Warm Autoimmune Hemolytic Anemia

Diagnosis, Treatment Options, and Treatments in Development

Irina Murakhovskaya, MD
Montefiore Medical Center
Albert Einstein College of Medicine
New York, NY

Bruno Fattizzo, MD
University of Milan, Milan, Italy
Fondazione IRCCS Ca' Granda Ospedale
Maggiore Policlinico, Milan, Italy

Disclosures

Irina Murakhovskaya, MD

Received consultancy honoraria and Speaker's bureau from Alexion, Apellis, Janssen, Novartis, Rigel, Sanofi; Grant/Research Support: Sanofi, Novartis, Alexion, Jansen, Apellis, Rigel, Incyte

Bruno Fattizzo, MD

Received consultancy honoraria and Speaker's bureau from Alexion, Janssen, Sobi, Annexon, Agios, Bristol Myers Squibb, and has served on the Speaker's bureau for Janssen, Sobi, Bristol Myers Squibb, Novartis

What is wAIHA

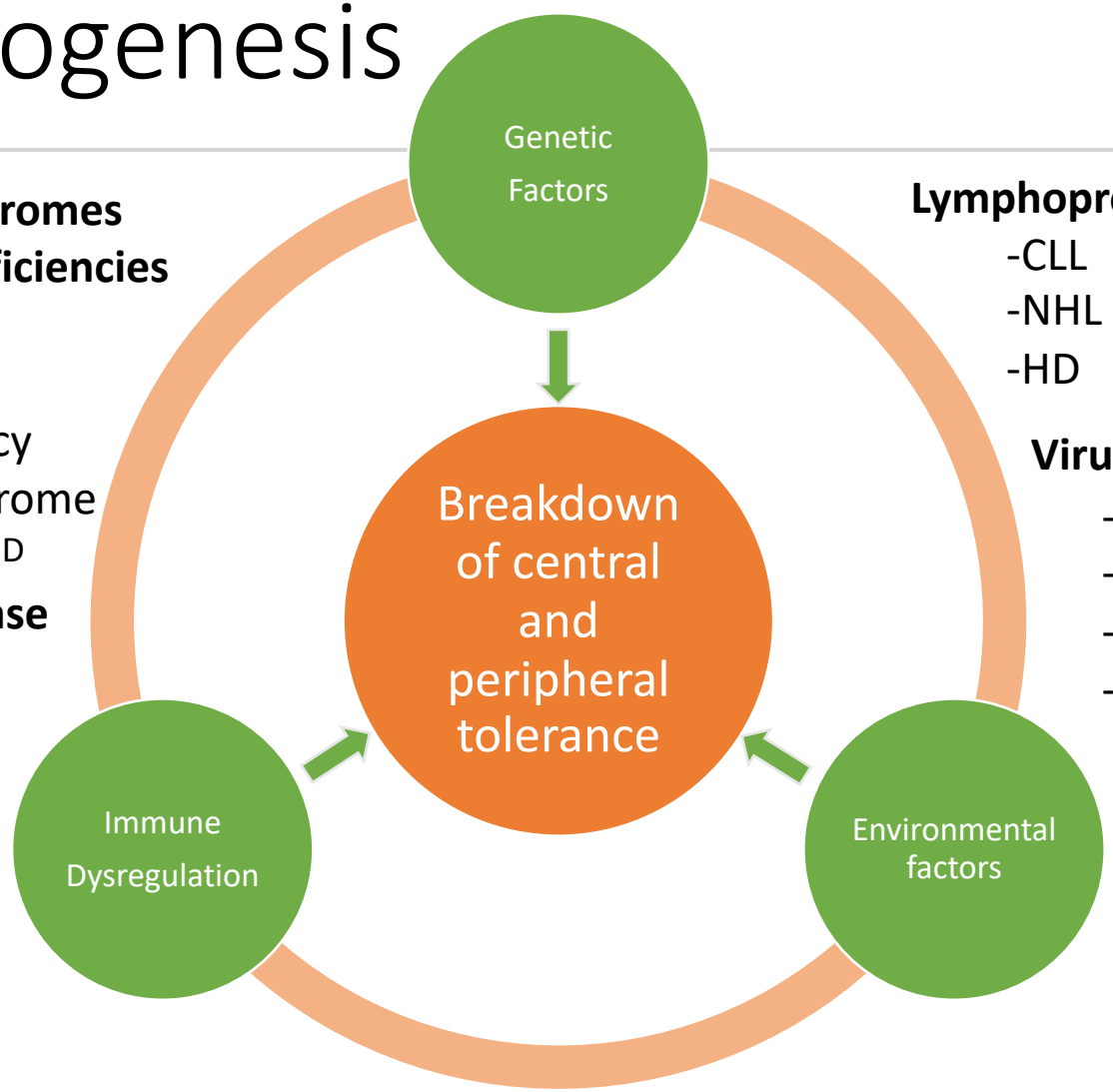
Autoimmune Hemolytic Anemia

- Antibody mediated RBC destruction with or without complement involvement
- Incidence 1-3/100,000/yr; prevalence 17/100,000

	Autoantibody Characteristics				
		Class	Optimal T of Reaction (Range)	Specificity	DAT Positivity
