Anemie Emolitiche Autoimmuni

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Il sottoscritto Alessandro Lanti in qualità di Relatore
dichiara che

nell’esercizio della Sua funzione e per l’evento in oggetto, NON È in alcun modo portatore di interessi commerciali propri o di terzi; e che gli eventuali rapporti avuti negli ultimi due anni con soggetti portatori di interessi commerciali non sono tali da permettere a tali soggetti di influenzare le mie funzioni al fine di trarne vantaggio.

SIMTI PRO

Autoimmune haemolytic anemia

- Haemolysis
  - IgG
  - IgM
  - IgA
  - C3d
- Annual incidence 1-3 in 100,000
- Mortality 4-10%
- DAT positive
  - Alone does not define AIHA
    - 0,1% healthy
    - Without haemolysis
    - AIHA in remission
  - AIHA DAT negative
- Types
  - Primary —> ~ 50 %
  - Secondary
    - Autoimmune disease
    - Lymphoproliferative disease
    - Infections
    - Neoplastic disease
    - HSCT allogeneic
    - Drug induced
- Classification
  - Warm autoantibodies (wAIHA)
    - IgG reactive 37°C
    - ~ 65-70%
  - Cold agglutinin (CAD)
    - IgM optimal reactivity at 4°C - 34°C
    - ~ 20-25%
  - Mixed type
    - IgG reative 37°C and IgM reactive > 30°C
    - ~ 5%
  - Paroxysmal cold haemoglobinuria (PCH)
    - IgG biphasic haemolysin reactive 4° and 37°C

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Clinical Epidemiology

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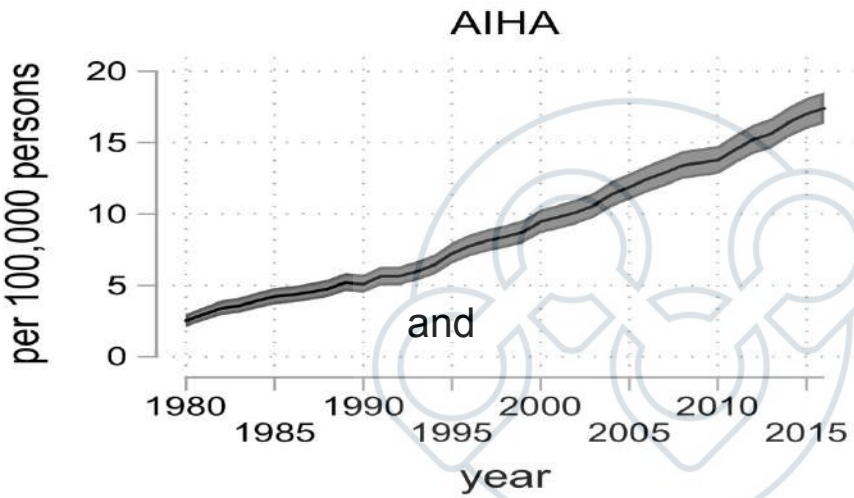
ORIGINAL RESEARCH

Increasing Incidence and Prevalence of Acquired Hemolytic Anemias in Denmark, 1980–2016



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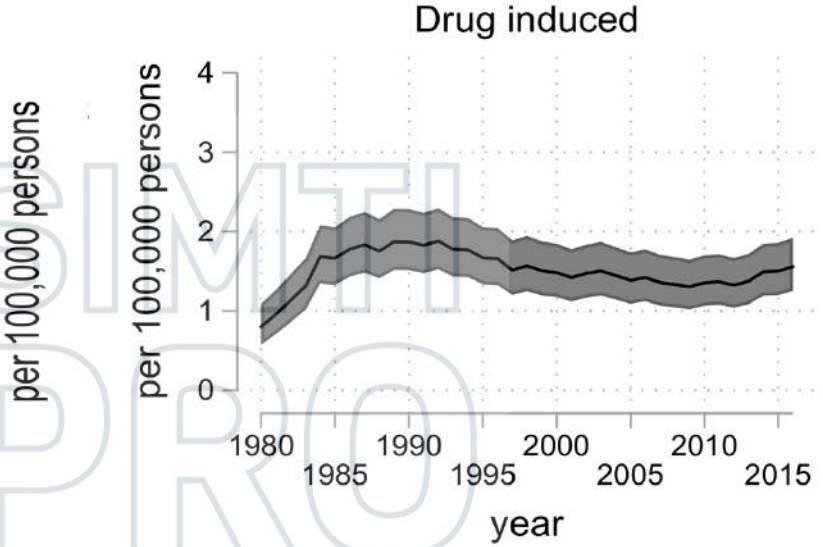
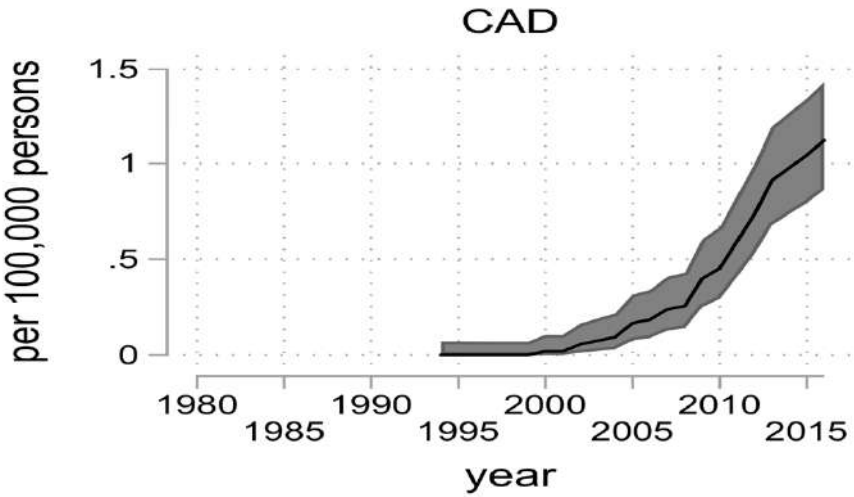




per 100,000 persons

The increasing incidence rate may be related to a more comprehensive diagnostic work-up, increased awareness, and a true increase of disease incidence and prevalence

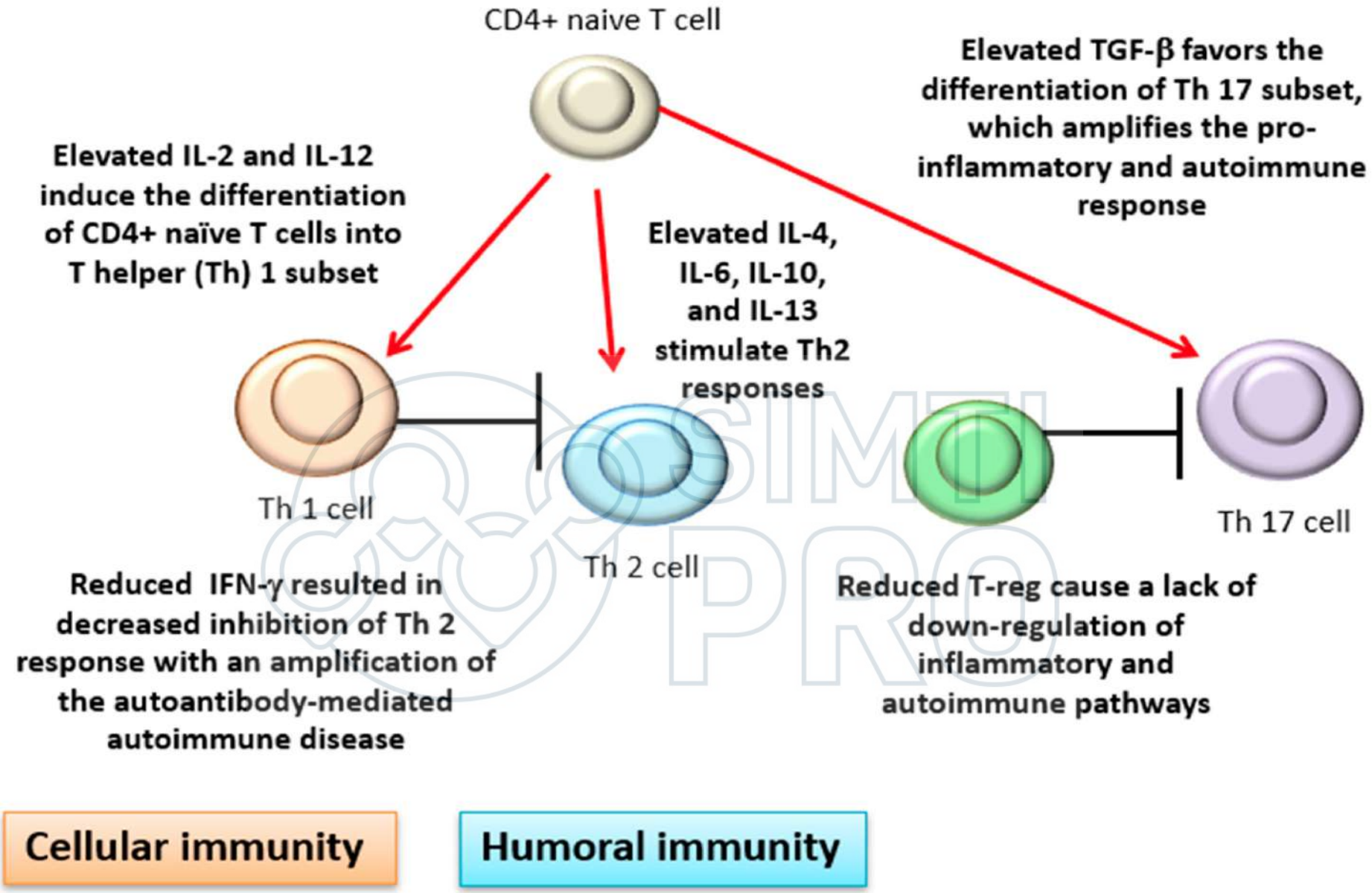
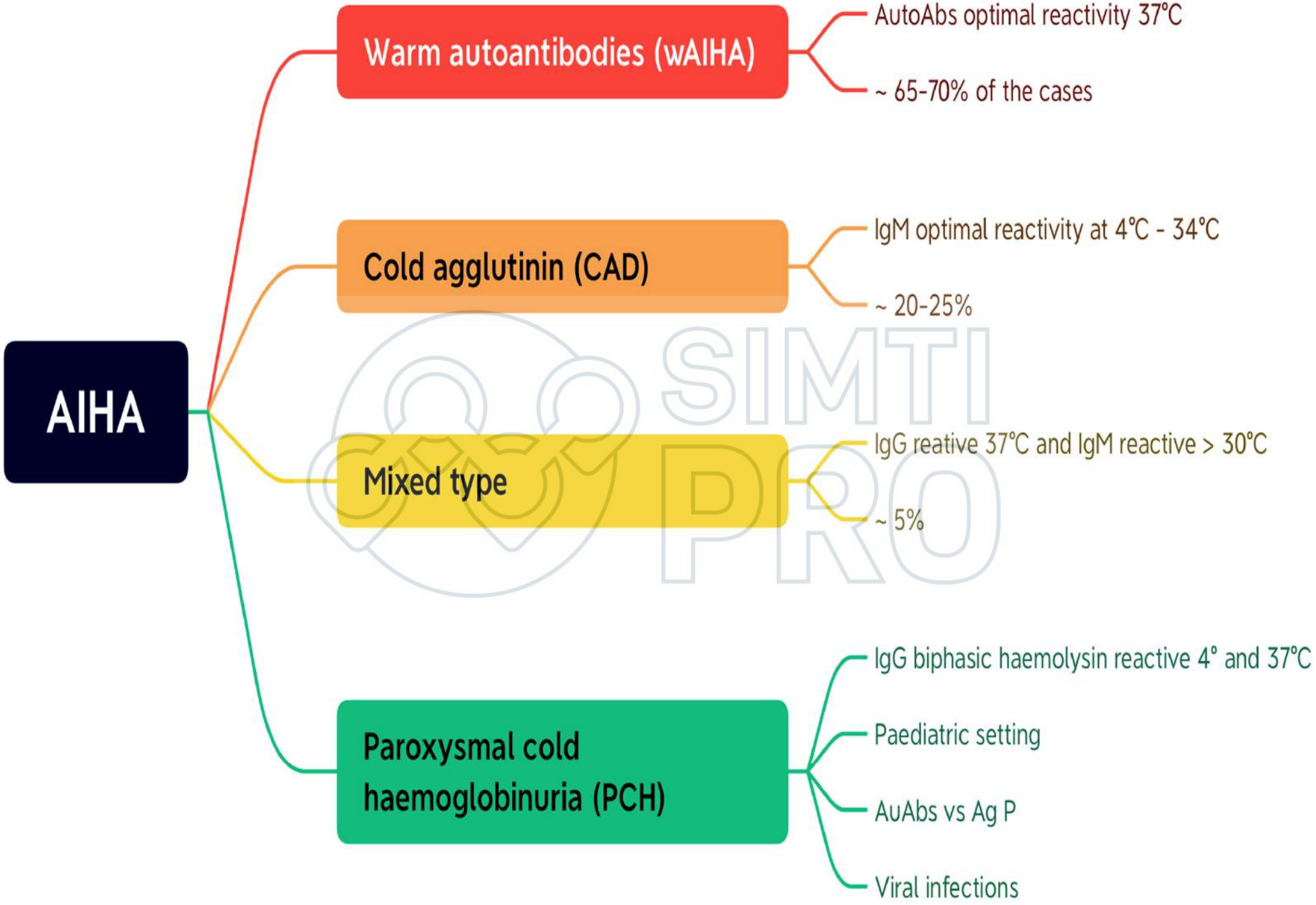


Figure 3. Cytokine dysregulation in AIHA. IL: interleukin; TGF-β: transforming growth factor β; IFN-γ: interferon γ. Red arrows indicate stimulation black lines inhibition/block.

- J. Clin. Med. 2020, 9, 3859


AIHA
Warm autoantibodies (wAIHA)
AutoAbs optimal reactivity 37°C
~ 65-70% of the cases
Cold agglutinin (CAD)
IgM optimal reactivity at 4°C - 34°C
~ 20-25%
Mixed type
IgG reative 37°C and IgM reactive > 30°C
~ 5%
Paroxysmal cold haemoglobinuria (PCH)
IgG biphasic haemolysin reactive 4° and 37°C
Paediatric setting
AuAbs vs Ag P
Viral infections

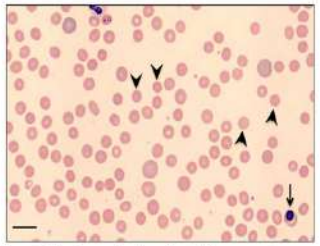


Figure 1. Blood smear of a patient with w-AIHA on presentation. Polychromasia reflecting reticulocytosis, many microspherocytes (few pointed by arrowheads), and a nucleated red blood cell (arrow), indicating stress erythropoiesis, are noted (Wright-Giemsa stain). Bar represents 14 µm.

