב)
- תגובה ראשונית לטיפול 80-90% , אבל רק 20-30% יכנסו לרמיסיה ממושכת ללא צורך בטיפול נוסף
- זמן הערכת תגובה לטיפול שבועיים –שלושה (המטרה המקובלת המוגלובין 10ג% גם אם עדיין יש המוליזה "מפוצה")
- הגמילה חייבת להיות איטית מאוד (לפחות כ – 6 ח')
- לא לשכוח טיפול מניעתי מגן מסיבוכי טיפול ממושך בפרדניזון



Berentsen et al.

לא לשכוח:
ח' פולית
טיפול נוגד קרישה?
אריטרופויטין?

תיאור מטופלת 1



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- DAT IgG 3+ C3d 1+
- בירור?

<u>ריטוקסימב (חידוש סטרואידים)</u>

קו טיפול שני – במקום כריתת טחול

בעבר

ניתן לחזור עליו

<u>לא לשכוח:</u>

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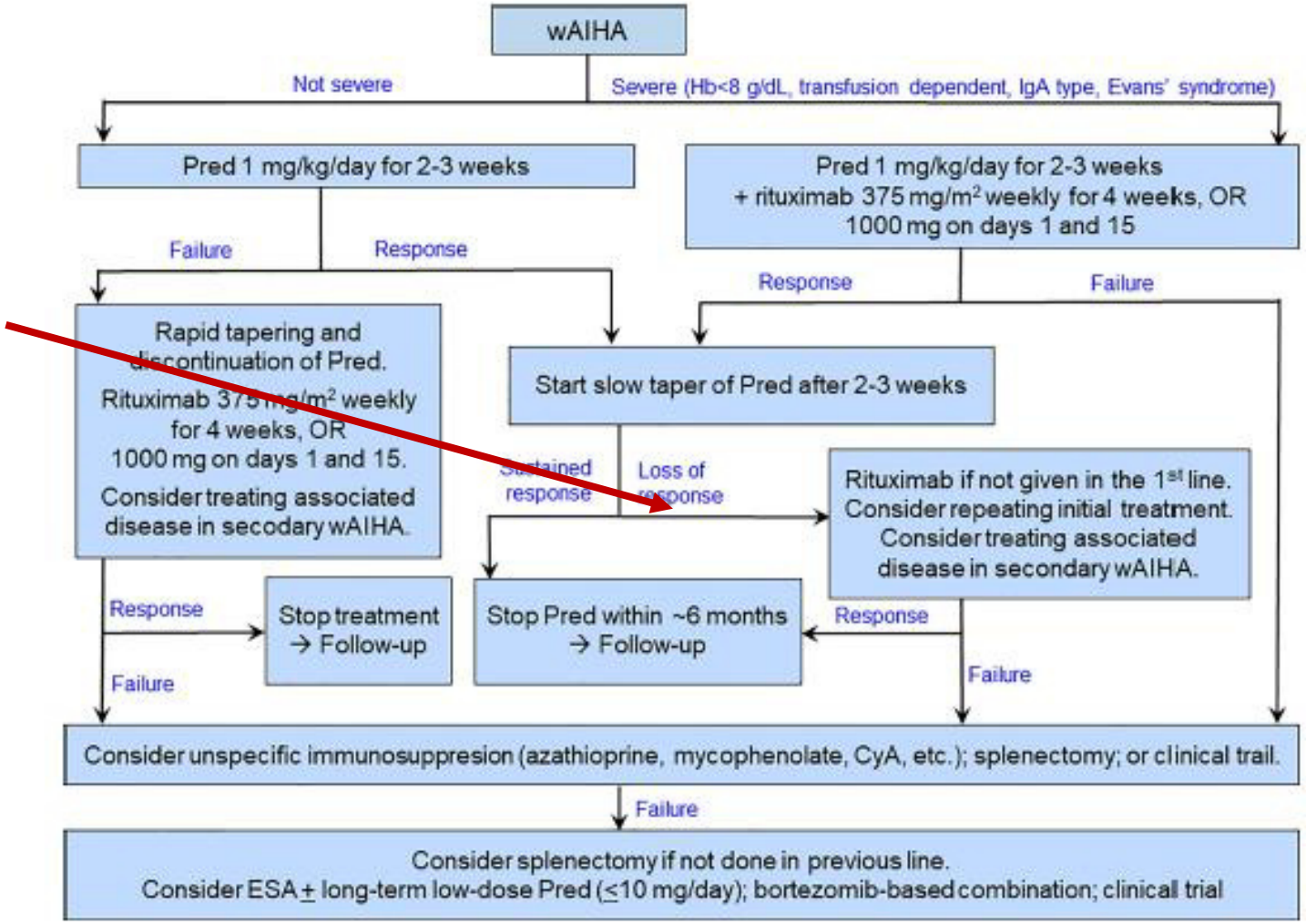

Rituximab?

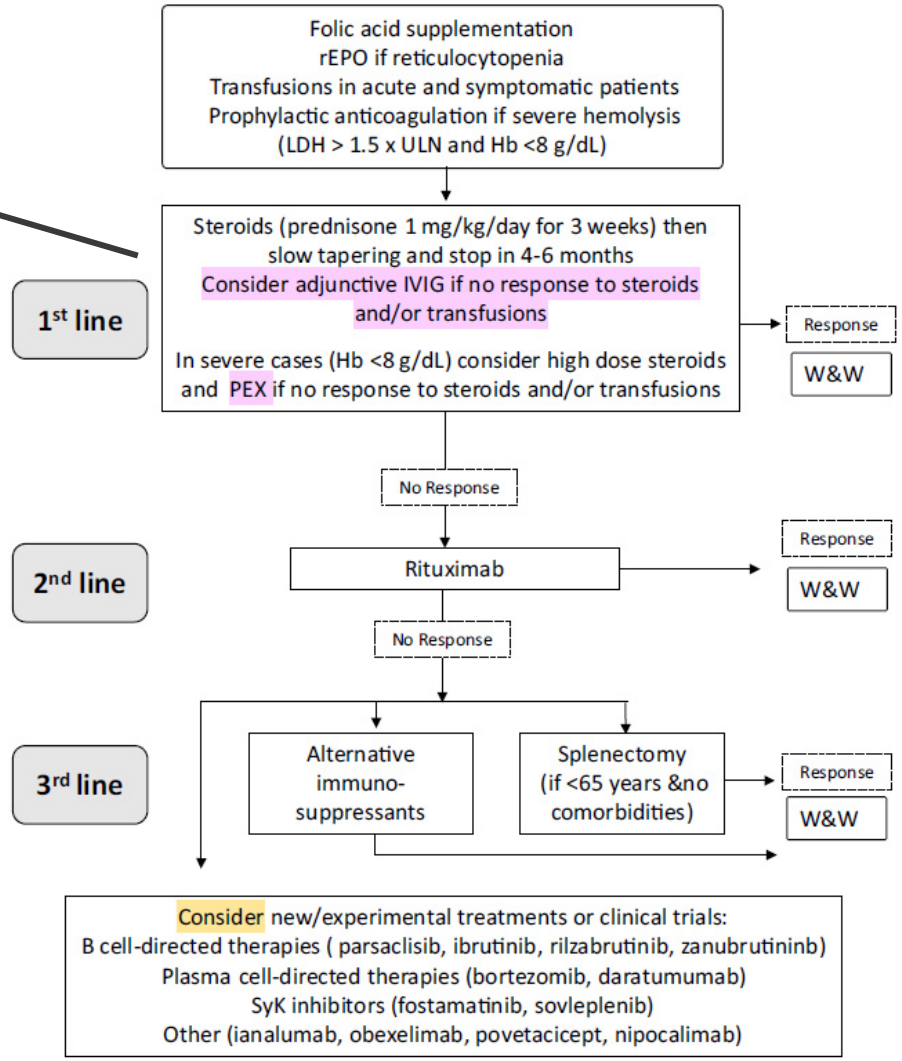

Figure 2. Therapeutic algorithm of warm autoimmune hemolytic anemia (wAIHA). IVIG, intravenous immunoglobulins; PEX, plasma exchange; rEPO, recombinant erythropoietin; ULN, upper limit of normal; W&W, wait and watch.