60-70%	Warm AIHA (wAIHA)	IgG (possible Complement fixation)	37 °C (0–40)	Rh system	IgG or IgG + C
20-25%	Cold Agglutinin Disease (CAD)	IgM (common complement fixation)	4 °C (4–34)	I/i system	C
5-10%	Mixed AIHA	warm IgG and cold IgM	4 °C and 37 °C	//	IgG + high titer cold IgM
1-5%	Paroxysmal Cold Hemoglobinuria (PCH)	IgG (common complement fixation)	Reacts at 4 °C and hemolyzes at 37 °C	P Antigen	Positive Donath-Landsteiner Test

Barcellini W et al. *J Clin Med.* 2020; 9: 3859.

AIHA Pathogenesis



Congenital syndromes and immunodeficiencies

-ALPS
-CVID
-IgA deficiency
-Kabuki syndrome
KDM6A, KMT2D

Autoimmune Disease

-SLE
-IBD
-Sarcoid
-RA

Hematopoietic and solid organ transplants

Lymphoproliferative disease

-CLL
-NHL
-HD

Viruses

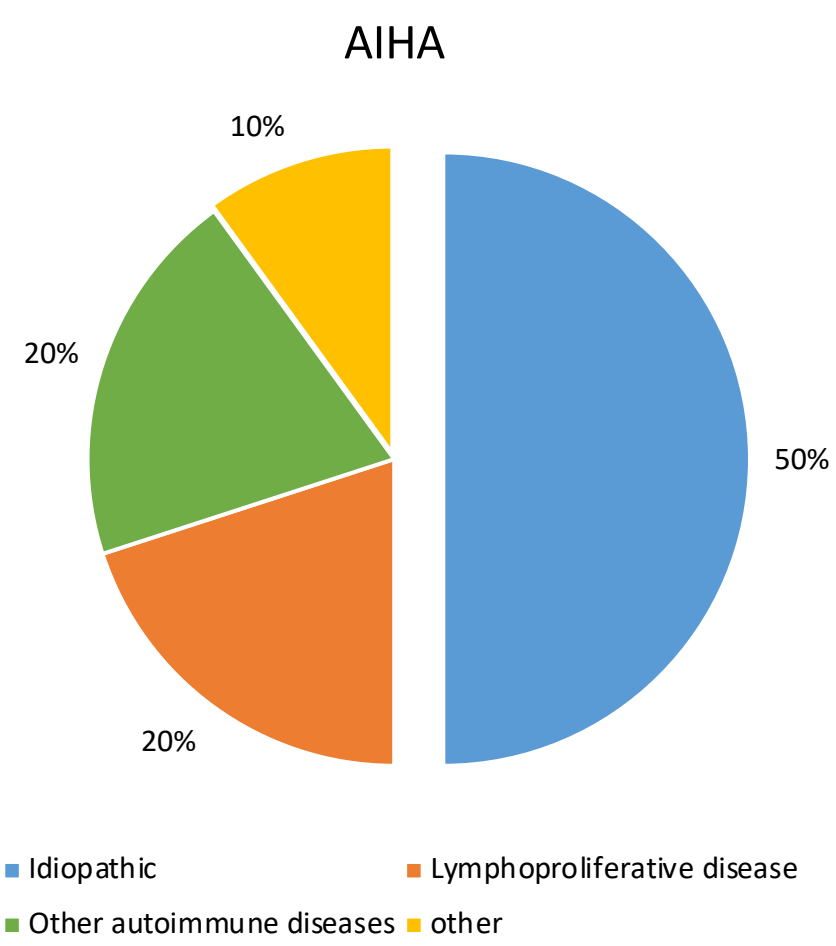
-HIV
-HCV, HBV
-Parvovirus
-SARS-CoV-2

Medications

-Penicillins
-Cephalosporins
-α-methyldopa
-Fludarabine
-BTKI
-Immune checkpoint inhibitors

Barcellini W, Fattizzo B. *Front Immunol.* 2020; 11: 946.Quinn R, Murakhovskaya I. *Hemato.* 2021; 2: 463-476.