Warm AIHA

AutoAbs

- Reactive at 37°C
- Tipically IgG
- Usually in combination with C3d
- Rare atypical cases
  - IgM or IgA
  - Only C3d (~ 10%)
  - IgM or IgA in association with IgG (~ 1%)

Secondary conditions associated

- Haematological disorders and lymphoproliferative disease
- Solid malignancies
- Autoimmune disease
- Infections
  - Viral
  - Bacterial
- Transplantation
  - HSC
  - Solid-organ
- Primary immuno deficiency syndromes

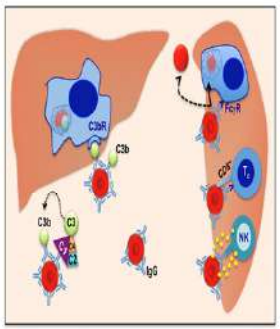
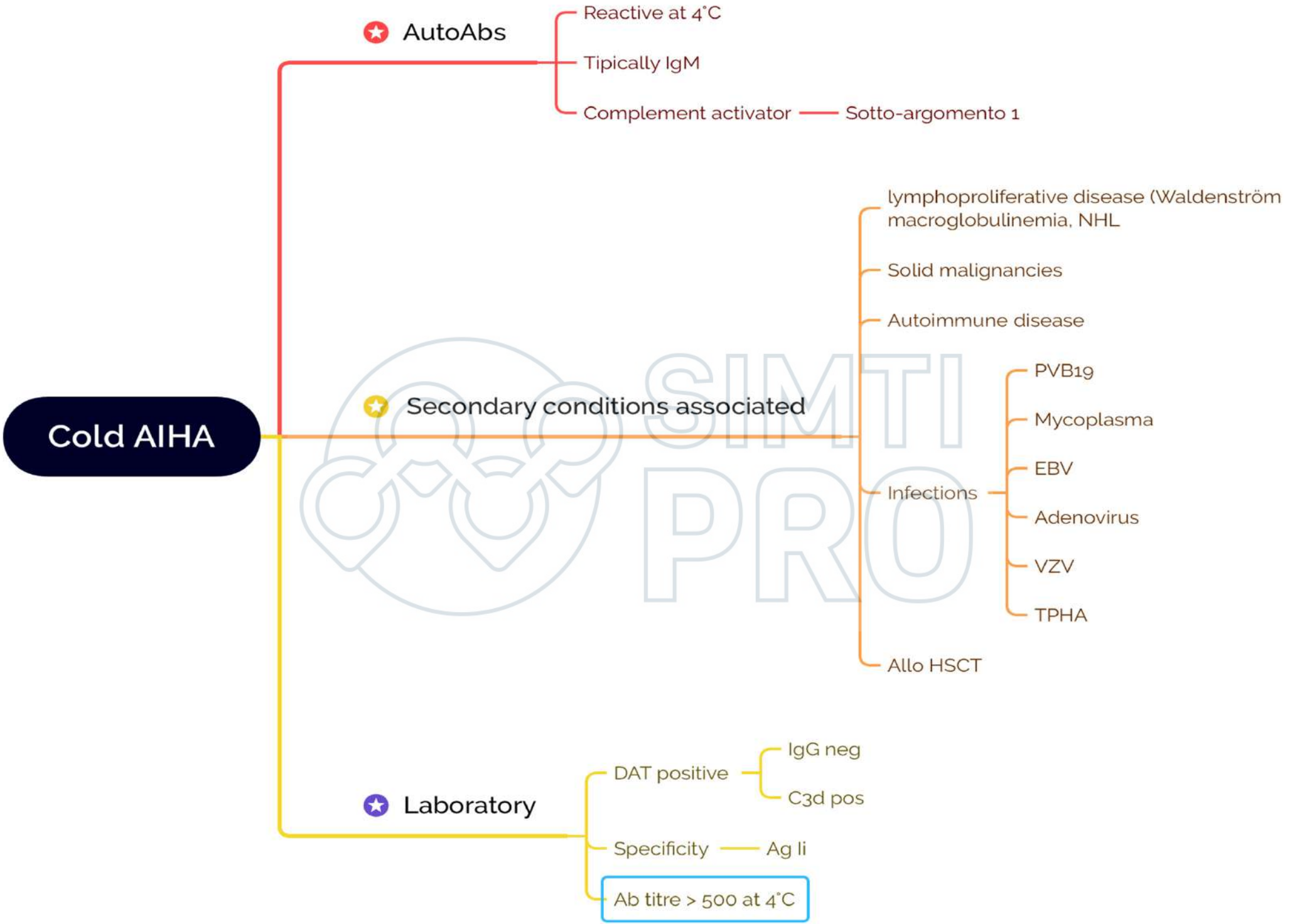


Figure 2. Mechanisms of antibody-sensitized RBC destruction in w-AIHA. Erythrocytes coated by warm-reacting IgG are bound by spleen macrophages carrying Fcγ receptors for the IgG heavy chain, and they are either phagocytosed or have part of their membrane removed, in which case they form microspherocytes subject to further destruction during their next passage through the spleen. ADCC, mediated by cytotoxic CD8+ T cells (Tc) and NK cells, is also contributing to extravascular hemolysis preferentially in the spleen and lymphoid organs. When either a high concentration of IgG or IgG with high affinity to complement is bound to the erythrocytes, complement (C1q) is bound and gets activated toward C3b. C3b-opsonized RBCs are next phagocytosed by liver macrophages that carry C3b receptors.

Laboratory

- DAT positive
  - IgG
  - IgG + C3d
  - IgM or IgA (rarely)
- Eluate — IgG
- Specificity
  - Generally panreactive
  - Rh system
  - Rarely Wr, Kp, Jk

SIMTI PRO


Cold AIHA
AutoAbs
Reactive at 4°C
Tipically IgM
Complement activator
Sotto-argomento 1
Secondary conditions associated
lymphoproliferative disease (Waldenström macroglobulinemia, NHL
Solid malignancies
Autoimmune disease
Infections
PVB19
Mycoplasma
EBV
Adenovirus
VZV
TPHA
Allo HSCT
Laboratory
DAT positive
IgG neg
C3d pos
Specificity
Ag Ii
Ab titre > 500 at 4°C

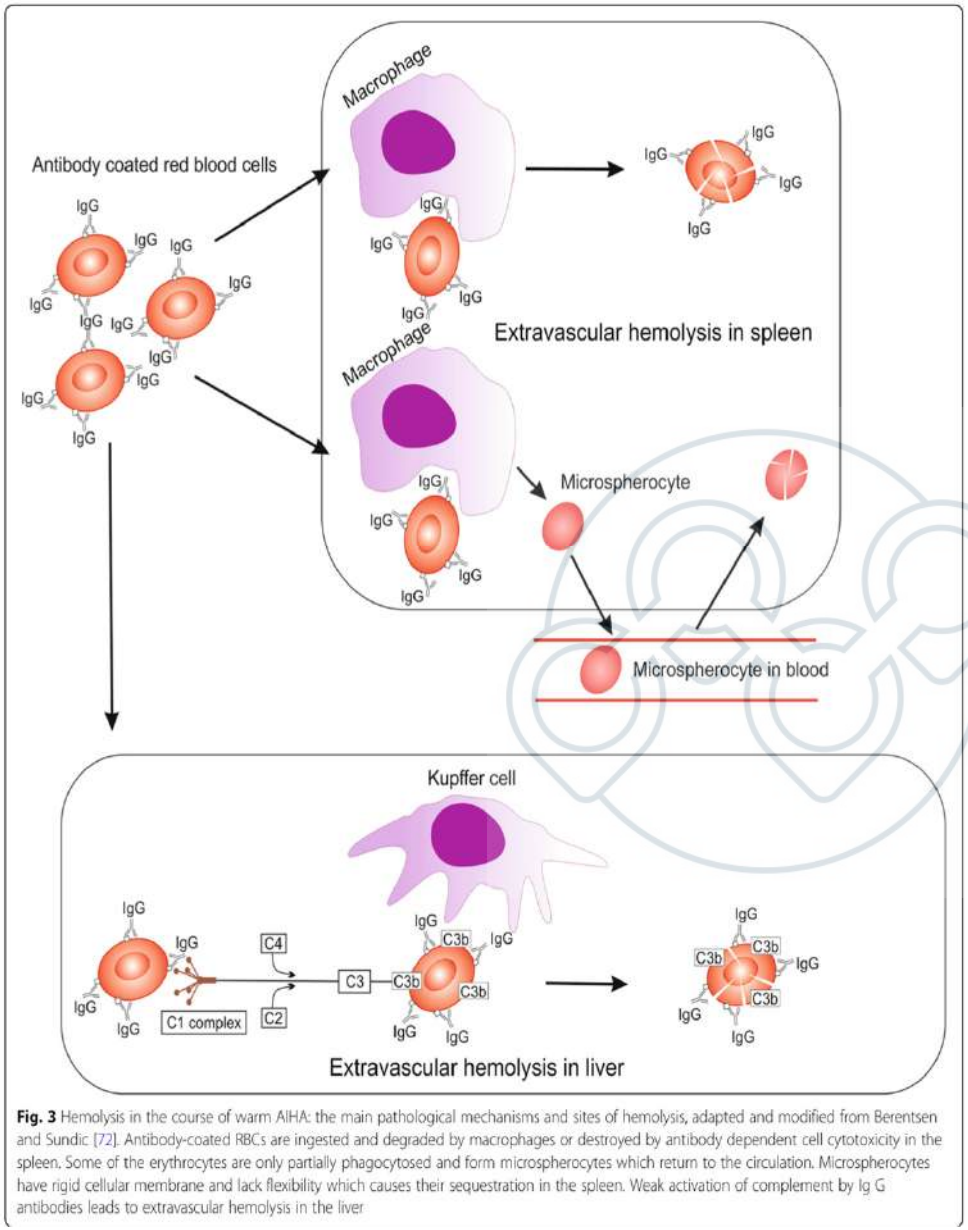


Fig. 3 Hemolysis in the course of warm AIHA: the main pathological mechanisms and sites of hemolysis, adapted and modified from Berentsen and Sundic [72]. Antibody-coated RBCs are ingested and degraded by macrophages or destroyed by antibody dependent cell cytotoxicity in the spleen. Some of the erythrocytes are only partially phagocytosed and form microspherocytes which return to the circulation. Microspherocytes have rigid cellular membrane and lack flexibility which causes their sequestration in the spleen. Weak activation of complement by Ig G antibodies leads to extravascular hemolysis in the liver

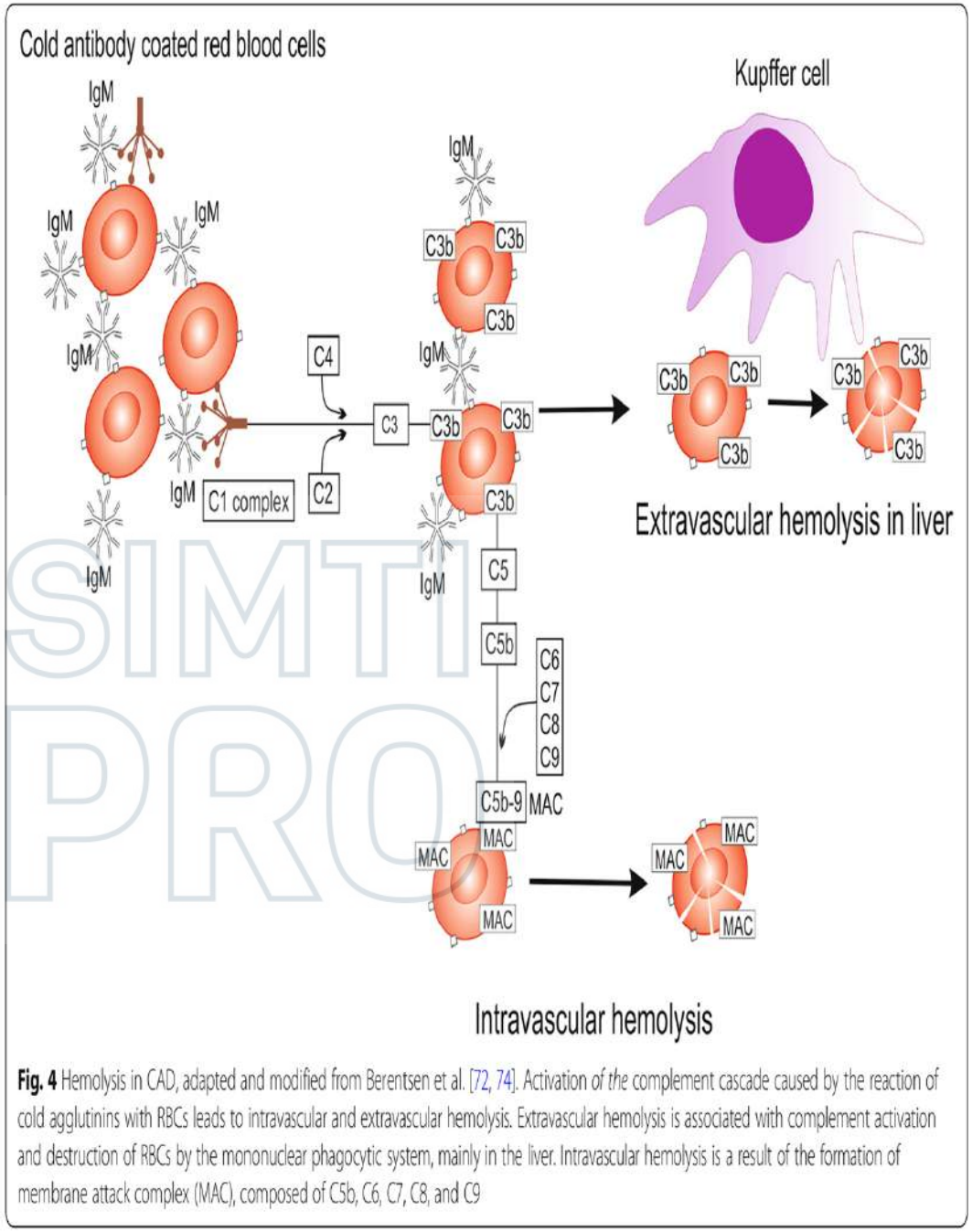


Fig. 4 Hemolysis in CAD, adapted and modified from Berentsen et al. [72, 74]. Activation *of the* complement cascade caused by the reaction of cold agglutinins with RBCs leads to intravascular and extravascular hemolysis. Extravascular hemolysis is associated with complement activation and destruction of RBCs by the mononuclear phagocytic system, mainly in the liver. Intravascular hemolysis is a result of the formation of membrane attack complex (MAC), composed of C5b, C6, C7, C8, and C9

Extravascular haemolysis —> destruction of 0,25 ml of RBCs x Kg of BW x Hour

Pt of 70 Kg —> of 420 ml of RBCs in 24 h

Intravascolar haemolysis —> destruction of 200 ml of RBCs x Kg of BW x Hour

Presentazione clinica

- **Gravità di presentazione eterogenea**
  - Acuta
  - Cronica compensata
  - 20-30% forma grave
    - AEA Ab caldi IgG + C3d
    - Mortalità 4-10%
- **Esami di laboratorio**
  - Hb ridotta
  - Reticolociti
    - Incremento
    - Nelle forme severe possibile decremento
  - Bilirubina indiretta incremento
  - LDH incremento
  - Aptoglobina ridotta
- **Esami immunoematologici**
  - TCD
    - IgG pos
    - C3d pos
    - IgG + C3d
    - Neg
  - TCI — Specificità a seconda del tipo
  - Eluato — Specificità a seconda del tipo
- **Segni clinici**
  - Anemia
    - Gravità variabile
    - Asintomatica se cronica compensata
  - Organomegalia — Nel 30-50% dei casi

SIMTI PRO

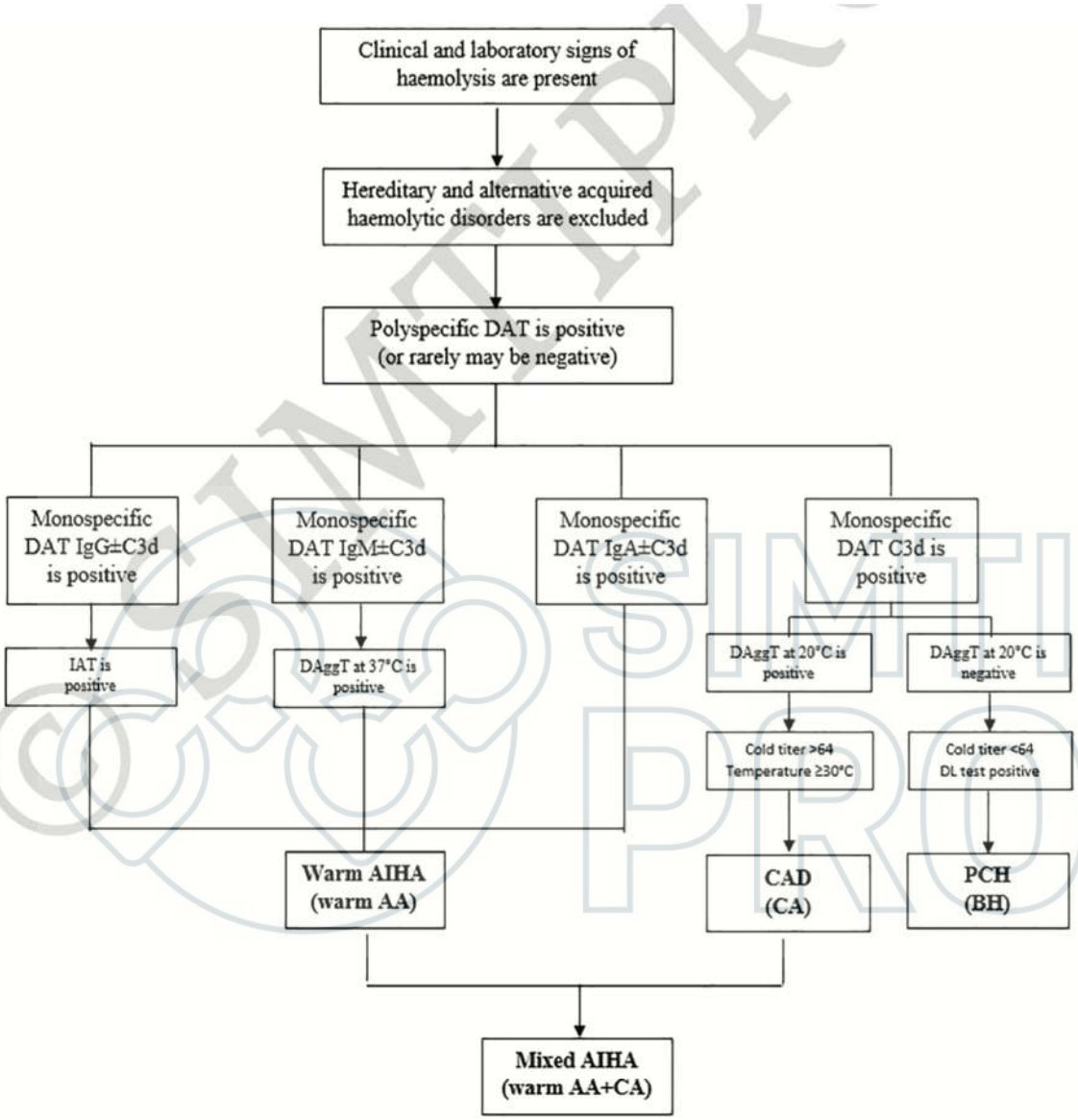


Figure 1 - Diagnostic algorithm for the investigation of autoimmune haemolytic anaemia
AA: autoantibodies; AIHA: autoimmune haemolitic anaemia; BH: biphasic haemolysins; CA: cold autoantibodies; CAD: cold agglutinin disease; DAggT: direct agglutinin test; DAT: direct antiglobulin test; DL: Donath-Landsteimer test; IAT: indirect antiglobulin test; PCH: paroxysmal cold haemoglobinuria.