Management of autoimmune hemolytic anemia

Wilma Barcellini[1] and Bruno Fattizzo[1,2]

[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; and [2]Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy

ASH educational 2025

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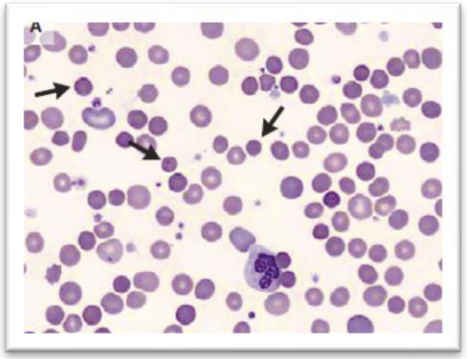

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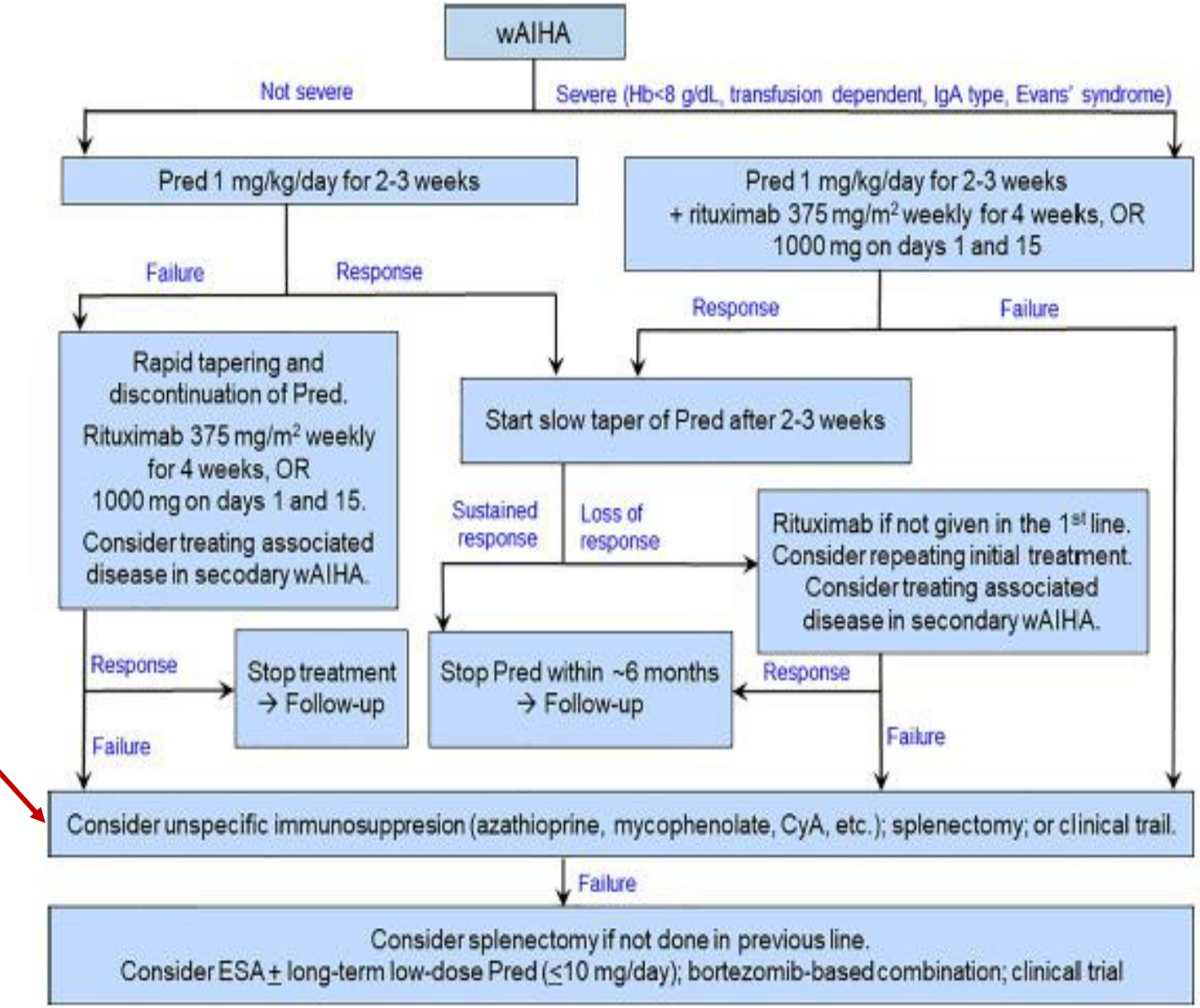
- 4 ח' אחרי הטיפול בריטוקסימב, עדיין על פרדניזון 15מ"ג, המוליזה קלה פעילה, המוגלובין 9 ג% ~

Steroid –sparing Agents



<u>לא לשכוח:</u>

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טיפול נוגד קרישה?

אריטרופויטין?

mmune hemolytic anemia

Milan, Italy; and [2]Department of Oncology and Hemato-Oncology, University of

2025

Drug	Phase/status	Mechanism of action	Route of administration	Efficacy
Agents targeting B-cells				
Parsaclisib	Phase 2/3	PI3K inhibitor	Oral	75% response rates in a phase 2 study of rel/ref wAIHA. Phase 3 study withhold.
Ibrutinib/rilzabrutinib	Phase 2	BTK inhibitor	Oral	Effective in reducing AIHA flares in CLL patients. Phase 2 of rilzabrutinib in primary rel/ref wAIHA showed a 64% response rate.
Obexelimab	Phase 2/3	Anti-CD19 and FcγRIIb bispecific MoAb	IV/SC	/
Inhibitors of IgG-mediated extravascular hemolysis				
Fostamatinib	Phase 2/3	SyK inhibitor	Oral	45% of patients responded in phase 2; 35.6% of fostamatinib treated patients achieved a durable Hb response >10 g/dL at week 24 vs 26.7% on placebo in phase 3.
Sovleplenib	Phase 2/3	SyK inhibitor	Oral	67% of sovleplenib treated patients had a Hb response versus 0% on placebo.
Nipocalimab	Phase 3	Anti-FcRn MoAb	IV	Phase 3 study for rel/ref wAIHAs. No results posted.
Complement inhibitors				
Pegcetacoplan	Phase 2	C3 inhibitor	SC	About 1/3 of wAIHA patients with IgG+C3d+DAT responded in a phase 2 study
ANX005	Phase 2	Anti-C1q MoAb	IV	The study included IgG+C3+wAIHA, withhold.