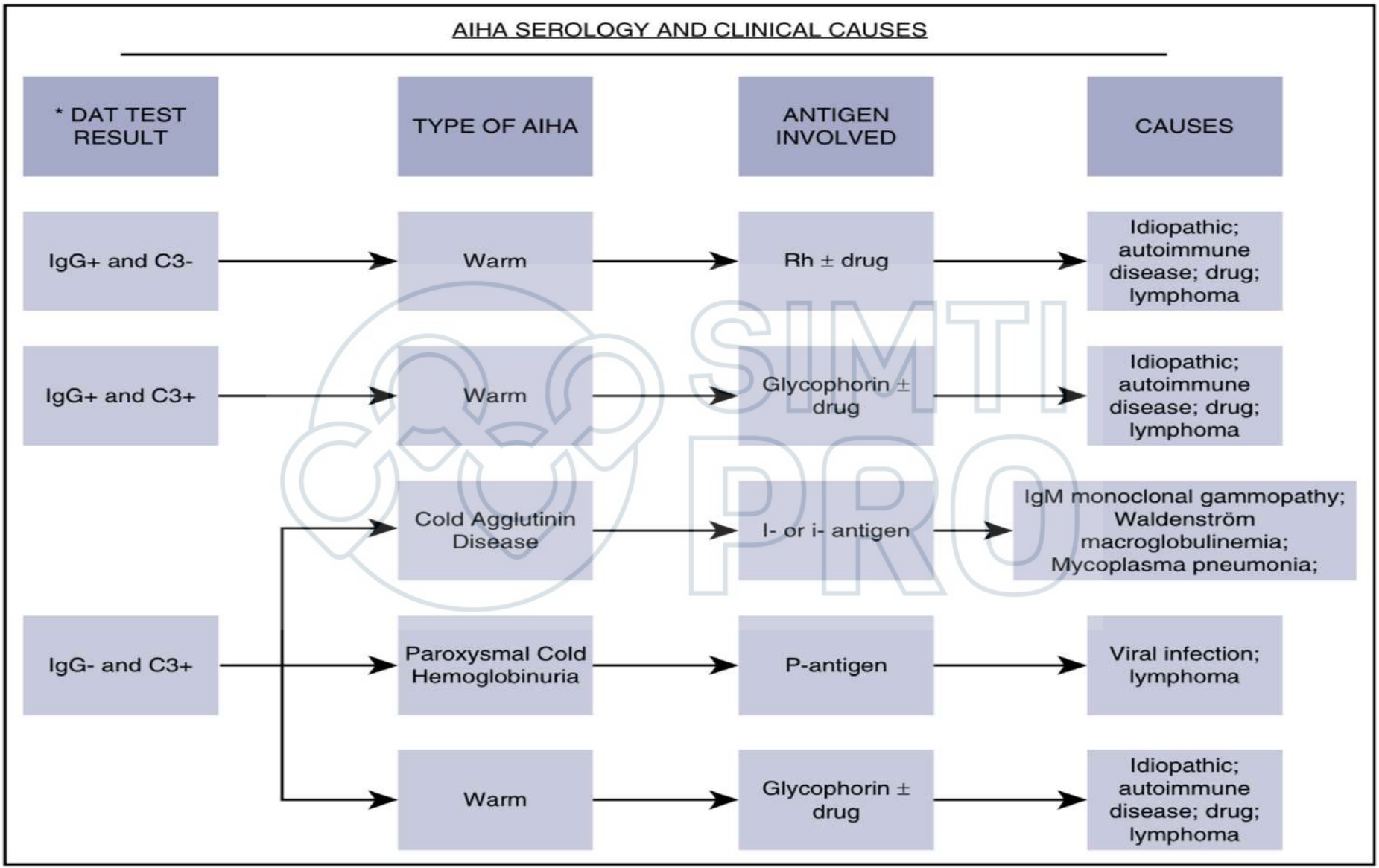


Figure 1. Direct antiglobulin test serology and clinical aspects. Shown are the spectrum of DAT serologic findings, autoimmune hemolytic classifications, antigen specificity, and medical/drug associations.[10,11] Drugs most commonly implicated[11-13,20] in drug-induced autoimmune hemolytic anemia are β lactam antibiotics (penicillin, ceftriaxone, cefotetan, and piperacillin), nonsteroidal anti-inflammatory drugs (tolmetin, sulindac, and diclofenac), quinine, purine nucleoside analogs (fludarabine and cladribine), and platinums (cisplatin and oxaliplatin).[12,13]

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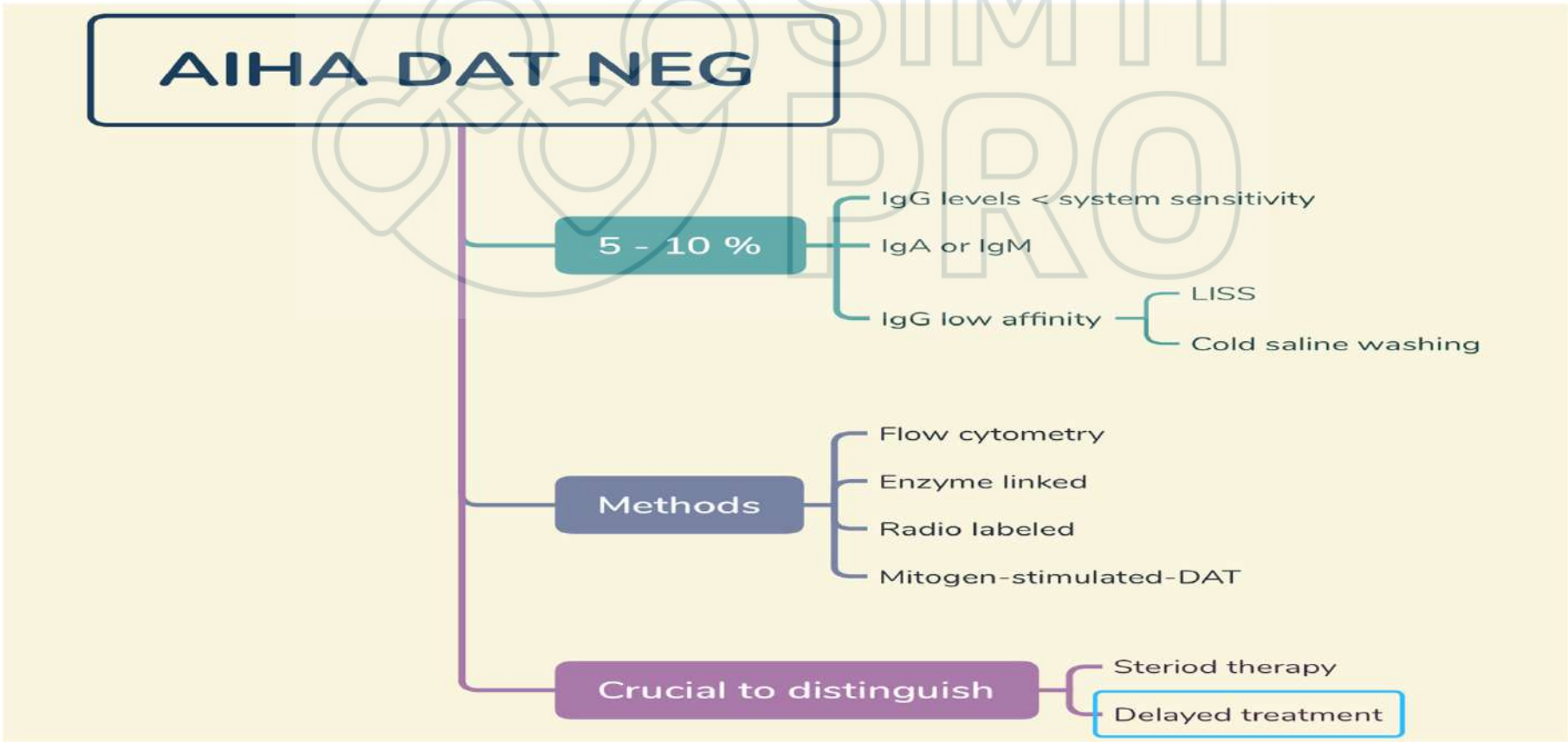
IMMUNOHEMATOLOGY

TRANSFUSION

Diagnostic algorithm for classification and characterization of direct antiglobulin test-negative autoimmune hemolytic anemia with 1-year clinical follow-up

Toyomi Kamesaki



A report of a rare case of autoimmune haemolytic anaemia in a patient with Hodgkin's disease in whom routine serology was negative

Archana Bajpayee, Anju Dubey, Anupam Verma, Rajendra K. Chaudhary

Department of Transfusion Medicine, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India

Laboratory investigations showed a haemoglobin concentration of 4.3 g/dL, haematocrit 13%, mean corpuscular volume 121 fL, reticulocyte count 36%, white blood cell count 13.1×109/L and platelet count 194×109/L. His plasma haemoglobin was 28.4 mg/dL and his lactate dehydrogenase level was 1,200 IU/L. Liver function tests showed albumin 4.2 g/dL, total proteins 7.5 g/dL, total bilirubin 7.47 mg/dL, an elevated indirect bilirubin level of 6.5 mg/dL, alkaline phosphatase 111 IU/L, alanine transaminase 24 IU/L and aspartate transaminase 80 IU/L. His peripheral blood smear showed marked anisocytosis, macrocytosis and 5-8 normoblasts/100 white blood cells. His bone marrow aspirate and biopsy showed megaloblastic erythroid hyperplasia.

On immunohaematological workup, his blood group was found to be A Rh(D) positive and the **DAT was negative** when tested by both a column agglutination technique (DiaMed GmbH, Cressier, Switzerland), as well as by the conventional tube technique using polyspecific anti-human globulin. The **indirect antiglobulin test (IAT) was also negative** when commercially available antibody screening cells were used. In the mean time, because of his persistently low haemoglobin level, the patient was **transfused with 13** units of packed red blood cells.

The DAT and IAT were repeatedly negative using the afore-mentioned techniques. Donath-Landsteiner antibody testing was negative. A test for paroxysmal nocturnal haemoglobinuria on a gel card (DiaMed GmbH, Switzerland) was also negative.

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A DAT, performed after washing the red blood cells in cold saline to rule out low affinity antibodies, was negative. Subsequently, DAT was performed using a monospecific antiglobulin gel card (DiaMed GmbH, Switzerland) and showed a **grade 3 reaction with IgA antiglobulin**. The reactions in other columns containing antiglobulin for IgG, IgM, C3c, C3d and control were negative, which established the **diagnosis of secondary IgA-mediated AIHA.**

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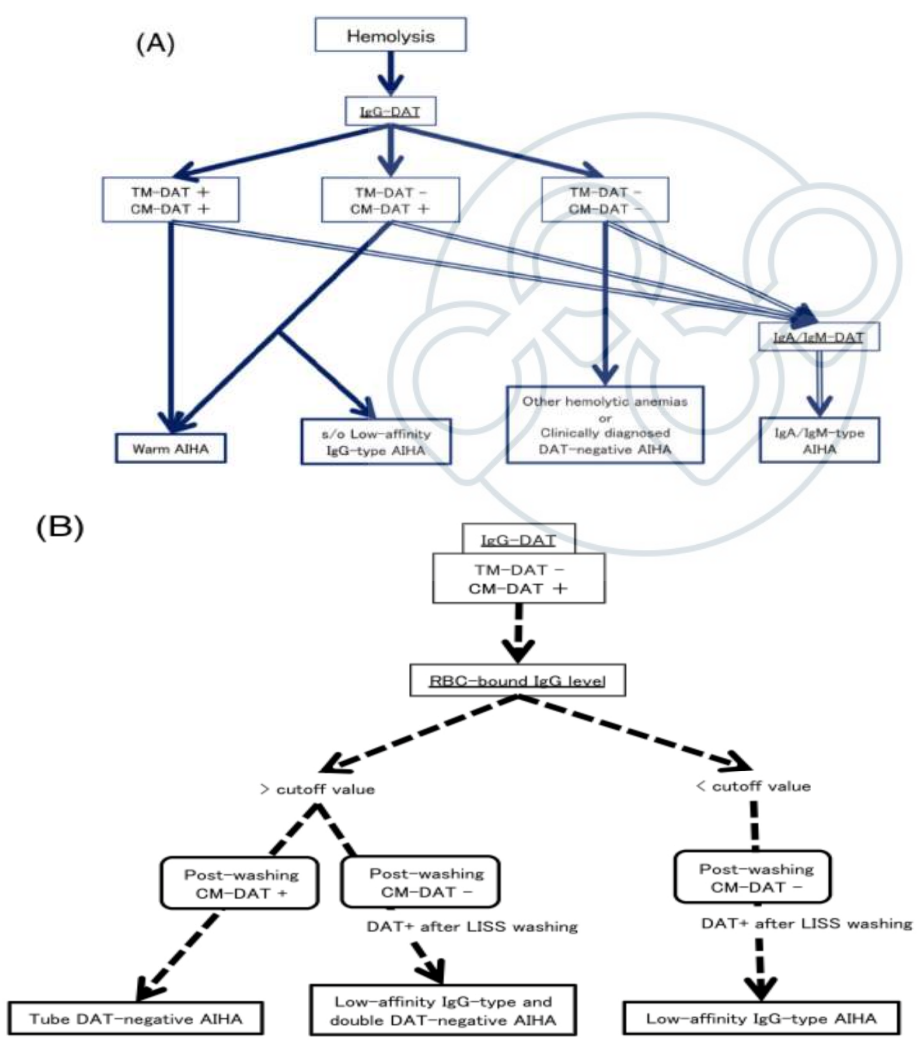

FIGURE 1 Algorithm for the diagnosis of warm AIHA. (A) Continuous bold lines indicate an ordinary diagnostic flow for warm AIHA. Double lines show a diagnostic flow for patients with IgA and/or IgM-type AIHA. (B) Dashed lines indicate a diagnostic flow for patients with tube-DAT-negative AIHA or low-affinity IgG-type AIHA. (C) Dotted lines indicate a diagnostic flow for double DAT-negative AIHA in patients with negative findings for both tube and column method DATs. If all tests are negative but hemolysis exists, then AIHA can be clinically diagnosed by exclusion of other hemolytic anemias and steroid effectiveness. AIHA, autoimmune hemolytic anemia; DAT, direct antiglobulin test; Ig, immunoglobulin; LISS, low-ionic strength solution; s/o, suspect of [Color figure can be viewed at wileyonlinelibrary.com]

Journal of Clinical Medicine

Review

Autoimmune Hemolytic Anemia in the Pediatric Setting

Aikaterini Voulgaridou [1] and Theodosia A. Kalfa [1,2,*]

- Rare in children
- Variable severity
- Most commonly wAIHA
- Often secondary to underlying immune dysregulation syndromes and thus, screening for such disorders is recommended at presentation, before initiating treatment with immunosuppressants, to determine prognosis and optimize long-term management potentially with novel targeted medications
- DAT negative results are seen in up to 11% of wAIHA

Table 2. Differential diagnosis of hemolysis in children.

HEREDITARY HEMOLYTIC ANEMIAS
Membrane defects
• Hereditary spherocytosis • Hereditary elliptocytosis and pyropoikilocytosis • Southeast Asian ovalocytosis • Dehydrated hereditary stomatocytosis or hereditary xerocytosis • RBC Overhydration syndromes
Enzymopathies
• Glucose-6-phosphate dehydrogenase (*G6PD*) deficiency • Pyruvate kinase (*PKLR*) deficiency • Other RBC enzyme disorders (*AK1, ALDOA, GCLC, GPI, GPX1, GSR, GSS, HK1, NT5C3A, PFKM, PGK1, TPI1*)
Hemoglobin disorders
• Sickle cell disease • Thalassemias • Unstable hemoglobins
Congenital dyserythropoietic anemias
ACQUIRED HEMOLYTIC ANEMIAS
Autoimmune hemolytic anemia (AIHA)
• Warm-reactive AIHA • Cold agglutinin syndrome • Paroxysmal cold hemoglobinuria (PCH) • Drug-induced (very rare in children)
Alloimmune hemolytic anemia
• Neonatal alloimmune hemolysis • Post-transfusion hemolysis • Acute hemolytic reactions • Delayed hemolytic reactions
Traumatic Hemolytic Anemia
• Impact • Macrovascular defects-prostheses (Waring blender syndrome with a dysfunctional mechanical heart valve) • Microvascular • Typical and Atypical Hemolytic uremic syndrome • Thrombotic thrombocytopenic purpura • Disseminated intravascular coagulation
Hypersplenism
Hemolytic Anemia due to toxic effects on the membrane
• Spur cell anemia in severe liver disease • External toxins • Animal or spider bites • Metals • Organic compounds • Infection
Paroxysmal nocturnal hemoglobinuria

TABLE 2 | Secondary conditions associated with autoimmune hemolytic anemia (AIHA).

	Frequency	Results
Lymphoproliferative disorders		
Chronic lymphoid leukemia and NHL	5–20%	Autoimmune cytopenias may frequently complicate chronic lymphoproliferative disorders and usually correlate with advanced disease and high biologic risk
KMT2D and CARD11	69 and 31% of cAIHA tested	Autoreactive B-cells display somatic mutations favoring proliferation
Congenital syndromes and immunodeficiencies		
Kabuki syndrome and Hemoglobinopathies	4–6%	AIHA and ITP are the most frequent autoimmune complications of Kabuki Syndrome; DAT positivity is frequent, but clinically overt AIHA is rarer in thalassemia (particularly beta intermedia, alloimmunized, and transfused pts)
ALPS; CVID; IgA deficiency	2–70%	AIHA is the most frequent autoimmune complication together with ITP and ES
Genes involved in PIDs TNFRSF6, CTLA4, STAT3, PIK3CD, CBL, ADAR1, LRBA, RAG1, and KRAS	40% of pediatric ES	Majority of pediatric ES display somatic mutations found in immunodeficiencies
Autoimmune diseases		
SLE, Systemic sclerosis; autoimmune thyroiditis; Sjogren Syndrome; IBDs; Autoimmune hepatitis/Primary biliary cirrhosis	1.4–14%	AIHA frequency is higher in pediatric than in adult patients with SLE. AIHA may be rarely associated to systemic sclerosis or Sjogren syndrome, Hashimoto thyroiditis and Graves' disease, ulcerative colitis, and autoimmune hepatitis.
Genetic findings		
HLA I and II	Case series	HLA-B8 and BW6 are strongly associated to wAIHA.
IGHV and IGKV region	>60% cAIHA	Specific IGVH and IGKV regions are related to AIHA development
TCRG and TCRB	50%	Pathogenic T-cells are clonally restricted in AIHA
CTLA-4 exon 1	73%	CTLA-4 signaling is defective in AIHA, particularly in CLL cases
Cytokine polymorphisms	41%	AIHA shows higher frequency of LT-α (+252) AG phenotype
Infections		
Parvovirus B19; HCV; HAV; HBV; HIV Mycoplasma spp.; Tubercolosis; Babesiosis; Brucellosis; Syphilis; EBV; Respiratory Syncytial Virus	0.02–20%	ParvoB19 infection and HCV and its treatment correlate with AIHA development; case reports of association with AIHA are available for the other infectious agents.
Drugs		
Antibiotics (penicillins, cephalosporins, etc.), cytotoxic drugs (oxaliplatin, etc.), antidiabetics (metformin), anti-inflammatory drugs (diclofenac, etc.), neurologic drugs (α-methyldopa, L-dopa, chlorpromazine, etc.), cardiologic drugs (procainamide, etc.)	Case reports and reviews	Various mechanisms are demonstrated: hapten and drug absorption mechanisms; Immune/ternary complex mechanisms; autoantibody mechanism; non-immunologic protein formation; unknown mechanisms.
CLL therapy: fludarabine and Tyrosin kinase inhibitors	6–21%	Fludarabine induced AIHA may be avoided by rituximab association. Ibrutinib was associated to low risk of AIHA development in registrative trials in CLL
Vaccines		
Vaccines	0.8/100.000 person-years	AIHA was the rarest autoimmune complication in a population study
Solid cancers		
Thymoma;Ovarian/Prostate	1.29–30% autoimmune phenomena	Thymoma, prostate and ovarian carcinomas have the highest association with autoimmunity

AIHA, autoimmune hemolytic anemia; wAIHA, warm; cAIHA, cold; ES, Evans syndrome; ITP, immune thrombocytopenia; DAT, direct antiglobulin test; CLL, chronic lymphocytic leukemia; ALPS, autoimmune lymphoproliferative syndrome; CVID, common variable immunodeficiency; SLE, Systemic lupus erythematosus; IBDs, inflammatory bowel syndromes.

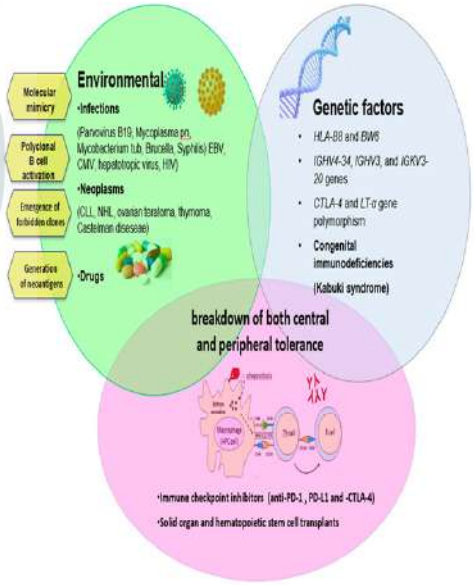

Figure 2. Immunologic, environmental, and genetic factors involved in the pathogenesis of autoimmune hemolytic anemia (AIHA). CLL: chronic lymphocytic leukemia, NHL: non-Hodgkin lymphoma, PD1-L: programmed death 1 and its ligand, CTLA-4: cytotoxic T-lymphocyte-associated protein 4.

SIMTI PRO

Severe drug-induced immune haemolytic anaemia due to ceftazidime

Fei Chen, Zhuying Zhan

Department of Haematology, Zhongnan Hospital of Wuhan University, Wuhan, People's Republic of China

Case report

Cephalosporin-induced haemolytic anaemia: a report of two cases

Massimo Franchini, Pier Luigi Piccoli, Giorgio Gandini, Annachiara Giuffrida, Fausto Bressan, Marzia De Gironcoli, Giuseppe Aprili

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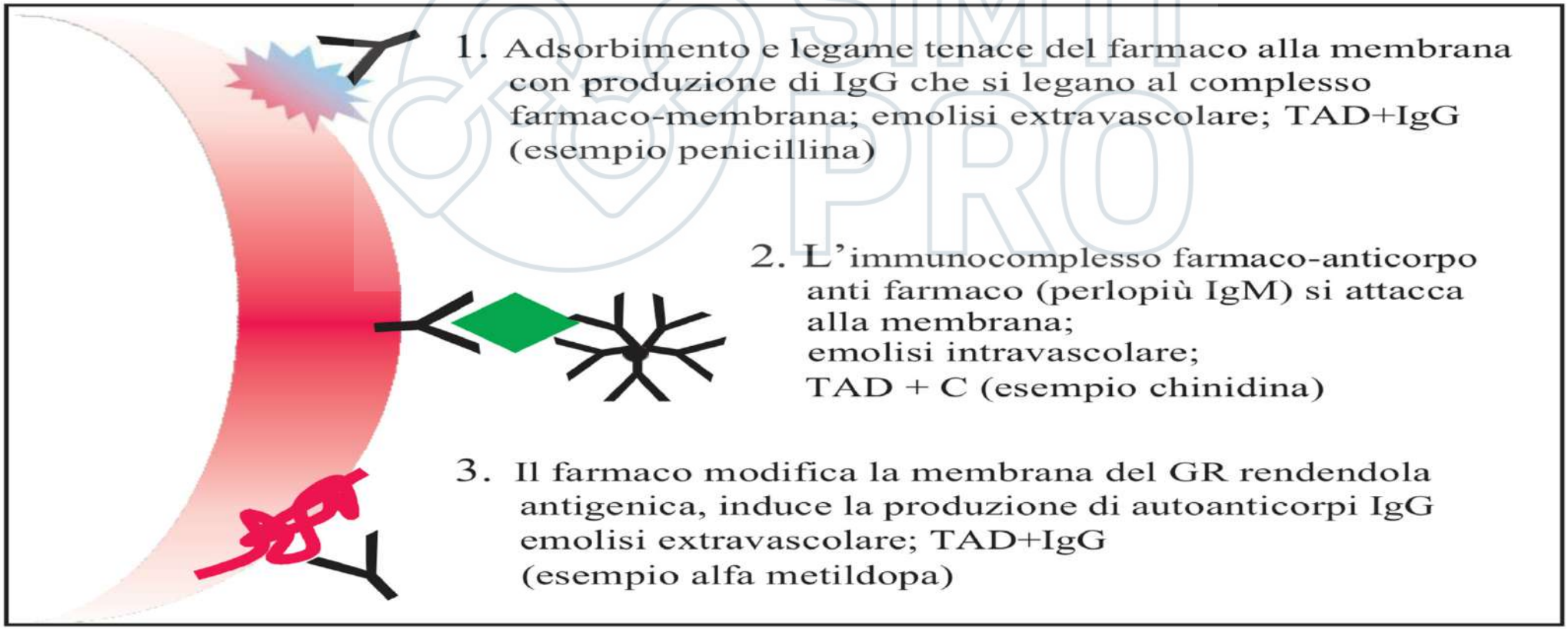

Figura 5. Meccanismi di induzione delle anemie emolitiche da farmaci

Transfusion Medicine Network

EDITORIALE

Transfusion Medicine Network 2022; 1-2 (Pubblicato settembre 2022)

Malattie emolitiche autoimmuni e farmaci inibitori di checkpoint

Bruno Fattizzo
Dipartimento di Oncologia ed Emato-Oncologia, Università degli Studi di Milano, Milano, Italy

- Neoplasie
  - Clone neoplastico → produzione autoAc
  - stato infiammatorio → alterazione del bilancio tra fattori soppressori regolatori
  - Terapie → (ad es Fludarabina) sbilanciamento Th17 e Treg
  - Immune escape → espressione di molecole di superficie che regolano i checkpoint di attivazione dei linfociti T → anergia dei T → elusione dell'immunosorveglianza da parte delle cellule tumorali
- Inibitori di checkpoint
  - Farmaci che permettono di ripristinare l'immunosorveglianza
  - Insorgenza di AEA

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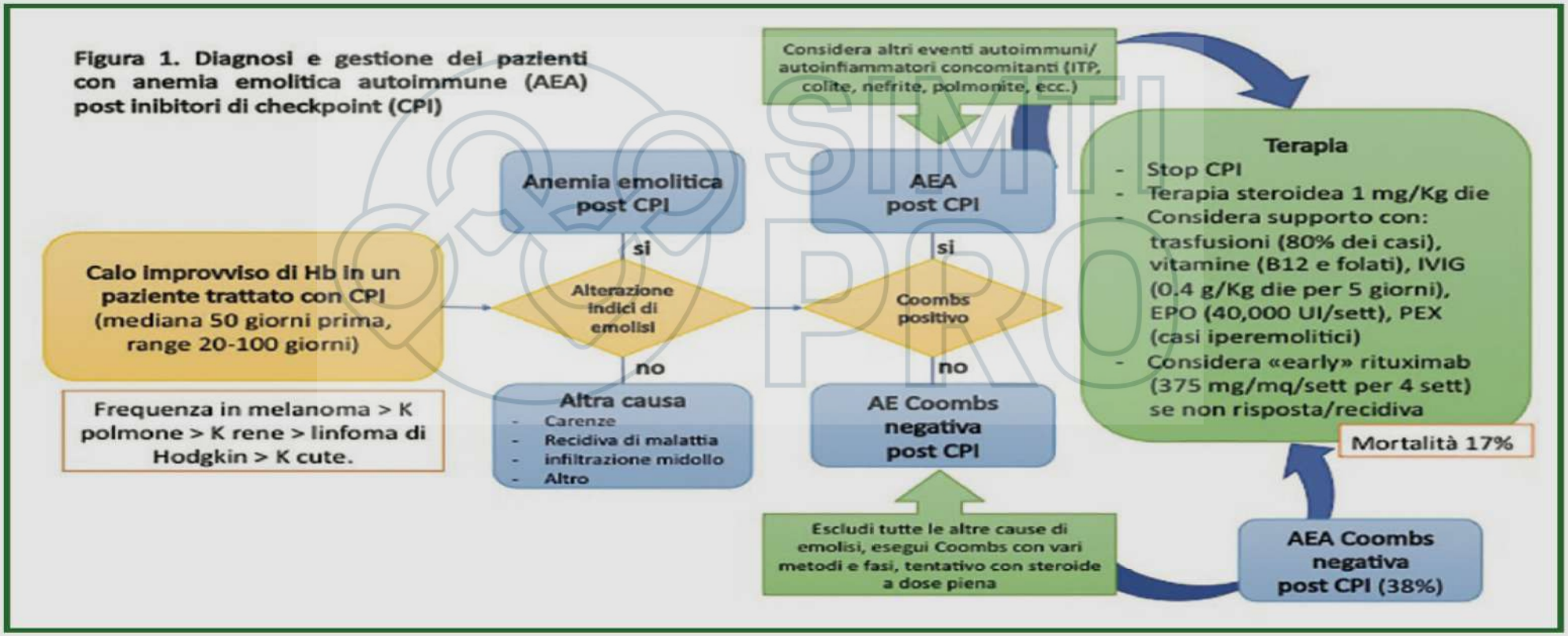

Figura 1.
Diagnosi e gestione dei pazienti con anemia emolitica autoimmune (AEA); post inibitori di checkpoint (CPI); K, carcinoma; ITP, piastrinopenia autoimmune; Sett, settimana; IVIG, immunoglobuline endovena; PEX, plasmaferesi.