All trials enrolled a variable proportion of patients relapsed/refractory to first (steroids with or without IVIG) or second line therapy (rituximab, splenectomy, immunosuppressants). APRIL, a proliferation-induced signal; BAFF, B-cell activating factor; BTK, Bruton's tyrosine kinase; FcγRIIb, inhibitory Fc gamma receptor; FcRn, neonatal Fc receptor; IV, intravenous; MoAb, monoclonal antibody; PI3K, phosphoinositide 3-kinase; rel/ref, relapsed refractory to first- or second-line therapy; SC, subcutaneous; SyK, spleen tyrosine kinase.

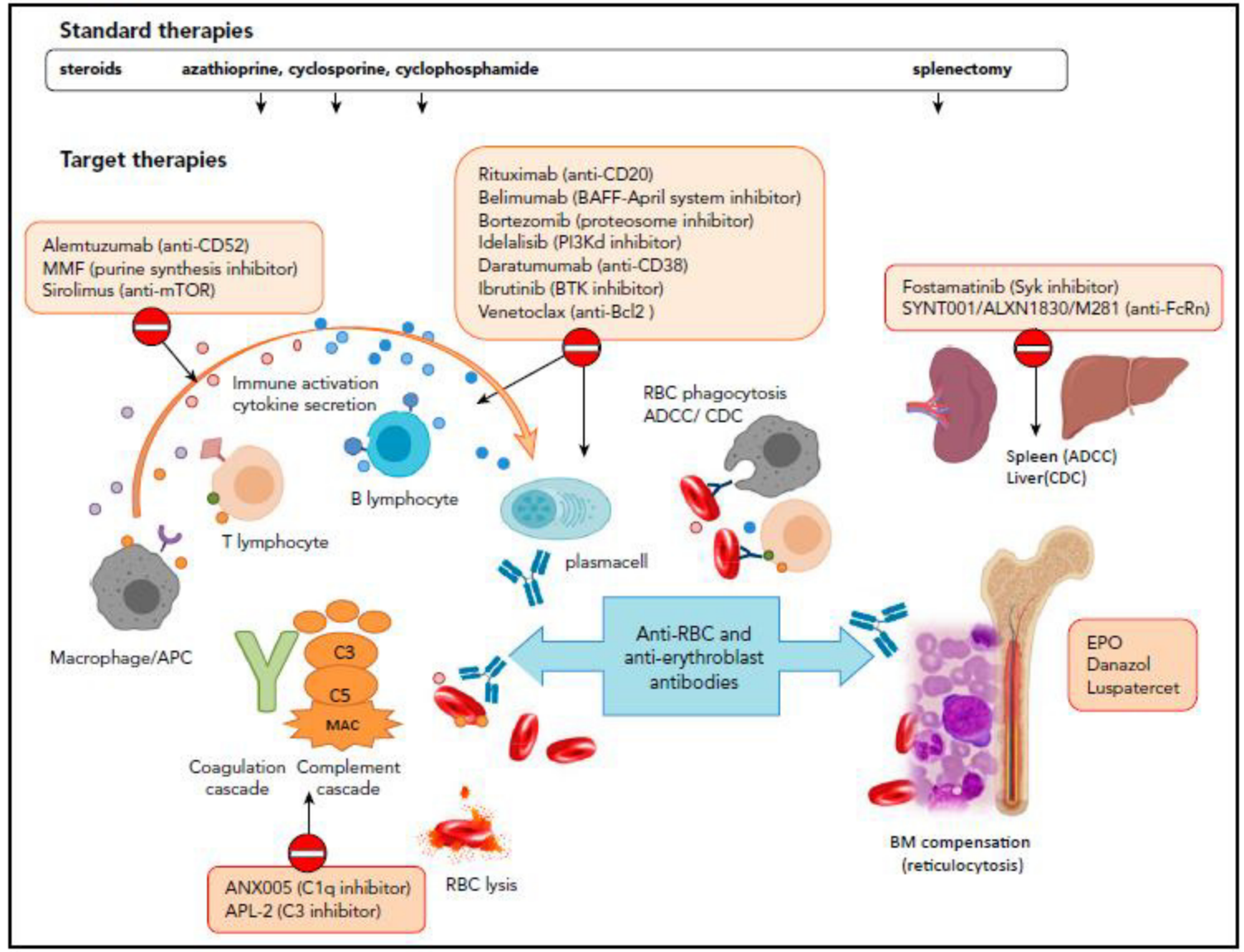
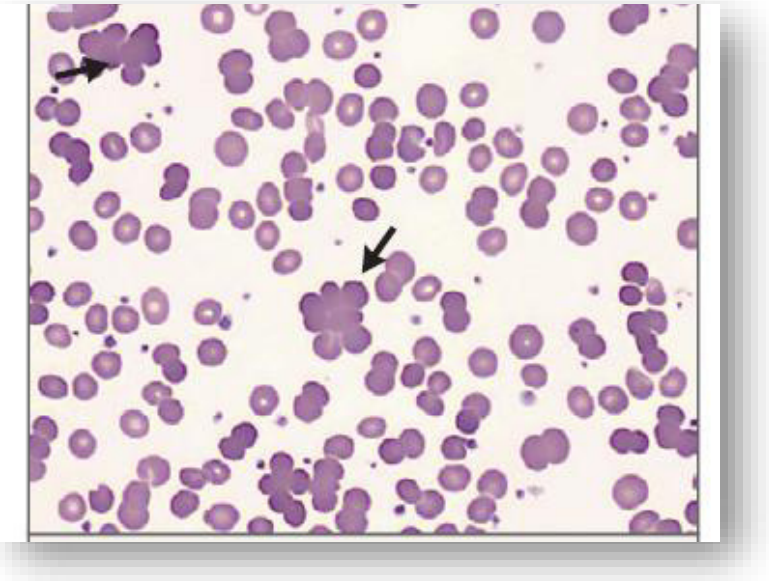


Figure 3. Standard and target therapies for wAIHA. This figure represents the various immunologic mechanisms involved in AIHA pathogenesis, including macrophages, T and B lymphocytes, cytokines, activation of the complement cascade, ADCC in the spleen, and/or complement-dependent cytotoxicity (CDC) in the liver, and lack of BM compensation. Standard therapies include steroids and immunosuppressors that do not act specifically on the various mechanisms and splenectomy. Target therapies are directed against specific immunological mechanisms. APC, antigen-presenting cell; BAFF, B-cell–activating factor; BTK, Bruton tyrosine kinase; CAD, cold agglutinin disease; MAC, membrane attack complex; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; Syk, spleen tyrosine kinase.