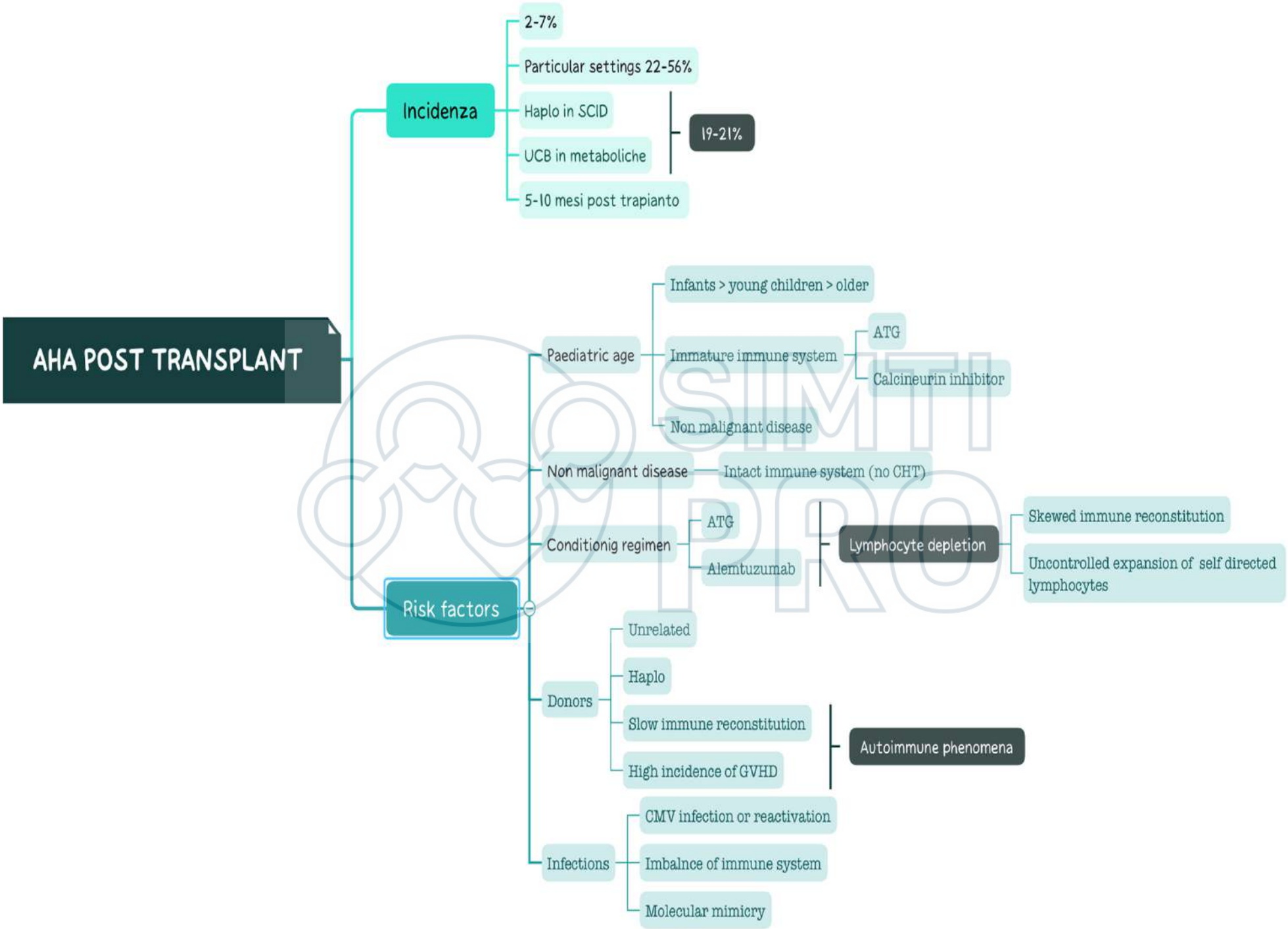
AHA POST TRANSPLANT
Incidenza
2-7%
Particular settings 22-56%
Haplo in SCID
UCB in metaboliche
19-21%
5-10 mesi post trapianto
Risk factors
Paediatric age
Infants > young children > older
Immature immune system
ATG
Calcineurin inhibitor
Non malignant disease
Non malignant disease
Intact immune system (no CHT)
Conditionig regimen
ATG
Alemtuzumab
Lymphocyte depletion
Skewed immune reconstitution
Uncontrolled expansion of self directed lymphocytes
Donors
Unrelated
Haplo
Slow immune reconstitution
High incidence of GVHD
Autoimmune phenomena
Infections
CMV infection or reactivation
Imbalnce of immune system
Molecular mimicry

Table I. Summary of relevant studies reporting incidence and risk factors of post-HSCT AIHA.

First author, year	Centre	Population	Prevalence of AIC	Prevalence of AIHA	Onset time post HSCT (median, range)	Risk factors-univariate analysis	Risk factors-multivariate analysis	Survival	Comments
Drobyski, 1996[60]	Single centre, Wisconsin, USA	Adults, 236 T cell depleted HSCT	Not reported	2·9%	10 months (7–25 months)	Not reported	Not reported	4/7 died of infectious complications or AIHA complication	
Chen, 1997[61]	Single centre, UK	Adults, 293 HSCT	Not reported	3·1%	wAIHA 6–18 months, cAIHA 2–8 months	Not reported	Not reported	5/9 died, none of AIHA	2/4 cAIHA had no clinically evident haemolysis
Horn, 1999[1]	Single centre, San Francisco, USA	Children with SCID, 41 haplo (T depleted) HSCT	Not reported	19·5%	Not reported	PBSC as source of stem cell	PBSC as source of stem cell	1/8 died at presentation, 3 of infections (2 with active haemolysis)	Abnormal T cell reconstitution and function in >70% of patients with AIHA
O'Brien, 2004[26]	Single centre, Minnesota, USA	Children, 439 HSCT	Not reported	Prevalence: 4·3%, 1-year CI 4%, 3-year CI 5%	4 months (2–32 months)	Age <10 years, metabolic disease	Metabolic disease	10/19 died, 3 because of AIHA, 5 of infection during AIHA treatment	All cases of AIHA occurred in MUD HSCT
Sanz, 2007[24]	Single centre, Spain	Adults, 272 HSCT for haematological malignancies	Not reported	3-year CI 4·4%	147 days (41–170)	HLA mismatch, unrelated donor, extensive cGVHD, UCBT	Unrelated donor, extensive cGVHD	10/12 died	
Page, 2008[2]	Single centre, Duke University, USA	19 UCBT in children with metabolic disorders (1 with thalassaemia)	2-year CI 56%	21%	AIC: 247 days (92–687)	Infants compared to older children	Not reported	5-year OS 80% (entire cohort)	High T cell dose in UCB could account for GVHD and immune dysregulation
Daikeler, 2013[22]	Multicentre, Eurocord	Adults and children, 778 UCBT	5-year CI of AID 6·6%, most frequently AIC	2·5%	AID: 191 days (27–4267)	For all AID: age <15 years, diagnosis of non-malignant disease, HLA match ≥5/6, no TBI conditioning, interval from diagnosis to UCBT <11·4 months	Risk factors for AID: diagnosis of non-malignant disease and interval from diagnosis to UCBT <11·4 months	5-year OS was 59% for AIHA, 67% for Evans syndrome, 91% for ITP. 6/52 died of AIC (2 AIHA)	8% mixed chimaerism in patients with AID (same as in control group)
Faraci, 2014[27]	Multicentre, Italy	Children, 1574 HSCT	3-year CI 2·13%, 10-year CI 2·5%	10-year CI 1·5%	AIHA 5·2 months (1·3–100·9)	For all AIC: younger age, HSCT from alternative donor, primary non-malignant disorder, UCBT	Alternative donor, primary non-malignant disorder	85%	87% achieved remission with Rtx (100% in AIHA)

Table I. (*Continued*)

First author, year	Centre	Population	Prevalence of AIC	Prevalence of AIHA	Onset time post HSCT (median, range)	Risk factors-univariate analysis	Risk factors-multivariate analysis	Survival	Comments
Gonzalez-Vicent, 2018[16]	Multicentre, Spain	Adults and children, 4099 HSCT	Not reported	1·5%	6 months (1–55 months)	Age <15 years, UCBT, MMUD	Not done	CI of AIHA related mortality is 17%	DFS 52% (at 40 months) Age <15 years and response to treatment have better DFS. Steroids +RTX should be offered upfront
Deambrosis, 2019[3]	Single centre, Manchester UK	Children with Hurler syndrome, 36 UCBT	22%	8·3%	AIC: 66 days (range, 22–96 days)	For all AIC: higher pre-transplant absolute lymphocyte count and FluBu conditioning	Higher pre-transplant absolute lymphocyte count	One death, 2 episodes of life threatening bleeding. 2 pts experience subsequent graft rejection	In 3 cases anti-RBC AB were of recipient origin. Hypothesis: inadequate recipient immunosuppression in FluBu-conditioned AIC
Neely, 2019[19]	Single centre, San Francisco, USA	Children, 442 HSCT	4·5%	2·0%	AIC: 5·2 months (1·5–15·1)	For all AIC; older age. In patients with malignancies, no T cell recovery at time of AIC	Not done	Higher mortality among AIC compared to controls (15% vs. 7%)	40% mixed chimaerism at AIC onset
Scordo, 2019[42]	Single centre, New York, USA	Adults, 408 CD34$^+$ selected HSCT for haematological malignancies	3-year CI 5·8%	2·4%	AIC: 189 days (39–840)	Diseases risk index >3		1 patient died of AIHA 6-month OS after AIC 74%	AIC is not a risk factor for NRM but increases relapse
Lv, 2019[25]	Multicentre, China	Adults, 1377 HSCT for haematological malignancies	Not reported	3-year CI 2·2%	215 days (34–756)	Haplo-HSCT, HLA mismatch, cGVHD, ATG	Haplo-HSCT, cGVHD		All full donor chimaerism Patients with AIHA have lower rate of relapse, higher DFS and OS
Szanto, 2020[20]	Single centre, the Netherlands	Children, 380 HSCT	5-year CI 7·8%	6·3% (mostly Evans)	AIC: 133 days (46–445)	For all AIC: UCBT, aGVHD grade II–IV, serotherapy, no chemotherapy before HSCT	All AIC: aGVHD grade II–IV, serotherapy, no chemotherapy before HSCT	OS 83%	All full donor chimaerism. Patients with AIC have lower T and NK and increased IgA, IgM, and IgG
Miller, 2020[29]	Multicentre, EBMT	Adults and children with AA, 530 HSCT	5-year CI 4·6%	1·3%	AIC: 10·6 months (2·6–91·5)	For all AIC: Alemtuzumab, RIC, PBSC	All AIC: RIC, PBSC	5 years OS 85·9%. 2 died of infection with AIC not in remission	
Lum, 2020[28]	Single centre, Newcastle, UK	Children with primary immunodeficiency, 502 HSCT	5-year CI 9·4%	3·7%	AIC: 6·5 months (2·5 months to 18·2 years)	For all AIC: pre-HSCT AIC, MMUD, alemtuzumab, ATG, aGVHD g II-IV, cGVHD	Alemtuzumab	5 years TRM 12% at median 5·8 years	RIC associated with the need for >2 lines of therapy

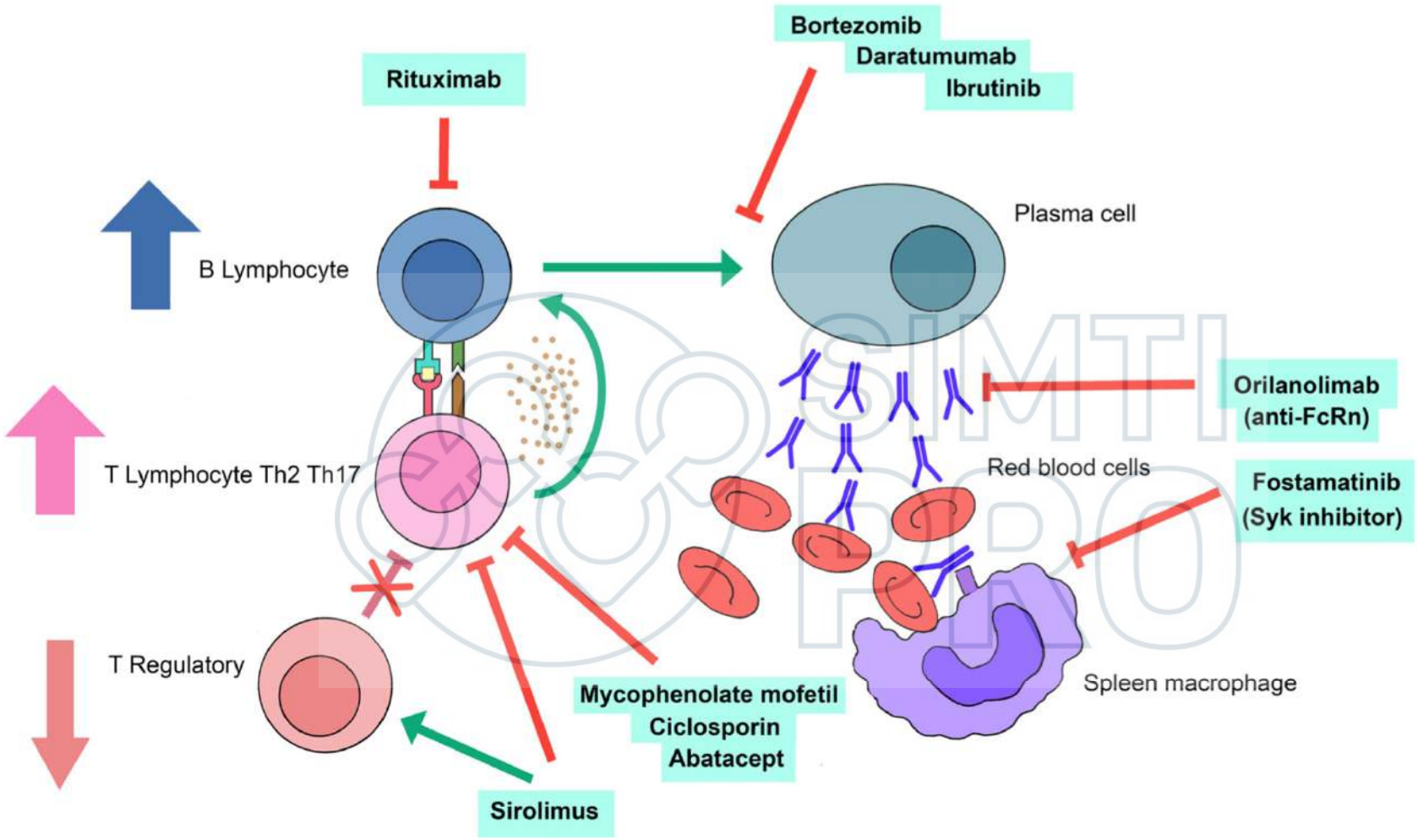

Fig 1. Pathogenesis of autoimmune haemolytic anaemia post haematopoietic stem cell transplantation and potential therapeutic targets.

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TABLE 4 | Risk factors and therapies for post-allogenic hematopoietic stem cell transplant (allo-HSCT) AIHA.

	Risk factor	Estimated risk	95% confidence interval	*P*-value
Risk factors associated with AIHA development post-allo-HSCT				
Recipient	Age < 15 years	n.a.	n.a.	0.005
Disease features	Nonmalignant diagnosis pre-HSCT	3.5 (Hazard risk)*	1.1–10.9	0.031
Donor	Unrelated donor	1.45 (Relative risk)	1.05–1.99	0.02
	Unrelated donor	5.28 (Hazard risk)	1.22–22.9	0.026
	HLA mismatch donor	n.a.	n.a.	0.005
Source of stem cells	Cord blood use	n.a.	n.a.	0.005
Conditioning	Alemtuzumab use	2.5 (Hazard risk)*	1.1–5.7	0.028
Allo-HSCT complications	Chronic GVHD	12.17 (Relative risk)	96–1.54	0.018
	CMV reactivation	3.4 (Hazard risk)*	1.2–9.6	0.02

Drug	**Dose**	**N of patients**	**ORR (range)**	**N of line**
Therapy of AIHA post-allo-HSCT				
Wait & See	–	6	83%	–
Steroids	1–2 mg/Kg day	125	20% (10–50)	1st line
IVIG	2 g/Kg × 2 days	51	12% (10–50)	1st line
Splenectomy	–	18	38% (0–100)	2nd line
PEX	–	10	10 (0–14)	>2nd line
Rituximab	375 mg/sm/week × 4 weeks	18	89% (75–100%)	1st line
		125	52% (36–100)	2nd line
Alemtuzumab	15 mg/day × 3/wk	2	50% (0–100)	>2nd line
Bortezomib	1,3 mg/mq	19	63% (25–100)	>2nd line
Sirolimus	3 mg/sm D1–1 mg/sm day	6	100%	>2nd line
Eculizumab	900 mg	3	33% (0–50)	>2nd line
Daratumumab	16 mg/Kg/week	3	100%	>2nd line
Abatacept	10 mg/Kg day	3	100%	>2nd line

*n.a. not available. *refers to all the autoimmune complications; PEX, plasma exchange.*

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Autoimmune haemolytic anaemia associated with COVID-19 infection

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Table I. Characteristics of seven patients with autoimmune haemolytic anaemia after the onset of COVID-19.

Patient	Age	Gender	Comorbidity	CT-scan*	Oropharyngeal swab (tested by PCR)	Haemoglobin (g/l)	Reticulocyte count (10^9/l)	Lymphocyte count (10^9/l)	Lactate dehydrogenase (U/l)	Haptoglobin (g/l)	DAT specificity	Optimum temperature	Day between COVID-19 symptoms and AIHA	Related pathology	AIHA treatment	Response
#1	61	M	Hypertension, chronic renal failure	Moderate	Positive	60	477	250	1000	<0·1	IgG + C3d	warm	13	CLL	Steroids	Ongoing
#2	89	F	Hypertension, chronic renal failure, atrial fibrillation	Mild	Positive	84	103	1·7	598	<0·1	IgG + C3d	warm	7	MGUS	Steroids	Ongoing
#3	62	F	Hypertension, cirrhosis	Severe	Positive	108	101	1·3	357	<0·1	C3d	cold	4	MZL†	1. Steroids 2. Rituximab	PR Planed
#4	69	F	Obesity	Moderate	Positive	38	215	5·9	2610	<0·1	IgG + C3d	cold	10	MZL	Steroids	PR
#5	61	M	Hypertension, chronic renal failure, diabetes, hypercholesterolaemia	Mild	Positive	72	145	3	807	0·8	C3d	cold	11	Prostate cancer	RBC infusion	Ongoing
#6	61	M	Diabetes	Severe	Positive	70	155	1·2	1800	<0·1	IgG	warm	9	None	1. Steroids 2. Rituximab‡	Failure Ongoing
#7	75	M	Diabetes, hypercholesterolaemia, cardiopathy, obesity, chronic obstructive bronchopneumopathy	Moderate	Positive	71	98	108	2000	<0·1	IgG	warm	6	CLL	RBC infusion	Ongoing

CT, computed tomography; PCR, polymerase chain reaction; DAT, direct antiglobulin test; AIHA, autoimmune haemolytic anaemia; CLL, chronic lymphocytic leukaemia; MGUS, monoclonal gammopathy of undetermined significance; MZL, marginal zone lymphoma; RBC, red blood cells; PR, partial response.
*Degree of involvement of the lung was classified as none (0%), minimal (1–25%), mild (26–50%), moderate (51–75%), or severe (76–100%).
†MZL B cell clone was detected in the bone marrow.
‡Patient 6 received rituximab injection because of corticosteroid failure.

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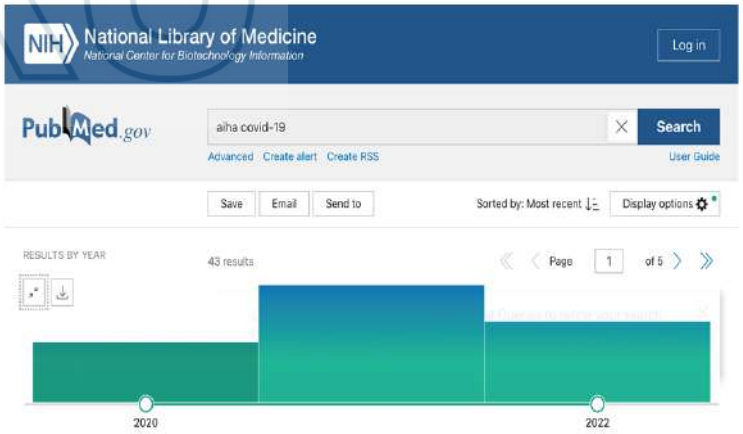
had at least partly recovered from COVID-19.

To conclude, we report seven cases of warm and cold AIHA associated with COVID-19 disease, all of them occurring after the beginning of the symptoms of the infection and within a timeframe compatible with that of the cytokine storm. Four out of the seven patients had indolent B lymphoid malignancy either already known or discovered because of the haemolytic episode. AIHA is a classical complication of both CLL and MZL,[6,7] and viral infections are known to trigger autoimmune cytopenias.[8] Whether the presence of an underlying malignant B lymphoid clone facilitated the onset of AIHA is unknown. Nonetheless, these observations argue for systematically investigating for the presence of a lymphoid clone in patients presenting with COVID-19 infections and autoimmune cytopenias.



OTHER

Case report

Blood Transfus 2022; 20: 168-172 DOI 10.2450/2021.0133-21

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Acute haemolysis by cold antibody during SARS-CoV-2 infection in a patient with Evans syndrome: a case report and literature review

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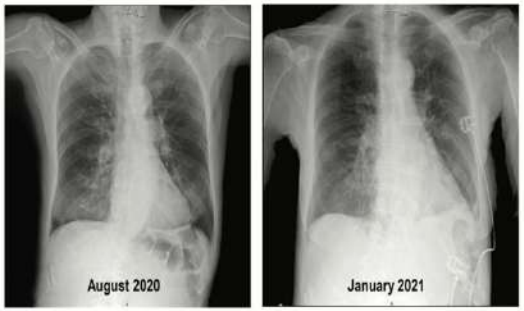
A

	Patient historical data	August 2020 (AIHA)	Outpatient	January 2021 (Covid-19 Infection)
Hb (12-14 g/dl)	12.8	12	13.3	5.7
Ht (34-47%)	38.4	35	39.5	15
MCV (80-99 fl)	90.8	94.3	92.3	132.2
MCHC (310 -360 g/dl)	333	343	337	342
RDW (11.5-15 %)	12.9	16.6	13.1	31.4
Retics (15-98 10^9 cell/L)	nd	125	nd	257.9
WBC (4.3-10.10^9 cell/L)	6.78	11.65	5.64	15.8
ANC (1.8-8.10^9 cell/L)	4.22	9.18	2.88	12.04
ALC (1.2 - 4.10^9 cell/L)	1.89	1.62	1.81	2
Platelets (150 - 400 10^9 cell/L)	247	15	305	286
Total bilirubin (< 1.05 mg/dl)	0.45	1.01	0.5	7.21
Direct bilirubin (< 0.35 mg/dl)	nd	nd	nd	0.97
Haptoglobin (0.3 – 2 g/L)	nd	0.26	nd	<0.08
LDH (135 – 214 U/L)	nd	199	nd	604
Direct antiglobulin test	nd	Positive	nd	Positive*
Anti – Poly	nd	++	nd	++++
Anti – IgG	nd	+++	nd	-
Anti - C3d	nd	++++	nd	++++
Indirect antiglobulin test	nd	Positive	nd	Positive*
Antibody specificity	nd	Warm autoantibodies	nd	Cold sensitive autoantibodies

*Details are reported in Figure legend.

Hb: hemoglobin; Ht: hematocrit; MCV: Mean corpuscular volume; MCHC: Mean corpuscular hemoglobin concentration; RDW: Red cell distribution width; WBC: White blood cells; ANC: Absolute neutrophil count; ALC: Absolute Lymphocyt count; LDH: Lactate dehydrogenase; nd: not determined.

B



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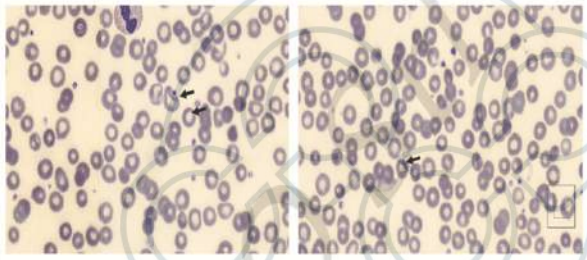

Figure 1 - (A) Haematologic, biochemical parameters and direct/indirect anti-globin tests

*In our case, a dramatic spontaneous agglutination was solved after heating the sample at 37°C for 2 hours. A search for plasma antibodies was positive using saline buffer with 4+ score at 4°C, 2+ score at 20°C, and with a score 0/1 at 37°C. IAT was slightly positive with polyspecific Coombs Igs. Direct antiglobulin test (DAT) was positive with polyspecific Coombs Igs, negative with Coombs anti-IgG but positive with Coombs anti-C3d. Tests with monospecific anti-IgA and anti-igM serums, normally performed in case of suspected DAT negative autoimmune haemolytic anaemia (AIHA), were not carried out in our case because of the exhaustive data that had been recently obtained.

(B) Patient's chest X-ray in August 2020 when AIHA was diagnosed (left panel) and in January 2021 when SARS-CoV-2-related interstitial pneumonia was diagnosed (right panel)

(C) Patient's peripheral blood smears on admittance to hospital for SARS-CoV-2 infection

Anisopoikilocytosis, red cells with basophilic stippling (black arrows) and knizocytes were observed. Erythrocyte morphology was assessed using May-Grünwald-Giemsa staining; smears were imaged under oil at 100x magnification using a PanFluor objective with 1.30 numeric aperture on a Nikon Eclipse DS-5M camera and processed with Nikon Digital Slide (DS-L1).

PDN 1 mg/kg + IVIG 0,4 mg/kg

CR

Table I - *Review of the literature on autoimmune haemolytic anaemia and SARS-CoV-2 infection*

Supplementary references*	DAT	Cold agglutinins	Antibody specificity	Thrombocytopenia[1]	Treatment[2]	Pts
Capes A, *et al.* 2020[s1]	C3d	Present	Anti-i	Absent	None	1
Demire N, *et al.* 2020[s2]	IgG + C3d	Absent	n.r.	Present (Evans syndrome)	Steroids (methylprednisolone 1 mg/kg), hydroxychloroquine, favirapir, plasmapheresis (2 consecutive days), IVIg	1
Georgy J, *et al.* 2021[s3]	Positive	Absent	n.r.	Present (Evans syndrome)	Steroids (dexamethasone 40 mg)	1
Hindilerden F, *et al.* 2020[s4]	IgG + C3d	Absent	n.r.	Absent	Steroids (prednisolone 1 mg/kg), favirapir, IVIg	1
Hiseh T, Sostier O, 2021[s5]	Positive	Absent	IgG panagglutinins + Anti-k	Absent	Steroids (dexamethasone), remdesivir, convalescent plasma	1
Huscenot T, *et al.* 2020[s6]	IgG + C3 positive Present	Present Present	n.r. n.r.	Absent Absent	None	2
Jacobs J, Eichbaum Q, 2020[s7]	IgG + C3	Present	Anti-i IgG panagglutinins	Absent	Steroids (prednisone 1 mg/kg), rituximab, tocilizumab	1
Jawed M, *et al.* 2020[s8]	C3d	Absent	n.r.	Absent	None	1
Jensen C, *et al.* 2020[s9]	C3 negative Present	Present Present	Anti-i Anti-i	Absent Absent	Hydroxychloroquine Hydroxychloroquine	2
Lazarian G, *et al.* 2020[s10]	IgG + C3d	Absent	n.r.	n.r.	Steroids	7
	IgG + C3d	Absent	n.r.	n.r.	Steroids	
	C3d	Present	n.r.	n.r.	Steroids, rituximab	
	IgG + C3d	Present	n.r.	n.r.	Steroids	
	C3d	Present	n.r.	n.r.	None	
	IgG	Absent	n.r.	n.r.	Steroids, rituximab	
	IgG	Absent	n.r.	n.r.	None	
Li M, *et al.* 2020[s11]	Positive	Absent	n.r.	Present (Evans syndrome)	IVIg, heparin (for DVT)	1
Lopez C, *et al.* 2020[s12]	IgG + C3d	Absent	n.r.	Present	Steroids (prednisone 60 mg) hydroxychloroquine, IVIg	1
Maslov D, *et al.* 2020[s13]	Not reported	Present	n.r.	Absent	None	1
Patil N, *et al.* 2020[s14]	C3	Present	n.r.	Absent	Steroids (methylprednisolone 120 mg), hydroxychloroquine	1
Whalster L, *et al.* 2020[s15]	IgG + C3d	Absent	n.r.	Present	Steroids (not specified)	1
Zagorsky E, *et al.* 2020[s16]	IgG + C3	Present	n.r.	Present	None	1

* See Online Supplementary Content; [1]Prior diagnosis or concomitant to AIHA; [2]Other than red blood cell transfusions, antibiotics and anticoagulants. DAT: direct antiglobulin test; IVIg: intravenous immunoglobulins; AIHA: autoimmune haemolytic anaemia; DVT: deep venous thrombosis; Pts: number of patient; n.r.: not reported.

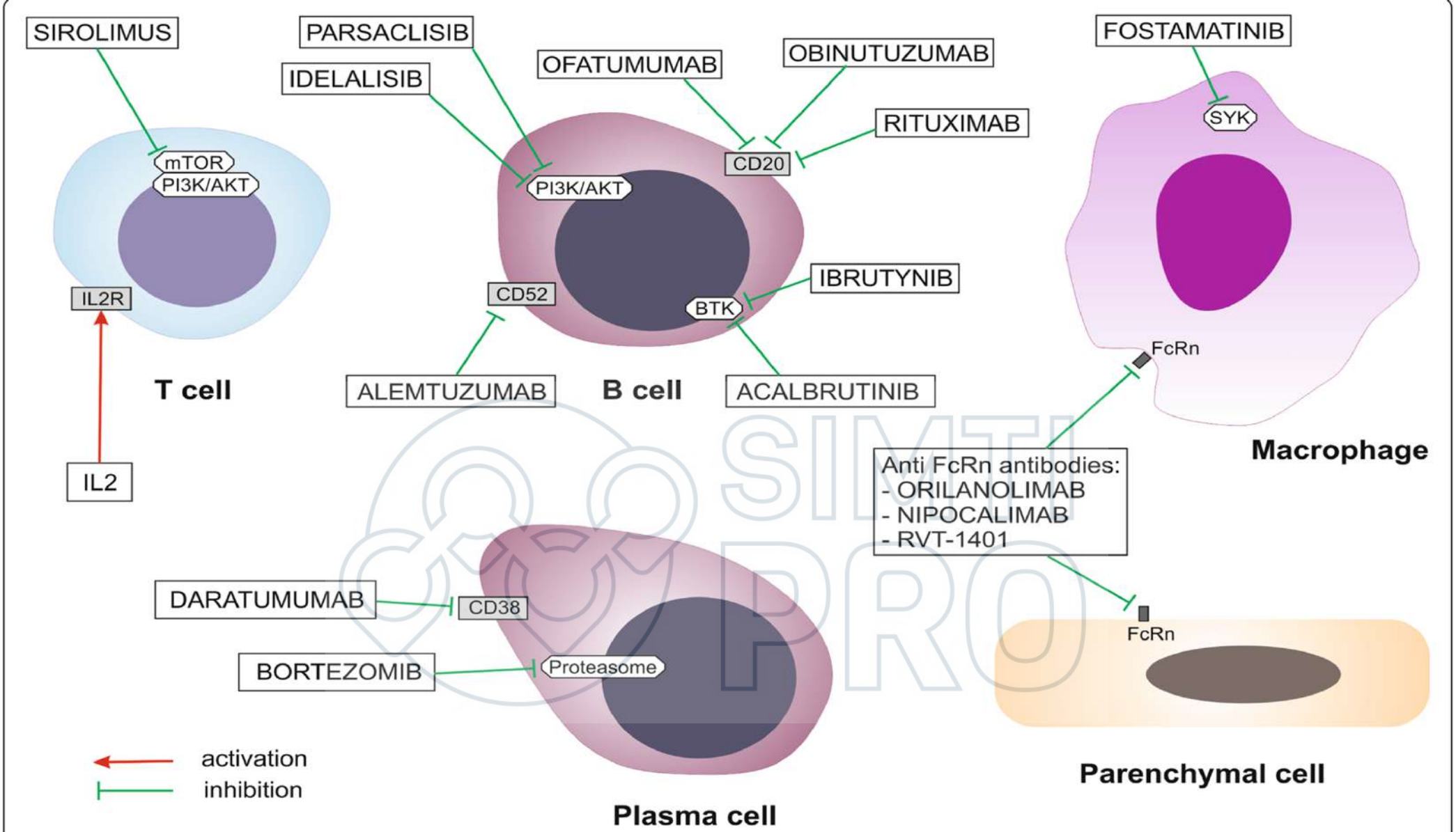

Fig. 5 New, potential drugs targeting mainly immune cells, adapted and modified from Michalak [108]. BTK - Bruton's tyrosine kinase, CD - cluster of differentiation - cell surface antigen, FcRn - neonatal crystallizable fragment of the receptor, IL 2 - interleukin 2, IL 2R - interleukin 2 receptor, mTOR - mammalian target of rapamycin kinase, PI3K - hosphatidylinositol 3-kinase, PI3K/AKT - intracellular signaling pathway, SYK - spleen tyrosine kinase, SYNT001 - monoclonal antibody (Orilanolimab)