מטופל 2

- בן 80, בד"כ בריא למעט יל"ד מאוזן פנה לבירור אנמיה ידועה כ 4 ח'
- בבדיקה מצב כללי טוב , חוורון קל, ללא הגדלת כבד או טחול
- מעבדה: המוגלובין 10.4 ג%, MCV – 120 פ"ל רטיקולוציטים 100,000, LDH ובילירובין בלתי ישיר בגבול העליון של הנורמה



- DAT: IgG-, C3d 3+

Warm type AIHA 60-70%	cold type AIHA 20-25%	Mixed type AIHA 5-10%	Paroxysmal cold AIHA 1-5%	Atypical AIHA 1-5%
Primary (50%)	**Primary (CAD)**	**Primary**	**Primary**	**IgA, DAT – Negative Warm-IgM**
Secondary (50%)	**Secondary (CAS)**	**Secondary**	**Secondary**	
Neoplasia (CLL, Lymphoma, Solid organ)	**Malignancy** (e.g. CLL, NHL, Solid organ)	**Infection** (e.g. Adenovirus, Influenza A, Syphilis, CMV, IM, VZV, Measles, Mumps, Mycoplasma pneumoniae, Haemophilus influenzae, E. coli)	Lymphoma, SLE	
Immune dysregulation	**Infection** (e.g. Mycoplasma, Viral infections, including IM)		Infection	
Connective tissue disorders (e.g. SLE, Sijogren syndrome, Scleroderma)	**Autoimmune disease**			
Ulcerative colitis, PBC, Sarcoidosis	Post-allogeneic HSCT			
Immune deficiency syndromes (e.g. CVID)				
Post transplantation				
Infection (e.g. Hepatitis C, HIV, CMV, VZV, Pneumococcal infection, Leishmaniasis, Tuberculosis)				
Drugs				

CAD – Retrospective Study (Berentsen S, et al *Blood. 2020;136(4)*)

- 232 CAD pts with a median follow-up of 6 years, median age at diagnosis was 68 years (range 33–96) with a 60% of patients diagnosed within 1 year of clinical onset but with the longest time to diagnosis of 32 years.
- Median hemoglobin at onset was 9.3 g/dL (range 4.5–15.3) with 27% of patients having Hb <8 g/dL
- The main symptoms, about 70% of patients had hemolytic anemia with no or mild peripheral circulatory symptoms, 21% hemolytic anemia with severe circulatory symptoms, and 9% circulatory symptoms with compensated hemolysis.

CAD – Retrospective Study (Berentsen S, et al *Blood. 2020;136(4)*)

- Around half of patients required transfusions during the chronic course/acute exacerbations of the disease
- Fatigue is a hallmark of chronic CAD, greater than expected for a given hemoglobin value, possibly related to continuous complement activation and production of pro-inflammatory mediators.
- An increased risk of thrombosis has been reported in this disease as in other complement-mediated hemolytic conditions

Cold Agglutinin Disease (CAD)

- AIHA (chronic hemolysis ± exacerbations)

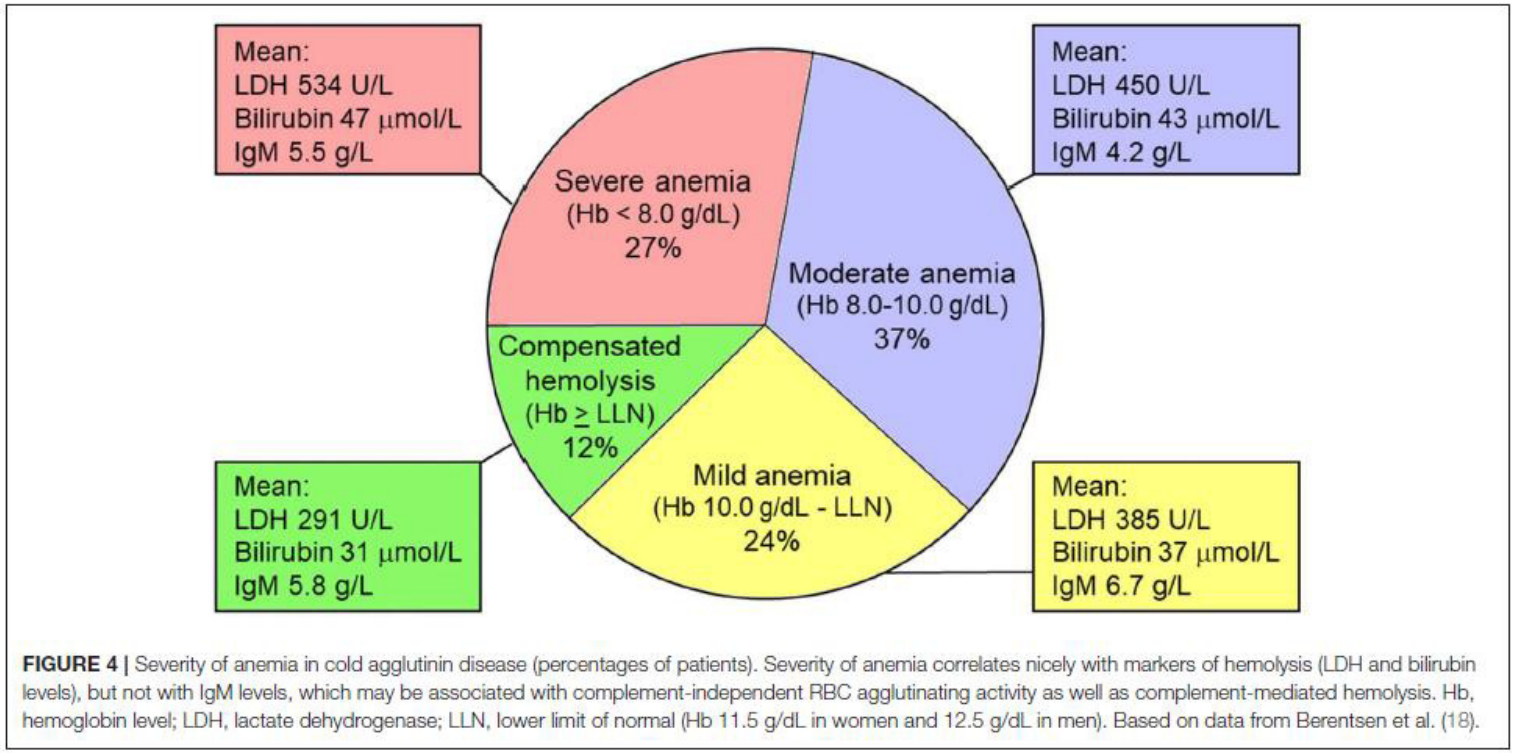


FIGURE 4 | Severity of anemia in cold agglutinin disease (percentages of patients). Severity of anemia correlates nicely with markers of hemolysis (LDH and bilirubin levels), but not with IgM levels, which may be associated with complement-independent RBC agglutinating activity as well as complement-mediated hemolysis. Hb, hemoglobin level; LDH, lactate dehydrogenase; LLN, lower limit of normal (Hb 11.5 g/dL in women and 12.5 g/dL in men). Based on data from Berentsen et al. (18).