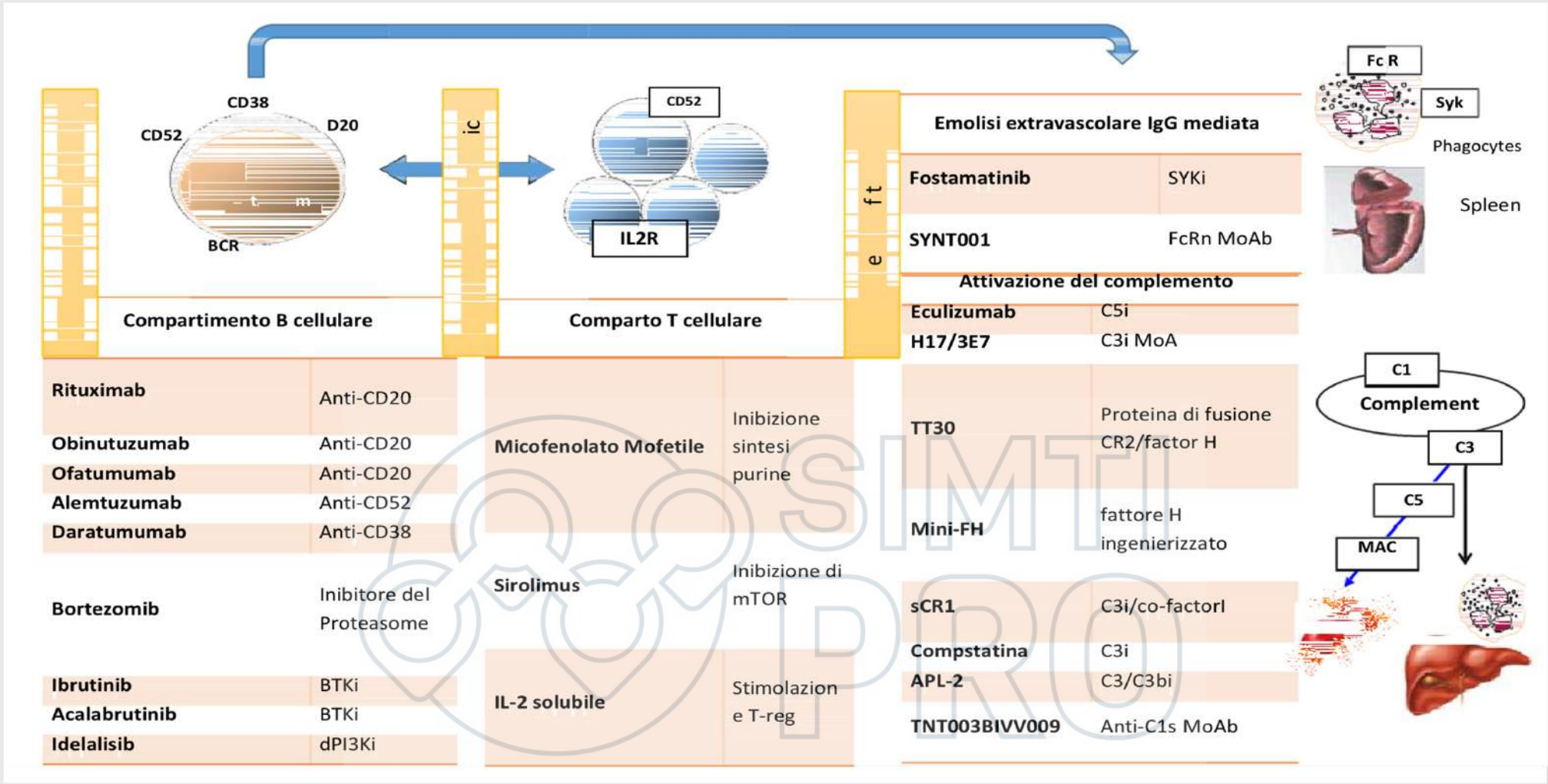

Figura 1

Momenti patogenetici, potenziali target e nuovi farmaci nella AEA

Il compartimento B cellulare produce gli autoanticorpi patogenetici e rappresenta dunque un ottimo target per numerosi nuovi farmaci ad azione intra (bortezomib) ed extra-cellulare (anticorpi monoclonali). L'attivazione dei linfociti B patogenetici avviene anche grazie al cross-talk con i linfociti T, che a loro volta offrono ulteriori target per nuovi farmaci immunosoppressori (anticorpi monoclonali, IL-2 solubile ecc…). Gli effettori finali dell'emolisi immuno-mediata sono rappresentati dalla fagocitosi in sede perlopiù splenica IgG mediata e dall'emolisi intra- ed extra-vascolare (questa prevalentemente epatica) complemento mediata. Entrambi questi momenti patogenetici trovano oggi specifici farmaci inibitori.

Table 1. B-cell-directed therapies.

Medication	Type of AIHA	Type of Study	Concurrent Disease	Regimen	Efficacy/Response Rate	Reference
Idelalisib	Mixed	Case report	CLL	175 mg bid, rituximab, steroids	Hemoglobin increment 3.6 g/dL	[68]
	Warm	Retrospective, N = 19	CLL	150 mg bid ± rituximab	ORR 95%, 71% discontinued steroids	[69]
Parsaclisib	Warm/cold/mixed	Open-label, phase 2	N/A	1 mg daily, 2.5 mg daily	CR 33%, PR 66.7%	[73]

Table 1. *Cont.*

Medication	Type of AIHA	Type of Study	Concurrent Disease	Regimen	Efficacy/Response Rate	Reference
Ibrutinib	N/A	Retrospective, N = 21	CLL	420 mg daily	Hemoglobin increment 2 g/dL	[75]
	Warm	Case report	MCL	560 mg daily	Hemoglobin increment 4.1 g/dL	[76]
	Mixed	Pilot study, N = 2	N/A	280 mg daily and 420 mg daily	CR 100%	[77]
	Cold	Retrospective, N = 10	CLL/SLL, WM	N/A	CR 90%, PR 10%	[78]
Sirolimus	Mixed	Case report	Post allo-SCT	3 mg/m^2 on day 1 followed by 1 mg/m^2 daily	CR	[79]
	Mixed and warm	Case series, N = 4	Solid organ transplant	N/A	Response rate 100%	[80]
	N/A	Retrospective, N = 14	N/A	1–3 mg daily	ORR 85.7%, CR 57.1%	[81]
	N/A	Prospective, N = 2	N/A	2–2.5 mg/m^2 daily	CR 50%, PR 50%	[82]

allo = allogeneic, CLL—chronic lymphocytic leukemia, CR = complete response, MCL = mantle cell lymphoma, ORR = overall response rate, PR = partial response, SCT = stem cell transplant, SLL = small lymphocytic leukemia, WM = Waldenstrogm's macroglobinemia.

Table 2. Plasma cell-directed therapy.

Medication	Type of AIHA	Type of Study	Concurrent Disease	Regimen	Efficacy/Response Rate	Reference
Bortezomib	Mixed	Case report	Post allo-SCT	1.3 mg/m^2 day 1, 4, 8, 11	Transfusion independent	[162]
	N/A	Case report	Post solid organ transplant	1.3 mg/m^2 day 1	Transfusion independent	[163]
	N/A	Case report	Post allo-SCT	1.3 mg/m^2 day 1, 8, 15, 22	Transfusion independent	[164]

Table 2. *Cont.*

Medication	Type of AIHA	Type of Study	Concurrent Disease	Regimen	Efficacy/Response Rate	Reference
	N/A	Case report	Post allo-SCT	1.3 mg/m^2 day 1, 4, 8, 11 for 2 cycles	Transfusion independent	[165]
	Warm	Case report	Post solid organ transplant	1.3 mg/m^2 day 1, 4, 8, 11 monthly	Transfusion independent	[166]
	Mixed	Case report	Post solid organ transplant	1.3 mg/m^2 D 1, 4, 8, 11	CR	[167]
	N/A	Case report	SLE	1.3 mg/m^2 D 1, 4, 8, cyclophosphamide, steroids	CR	[172]
	Warm	Retrospective, N = 7	N/A	1.3 mg/m^2 D 1, 8, 15, 22, rituximab, steroids	ORR 85.71%	[171]
	Warm	Retrospective, N = 7	N/A	1.3 mg/m^2 D 1, 4, 8, 11, rituximab	CR 71.4%	[173]
	Warm	Retrospective, N = 8	N/A	1.3 mg/m^2 D 1, 4, 8, 11, steroids	ORR 75%	[168]
	Warm	Case report	N/A	1.3 mg/m^2 D 1, rituximab	PR	[174]
	Warm	Case series, N = 2	N/A	1.3 mg/m^2 D 1, 4, 8, 11, dexamethasone	PR 2/2	[169]
	Warm	Case series, N = 4	N/A	1.3 mg/m^2 D 1, 4, 8, 11, dexamethasone	CR 1/4, PR 2/4	[169]
	Cold	Open-label, phase 2	42.9% B-LPD	1.3 mg/m^2 D 1, 4, 8, 11	ORR 31.6%	[54]
Daratumumab	N/A	Case report	Post allo-SCT	16 mg/kg weekly in 4 doses	CR	[182]
	N/A	Retrospective, N = 3	Post allo-SCT	N/A	CR 67%	[183]
	N/A	Retrospective, N = 3	Post allo-SCT	N/A	CR 67% PR 33%	[184]
	N/A	Case report	Post allo-SCT	16 mg/kg weekly in 6 doses	CR	[185]
	Warm	Case report	N/A	16 mg/kg weekly	CR	[186]
	Warm	Retrospective, N = 4	50% post allo-SCT	16 mg/kg weekly	ORR 100%, CR 50%	[188]
	Cold	Case report	N/A	16 mg/kg weekly	Response	[187]

allo = allogeneic, B-LPD = B-cell lymphoproliferative disorder, CR = complete response, D = day, ORR = overall response rate, PR = partial response, SCT = stem cell transplant.

Terapia

- Rapidità di comparsa dell'anemia
- Gravità dell'anemia
  - Hb > 8 gr/dL → astensione terapeutica fino ad inquadramento
  - HB 6-8 G/dL → valutare quadro clinico e se possibile prima inquadramento diagnostico
  - Hb < 6 g/dL → intervento terapeutico immediato

Terapia

- AEA Ab Caldi I linea
  - Steroidi
    - Risposta nel 70-85% entro 15-30 gg
    - 1 mg/kg/die 2-3 settimane
  - Associazione di Rituximab 100mg/kg

SIMTI PRO

Terapia

- AEA Ab Caldi II linea
  - Rituximab 375 mg/mq a settimana per 4 settimane
    - 80% di risposta
  - Farmaci citotossici/immunosoppressivi (azatioprina, ciclofosfamide, ciclosporina, micofenolato)
    - 50-70% di risposta
  - Splenectomia
    - Risposta nel 70% dei casi

SIMTI PRO

AEAI Ab caldi – algoritmo terapeutico

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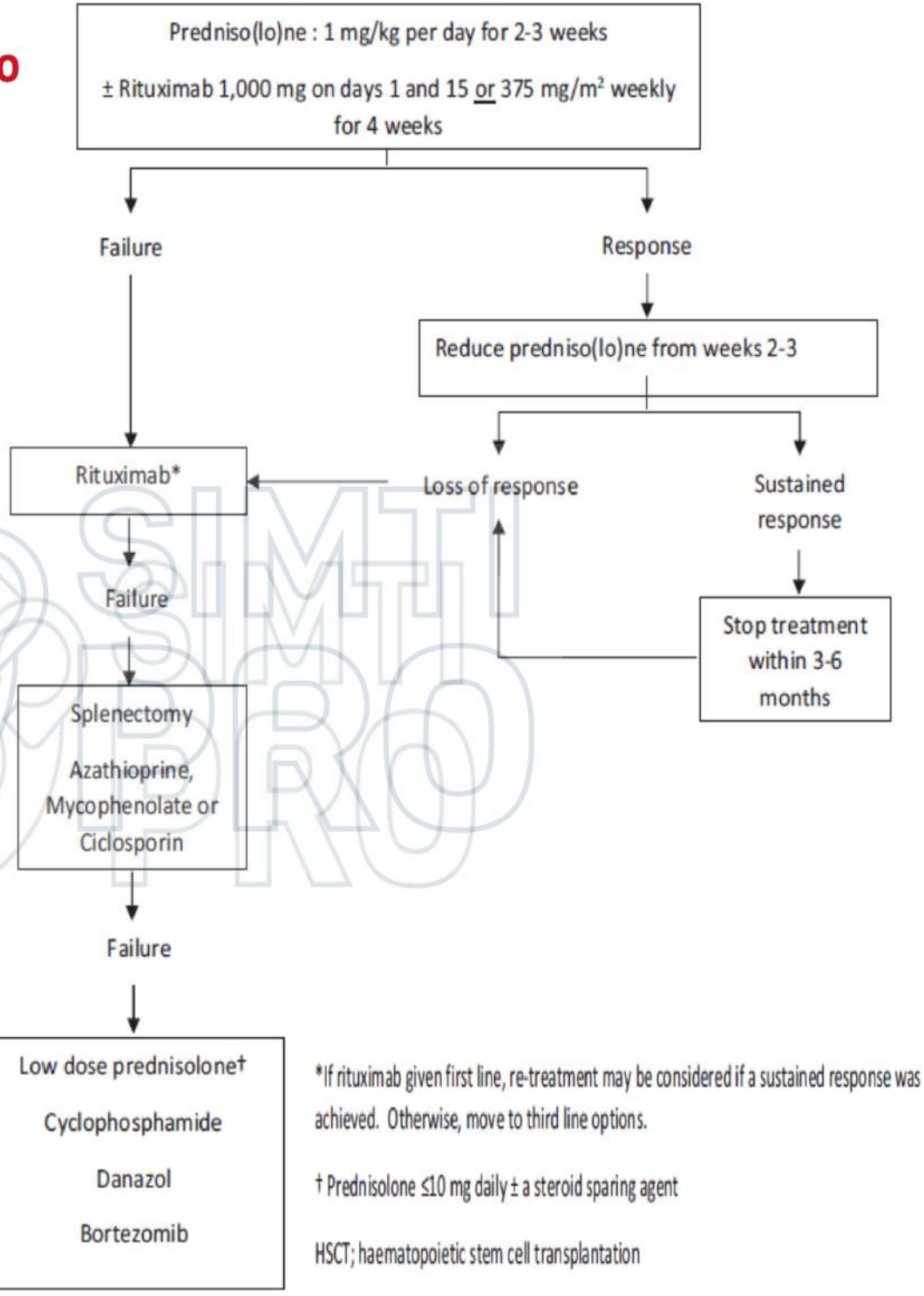

Terapia

- AEA da Ab freddi
  - 10-20% non richiede terapia
  - Evitare esposizione al freddo
  - Steroidi e splenectomia → inefficaci
  - I linea
    - Rituximab → 50% di risposta
    - Rituximab + Bendamustina —> 70%
  - II linea
    - Associare bortezomib