Cold Agglutinin Disease (CAD)

- AIHA (chronic hemolysis ± exacerbations)
- a specific clonal B-cell disorder of the bone marrow, and a monoclonal gammopathy of clinical significance

Cold Agglutinin Disease (CAD)

- a specific clonal B-cell disorder of the bone marrow, and a monoclonal gammopathy of clinical significance

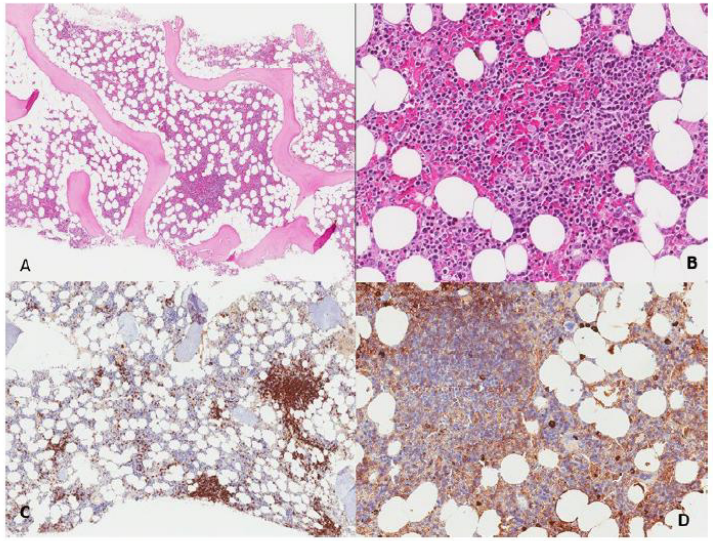


Figure 1. Cold agglutinin–associated lymphoproliferative bone marrow disorder. A, B. Bone marrow trephine biopsy showing intertrabecular nodular lymphoid lesions (hematoxylin-eosin staining, 50× and 280×, respectively). C. CD20 staining shows nodular and diffuse infiltration of B cells (35×). D. IgM-positive B cells within the infiltrate; scattered IgM-positive plasma cells around the infiltrate and diffuse throughout the bone marrow (145×). Courtesy of Dr. Ulla Randen Haave. IgM, immunoglobulin M.

Infiltrates of mature lymphoid cells expressing B-cell markers

Recurrent molecular changes mutations: of *KMT2D* (69% of samples) *CARD11* (31%), while the

frequent cytogenetic abnormality: Trisomy 3 combined with trisomy 12 or 18

MYD88 L265P mutation is typically not found in CAD

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms

WHO Classification, 5th edition	WHO Classification, revised 4th edition
Plasma cell neoplasms and other diseases with paraproteins	
Monoclonal gammopathies	
Cold agglutinin disease	*Not previously included*
IgM monoclonal gammopathy of undetermined significance	(Same)
Non-IgM monoclonal gammopathy of undetermined significance	(Same)
Monoclonal gammopathy of renal significance	*Not previously included*
Diseases with monoclonal immunoglobulin deposition	

noglobulin deposits are grouped together. The heavy chain diseases (HCD) are now included in the plasma cell neoplasms section.

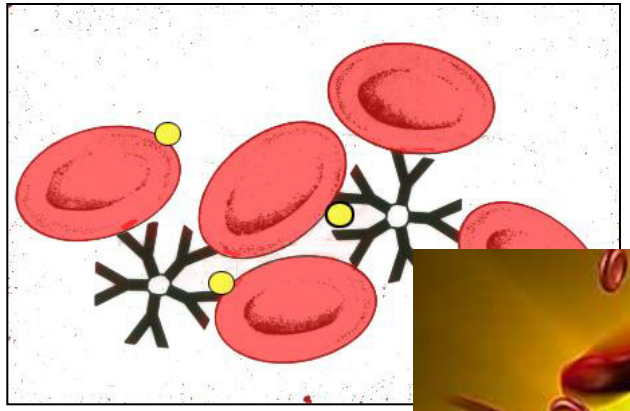
Cold agglutinin disease (CAD) is an autoimmune haemolytic anemia mediated by monoclonal cold agglutinins and driven by an underlying clonal B-cell lymphoid proliferation not fulfilling criteria for a B-cell lymphoma. The annual incidence of this rare disease is estimated at 1–1.8 per million; its prevalence is four-fold higher in colder countries [182–184]. **Monoclonal gammopathy of renal significance (MGRS)** represents a plasma cell or B-cell proliferation that does not meet accepted criteria for malignancy but secretes a monoclonal immunoglobulin or immunoglobulin

Cold Agglutinin Diseaes (CAD) pathogenesis

- נוגדן קור – אופטימום הפעילות ב – 4-6^{0}C
- ברב המכריע של המקרים IgM
  - ב Chronic CAD הנוגדן מונוקלונלי (>80% IgMκ)
  - ב – Transient CAD הנוגדן פוליקלונלי משני לזיהום (מיקופלסמה פנוימוניה, EBV, CMV)
- Panagglutinin – מגיב עם כל התאים האדומים, כולל תאים עצמיים
  - ספציפיות בעיקר לקבוצת הדם Ii
- התמונה הקלינית השכיחה : אקרוציאנוזיס בחשיפה לקור ואנמיה מתונה
- ההמוליזה – אקסטרה-וסקולרית, בכל המערכת הרטיקולואנדותליאלית אבל בעיקר בכבד
- יתכנו אירועים חריפים של המוליזה אינטרה-וסקולרית
- חומרת המחלה תלויה בכיל הנוגדן אך בעיקר באופטימום הטמפרטורה (יכול להגיע עד 32^{0}C)

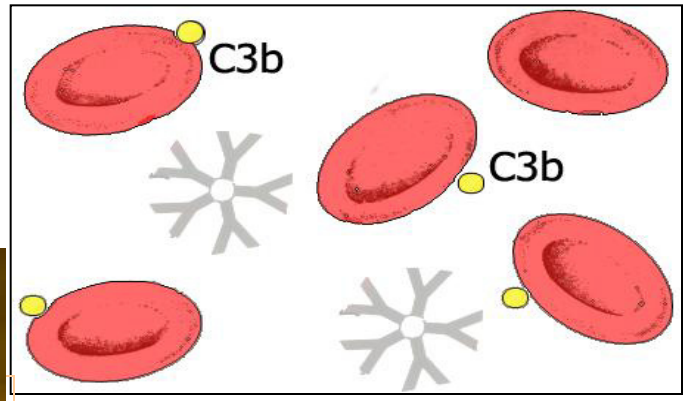
Peripheral circulation

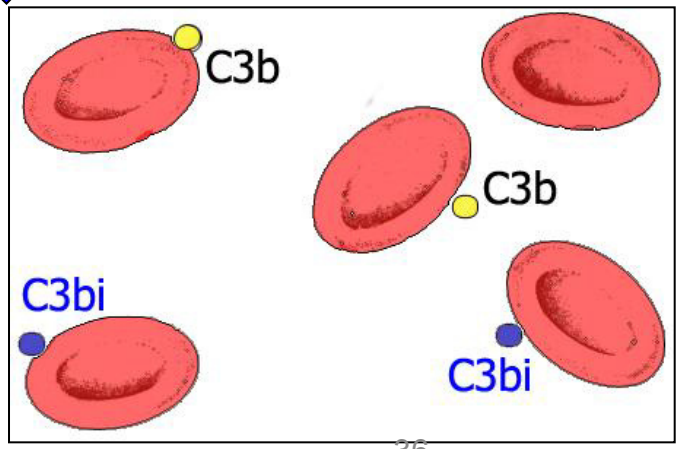
(↓ temperature)



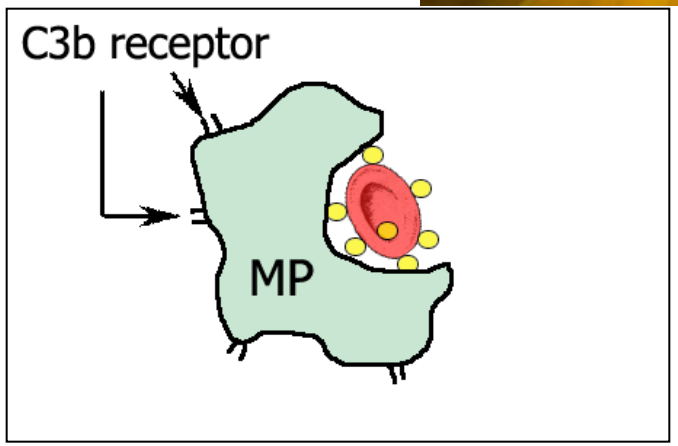
Core circulation

(↑ temperature)





Phagocytosis
liver MPs)



אבחנה - CAD

A negative DAT for C3 rules out CAD (and CAS)!!!

Table 1. Diagnostic criteria for CAD

Level	Criteria	Procedures and comments
Required for diagnosis	Chronic hemolysis	As assessed by high bilirubin, low haptoglobin, high LDH, and, often, high absolute reticulocyte count
	Monospecific DAT strongly positive for C3d	DAT is usually negative for IgG but occasionally weakly positive
	Cold agglutinin titer ≥64 at 4°C	Specimen must be kept at 37–38°C from sampling until serum/plasma has been removed from the clot/cell pellet
	No overt malignant disease or relevant infection	Clinical assessment for malignancy. Radiology as required. Exclude recent infection with *Mycoplasma* or Epstein-Barr virus
Confirmative criteria not required for diagnosis	Monoclonal IgMκ in plasma/serum (or, rarely, IgG or λ phenotype)	Specimen must be kept at 37–38°C from sampling until serum/plasma has been removed from the clot/cell pellet
	Ratio between κ- and λ- positive B cells >3.5 (or, rarely, <0.9)	Flow cytometry in bone marrow aspirate
	Cold agglutinin–associated lymphoproliferative disorder by histopathology	Bone marrow biopsy
	MYD88 L265P mutation not found	As assessed in bone marrow

CAD, cold agglutinin disease; DAT, direct antiglobulin test; IgMκ, immunoglobulin M kappa; LDH, lactate dehydrogenase.

- Clinical assessment should not be forgotten:

CAD or CAS should be suspected in patients with cold induced circulatory symptoms and hemolytic anemia, although circulatory Symptoms are absent in 20% to 50% of patients

- Blood smear

Diagnosis and management of cold agglutinin disease

Sigbjørn Berentsen

| Hematology 2025 | ASH Education Program

Sutimlimab

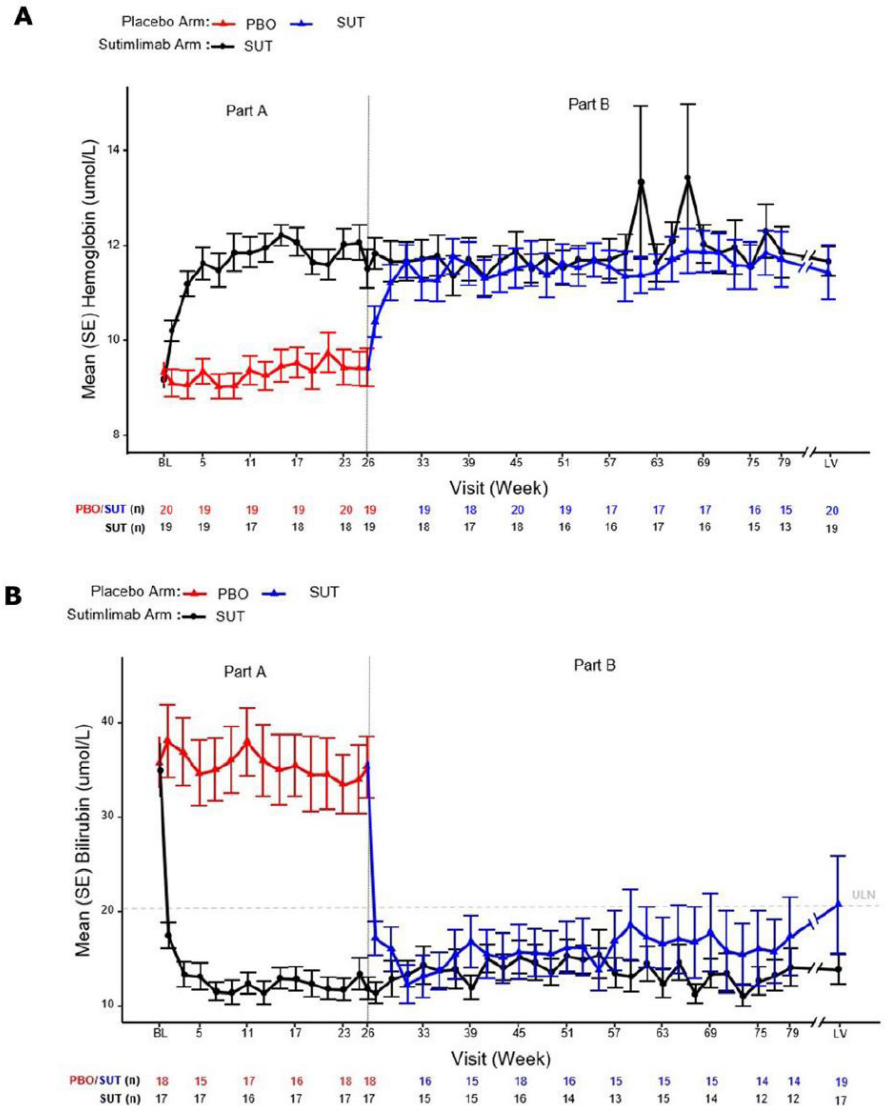


Figure 5. Treatment with sutimlimab vs placebo in 42 patients with CAD in a randomized controlled trial. Marked and rapid improvements in hemoglobin and bilirubin levels were observed in the sutimlimab arm, compared to no changes in the placebo arm. When patients on placebo were given active treatment after 26 weeks, improvement was nearly identical to that seen in the treatment arm. PBO, placebo; SE, standard error of the mean; SUT, sutimlimab. Reproduced with permission from Röth et al.[45]

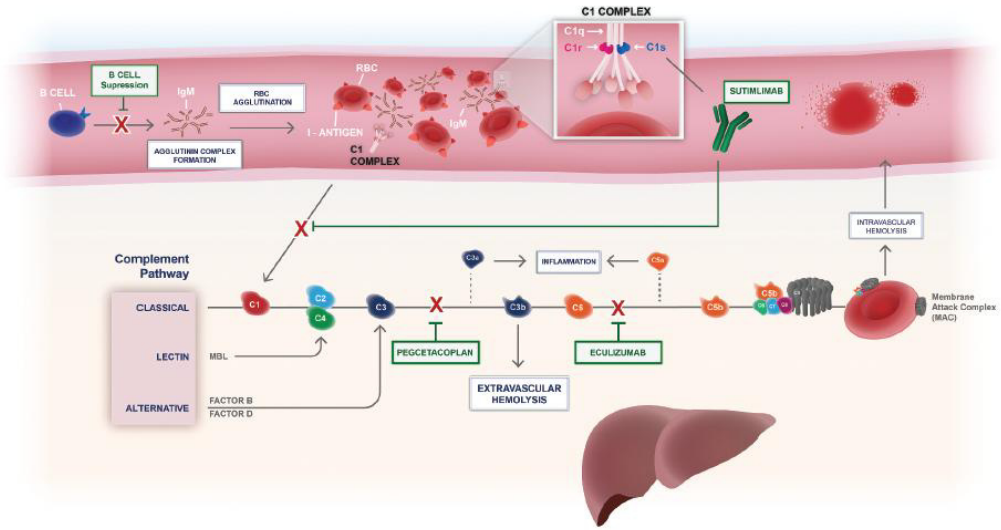


Figure 1. The role of the complement pathway in CAD and mechanism of action of sutimlimab [3,10,18–21].
C, complement protein; Ig, immunoglobulin; MAC, membrane attack complex; MBL, mannose-binding lectin; RBC, red blood cell