Malattia da agglutinine fredde – algoritmo terapeutico

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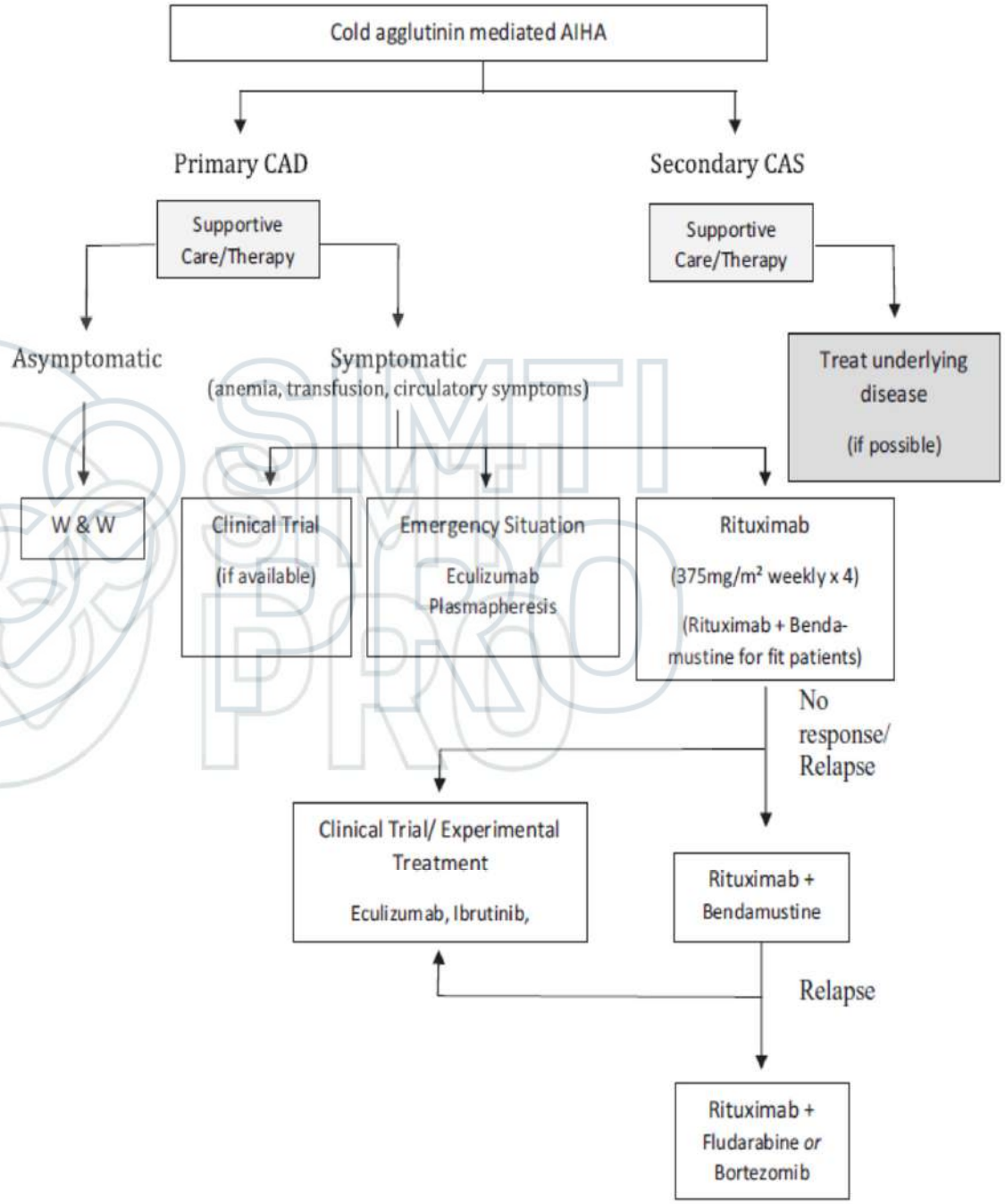

Terapia di supporto	Quando	Commenti
Trasfusione	Hb < 7g/dL o in base a sintomi, età, patologie concomitanti	Inefficace nel 30% dei casi
EPO	In pz con reticolocitosi ed EPO endogena inadeguate	40000UI efficace nel 70%
Vit. B12 e ac. Folico	In caso di carenza. Sempre ac folico se emolisi attiva	Folati scorte a rapido consumo
Ferro	Se carenza	Correggere per consentire crisi reticolocitaria
Protezione dal freddo e dagli sbalzi termici	Nelle AEA da Ac Freddi	
Profilassi antiinfettiva	In terapia cortisonica prolungata ad alte dosi In HBV o TBC In previsione di splenectomia	In particolare se rituximab
Profilassi anticoagulante	Con emolisi attiva e/o pregressa splenectomia e/o altri fattori di rischio	Indagare sempre fattori di rischio

Trasfusione

- Necessità cliniche del paziente
- Prove di compatibilità generalmente con esito positivo
- Difficile escludere la presenza di allo-Ab
- Preferibile trasfondere emazie con specificità antigenica dell'autoAb evitando eventuale rischio di alloimmunizzazione

- Difficoltà nella determinazione del gruppo
  - AbCaldi → panagglutinazione su colonna
  - Ab freddi → autoagglutinazione da crio
- Difficoltà di determinazione Rh debole
- Difficoltà di interpretazione antigeni altri sistemi (Duffy, Ss ecc.)

Alloimmunizzazione

- Presenza di alloAb eritrocitari in associazione agli autoAb
  - 15% -40% Branch D.R. et al., 1999
  - 11,8% Garratty G., 2004
  - 11,8% Coluzzi et al., 2009
- Diluizione (titolazione) del siero
- Tecniche “prewarmed”
- Adsorbimento del siero (a caldo, a freddo)
- Uso di reagenti tiolici (Mercaptoetanolo, DDT

Conclusione

- Aumento incidenza delle AEA
- Difficoltà di diagnosi
- Possibilità di avvalersi della biologia molecolare
- Approccio diversificato a seconda della tipologia di AEA
- In presenza di anemia molto grave e sintomatica la terapia trasfusionale non va ritardata (me evitata quando non necessaria)
- Adeguate terapie di supporto
- Dialogo attivo tra clinico e trasfusionista

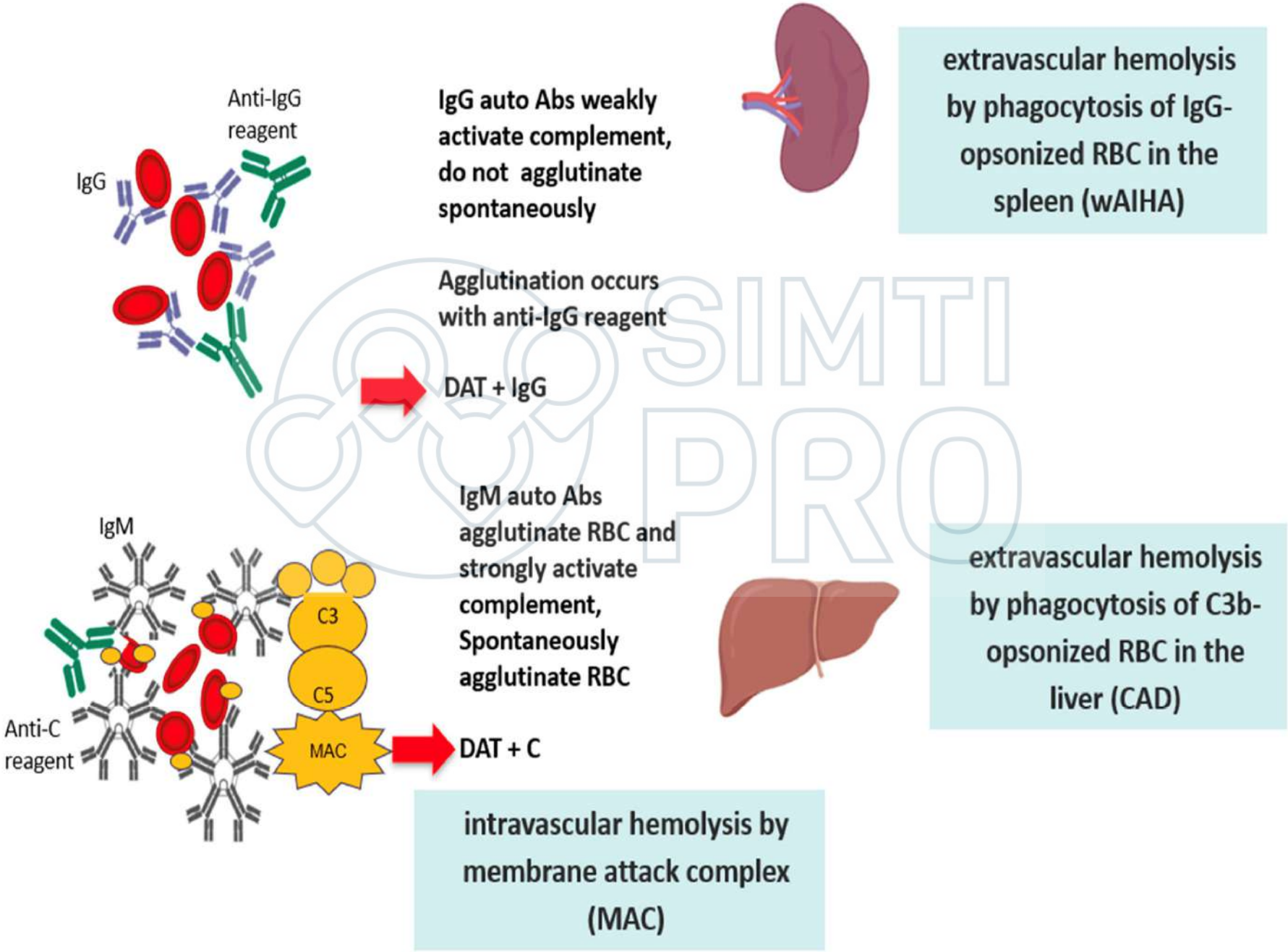
Anti-IgG reagent
IgG
IgG auto Abs weakly activate complement, do not agglutinate spontaneously
Agglutination occurs with anti-IgG reagent
DAT + IgG
extravascular hemolysis by phagocytosis of IgG-opsonized RBC in the spleen (wAIHA)
IgM
C3
C5
MAC
Anti-C reagent
IgM auto Abs agglutinate RBC and strongly activate complement, Spontaneously agglutinate RBC
DAT + C
extravascular hemolysis by phagocytosis of C3b-opsonized RBC in the liver (CAD)
intravascular hemolysis by membrane attack complex (MAC)

Table II - *Types of autoimmune haemolytic anaemia according to laboratory investigation*

Type of AIHA	Laboratory investigation
Warm AIHA	DAT IgG±C3d (rarely IgA, IgM) positive, and IgG reactive by IAT in serum and eluate, or rarely DAT C3d±IgM positive (or negative), IgM optimally reactive at 37°C in serum and eluate, and a cold antibody titre <64 at 4°C
CAD	DAT C3d positive (IgG negative or weakly positive), DAggT positive, and a cold antibody titre ≥64 at 4°C
Mixed AIHA	DAT IgG±C3d (rarely IgA, IgM) positive, IgG reactive by IAT in serum and eluate by warm technique using anti-IgG, and IgM with a thermal amplitude ≥30°C, and a cold antibody titre ≥64 at 4°C (but may be <64)
PCH	DAT C3d positive, DAggT negative, a cold antibody titer <64 at 4°C, and a Donath-Landsteiner test positive
DAT negative AIHA	DAT IgG or C3d negative, DAT IgA, IgM positive or negative, IgG reactive by IAT in eluate, or IgG, IgA, IgM detected by more sensitive tests

AIHA: autoimmune haemolytic anaemia; CAD: cold agglutinin disease; DAggT: direct agglutination test; DAT: direct antiglobulin test; IAT: indirect antiglobulin test; PCH: paroxysmal cold haemoglobinuria

Table I - *Tests for differentiating types of autoimmune haemolytic anaemia*

	Warm IgG AIHA	Warm IgM AIHA	Warm IgA AIHA	CAD	Mixed AIHA	PCH	DAT negative AIHA
Ig	IgG	IgM	IgA	IgM	IgG+IgM	IgG	IgG, IgA, IgM
DAT poly	+	-	-	+	+	+	-
DAT mono anti-IgG	+	-	-	- or +	+	-	-
DAT mono anti-C3d	+ or -	+ or -	+ or -	+	+	+	-
DAT mono anti-IgM	-	+ or -	-	-	+ or -	-	+ or -
DAT mono anti-IgA	+ or -	-	+	-	+ or -	-	+ or -
Eluate	IgG	IgM	IgA	-	IgG (IgM)	-	IgG (IgM) or -
DAggT	-	+	-	+	+	-	-
IAT	+	-	-	-	+	-	-
Thermal amplitude	Optimally at 37°C	Optimally at 37°C	Optimally at 37°C	Optimally at 4°C	Usually ≥30°C	Biphasic 4°C→ 37°C	Optimally at 37°C
Cold antibody titre	NA	<64	NA	≥64	≥64 (<64)	<64	NA
Donath-Landsteiner test	NA	NA	NA	NA	NA	+	NA
Other tests*	NA	NA	NA	NA	NA	NA	+

*Enzyme-linked antiglobulin test, radiolabelled anti-IgG tests, flow-cytometry, monocyte monolayer assay, concentrated eluates, mitogen-stimulated-DAT. AIHA: autoimmune haemolytic anaemia; CAD: cold agglutinin disease; DAggT: direct agglutination test; DAT mono: direct antiglobulin test monospecific; DAT poly: direct antiglobulin test polyspecific; NA: not applicable; IAT: indirect antiglobulin test; Ig: immunoglobulin; PCH: paroxysmal cold haemoglobinuria. +positive; - negative.

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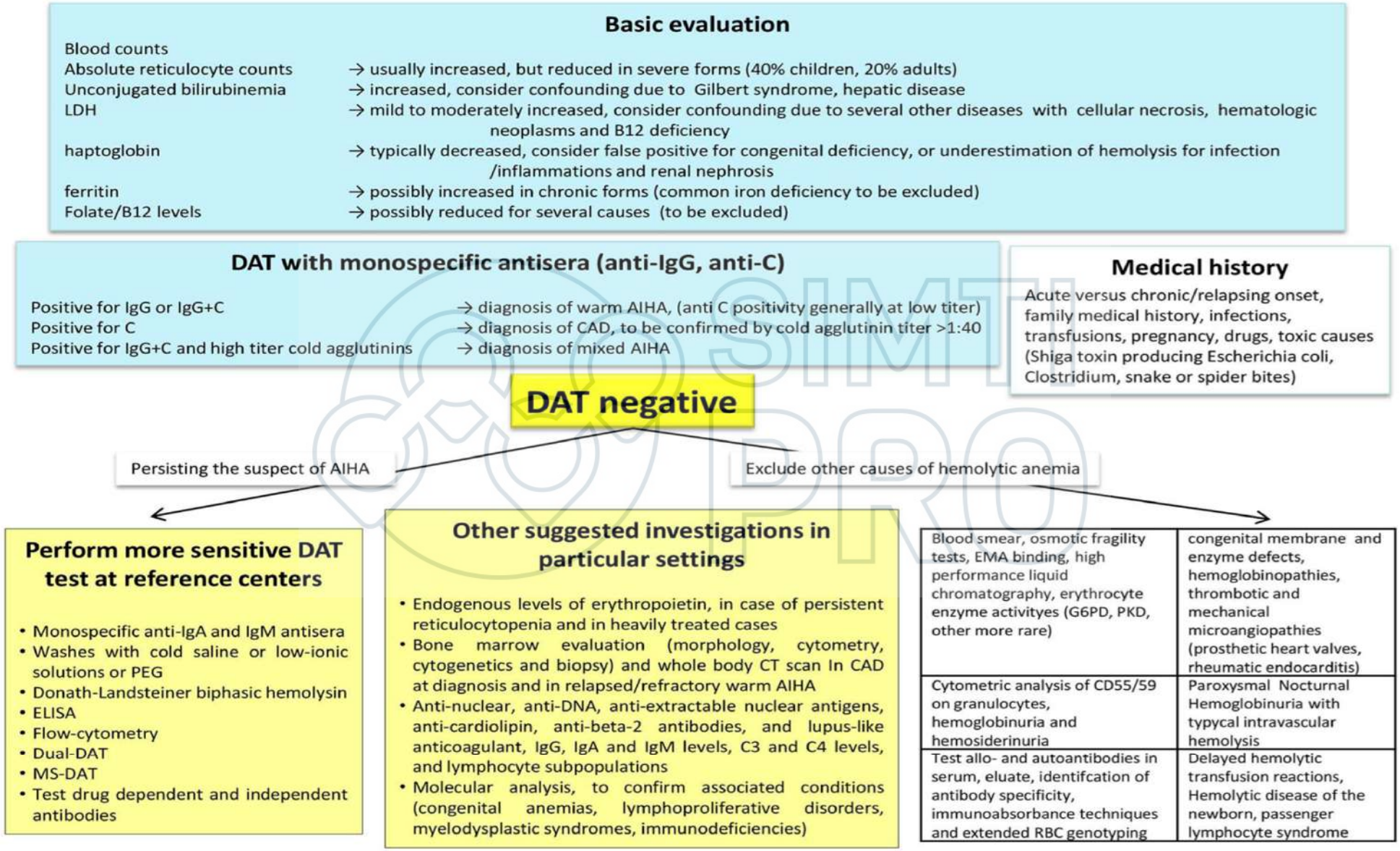

FIGURE 1 | Diagnostic algorithm of autoimmune haemolytic anemia (AIHA). DAT, direct antiglobulin test or Coombs test; MS-DAT, mitogen-stimulated DAT; CAD, cold agglutinin disease; CT, computed tomography; G6PD, glucose-6-phosphate dehydrogenase deficiency; PKD, pyruvate kinase deficiency; EMA-binding, eosin-5′-maleimide-binding test.