טיפול - CAD

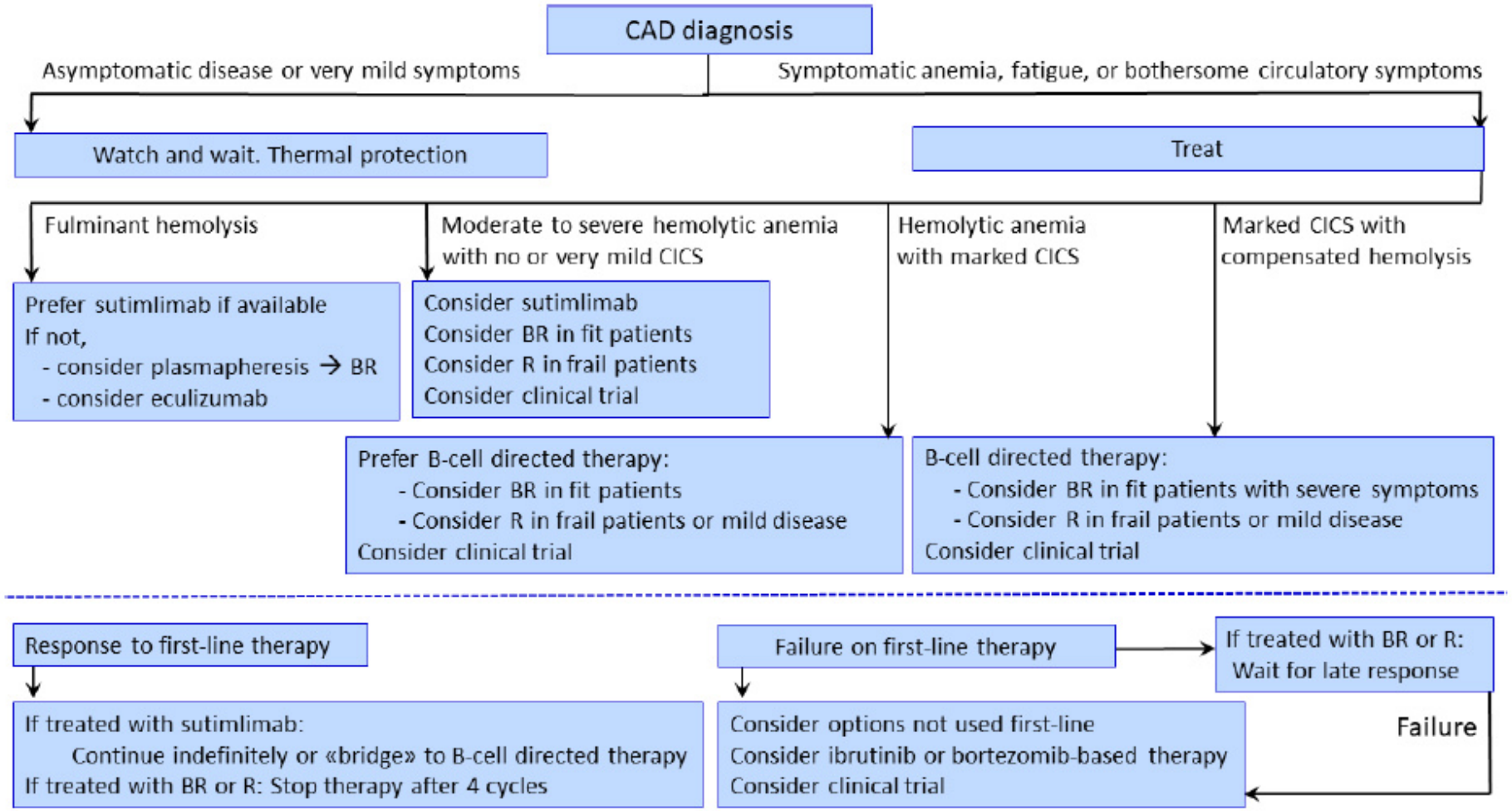


Figure 6. Therapeutic algorithm in CAD. BR, bendamustine plus rituximab; CICS, cold-induced circulatory symptoms; R, rituximab monotherapy.

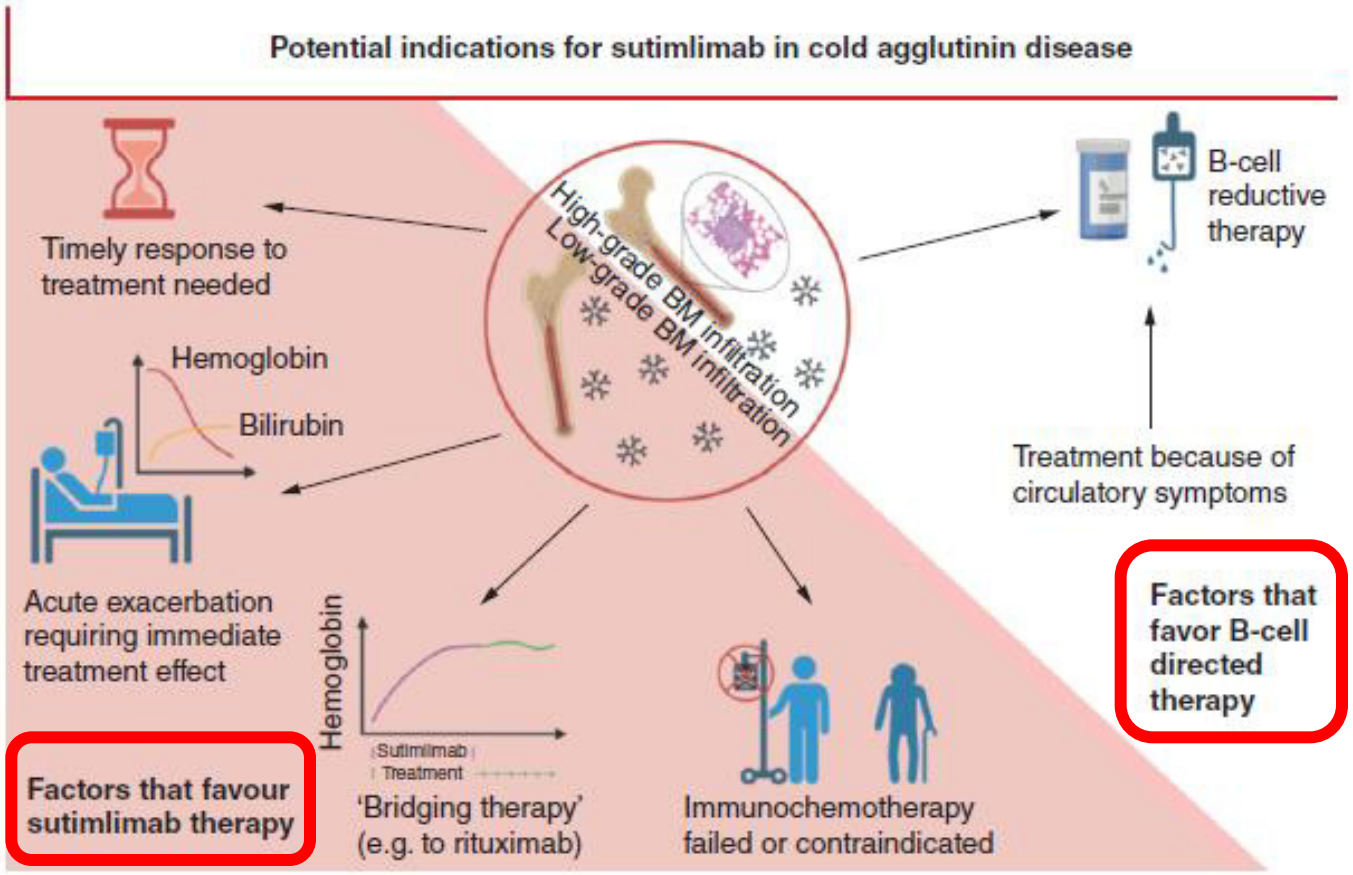
Diagnosis and management of cold agglutinin disease

Sigbjørn Berentsen

Sutimlimab for treatment of cold agglutinin disease: why, how and for whom?

Sigbjørn Berentsen*,[1], Wilma Barcellini[2], Shirley D'Sa[3] & Bernd Jilma[4]

Graphical abstract:



Immunotherapy (2022) 14(15), 1191–1204

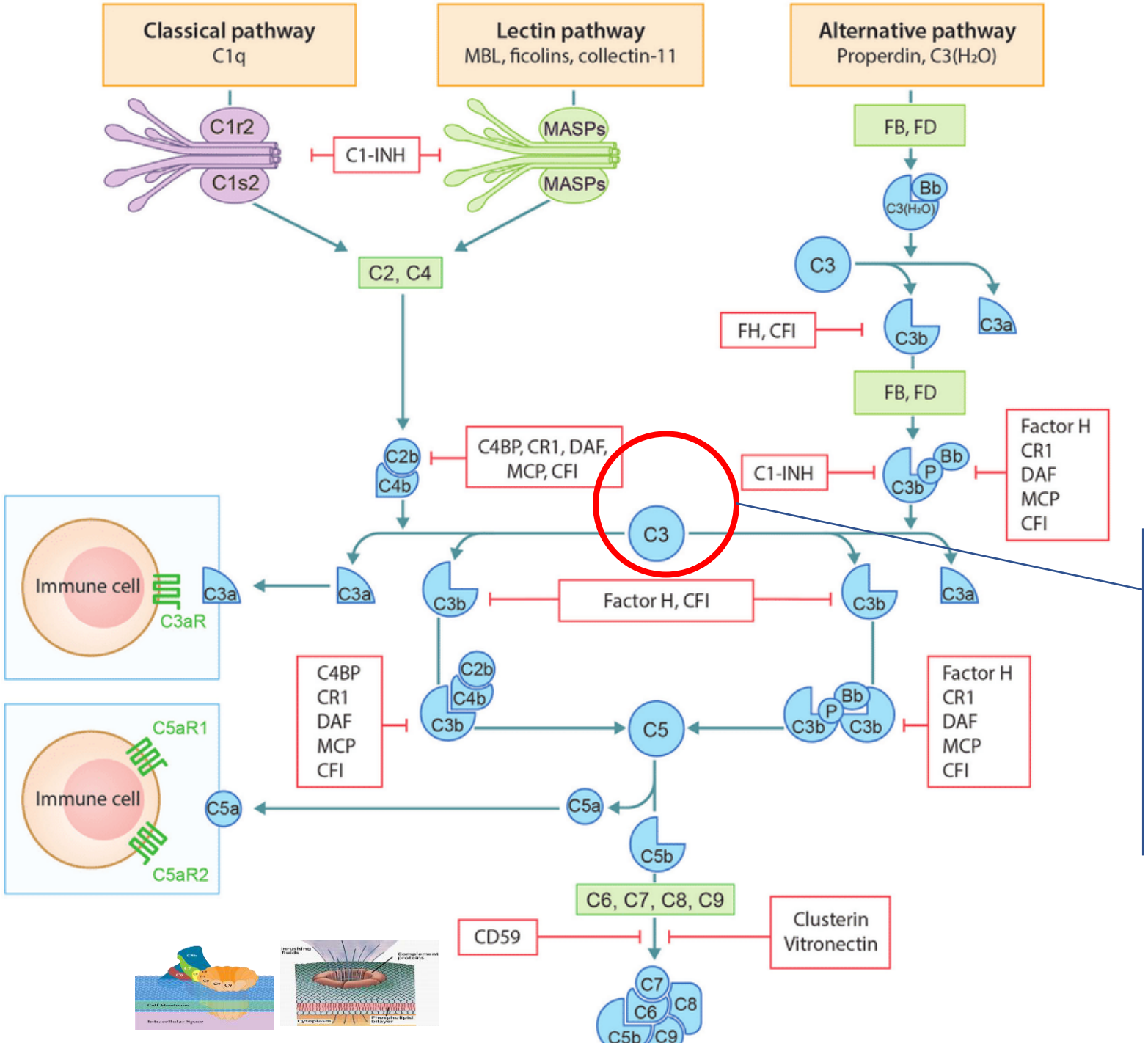
B cell directed therapy

- Rituximab monotherapy is still the most used option
  - Overall response rate (ORR) ~ 50%, very few complete responses (CR), median response duration >1 year
- Rituximab plus bendamustine combination therapy (a prospective uncontrolled trial)
- 71% ORR and 40% CR rate, which increased to 78% and 53%, respectively, after longer observation, median response duration
- was more than 88 months.

Table 2. Novel drugs for cold agglutinin disease (CAD)

Drug	Phase/status	Target	Comments
Plasma cell targeting agents			
Bortezomib	Phase 2/case reports	Proteasome inhibitor	30% response after one course; some patients repeated treatment with efficacy
Daratumumab/ Isatuximab	Case reports	Anti-CD38 MoAb	Case reports of daratumumab efficacy in severe multi-refractory CAD. Efficacy on cold induced symptoms reported
B-cell targeting agents			
Ibrutinib	Retrospective study	BTK inhibitor	Effective in a recent case series of 15 patients, 4 CAD and 11 CAS. 13 responded, 2 died due to underlying disease. Benefit on peripheral symptoms too
Parsaclisib	Phase 2/3	PI3K inhibitor	64% response rates in a phase 2 study of rel/ref wAIHA and CAD. Phase 3 study withhold
Complement inhibitors			
Eculizumab	Phase 2 study	Anti-C5 MoAb	Improved hemolysis and transfusion need in about 1/3 of CAD patients. No effect on peripheral symptoms
Sutimlimab	FDA and EMA approved	Anti-C1s MoAb	>80% anemia response in two phase 3 studies open label and placebo controlled. No effect on peripheral symptoms
Riliprubart	Phase 1b	Anti-active C1s MoAb	Rapid and sustained improvement of hemoglobin and bilirubin
Pegcetacoplan	Phase 2/3	C3 inhibitor	About 2/3 of CAD patients responded in the phase 2 study. A phase 3 study was withheld
Iptacopan	Phase 1	Factor B inhibitor	/

The Complement System



C3

"מנקז" את שלושת מסלולי ההפעלה

שלב אמפליפיקציה של התהליך

שוקע בממברנת הפתוגן ומוביל את השלב האפקטורי

מפעיל את השלב הסופי ליצירת MAC (membrane Attack Complex)

תודה על ההקשבה !!!

ובהצלחה