Causes of Autoimmune Hemolytic Anemia

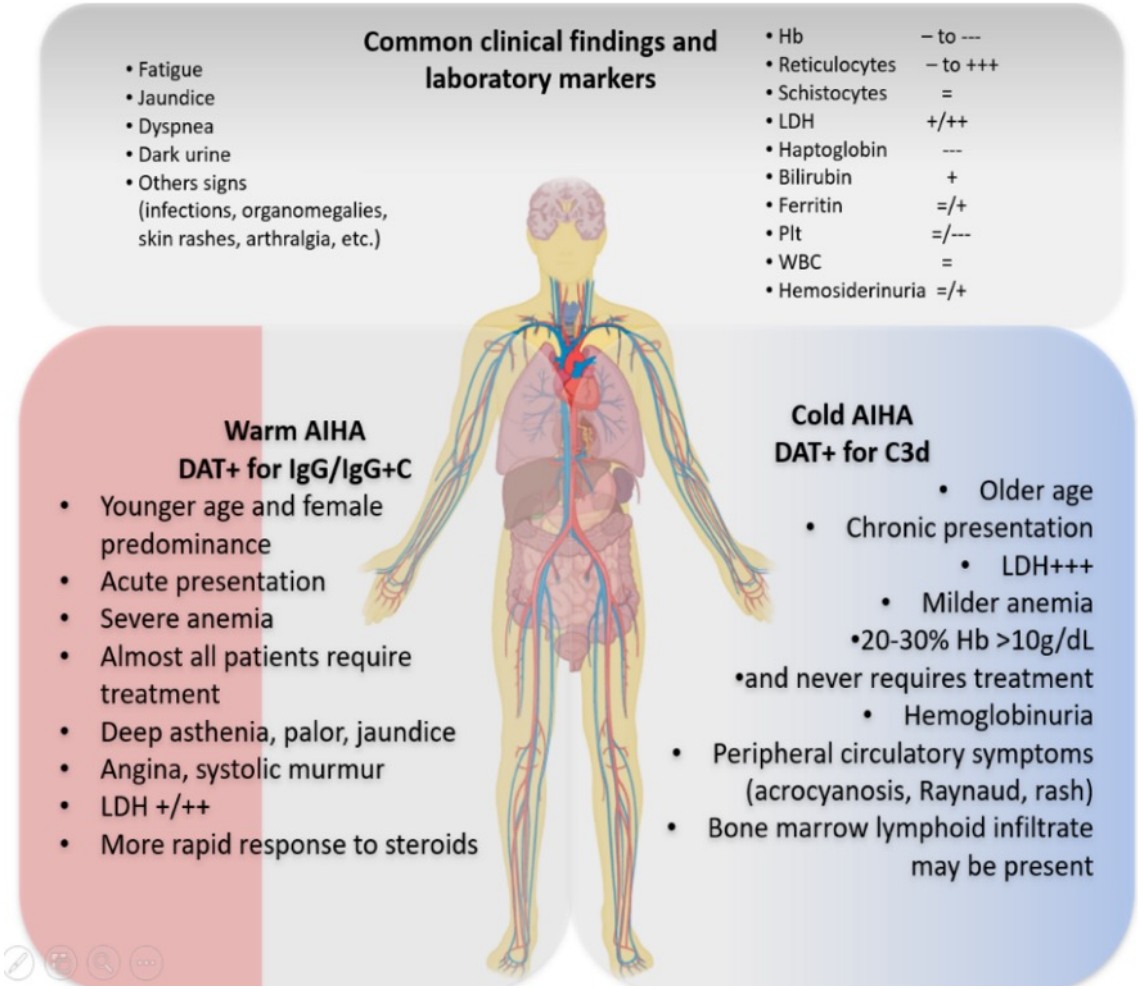


Lymphoproliferative Disease

Valent P, Lechner K. *Wein Klin Wochenschr.* 2008; 93: 447-450.

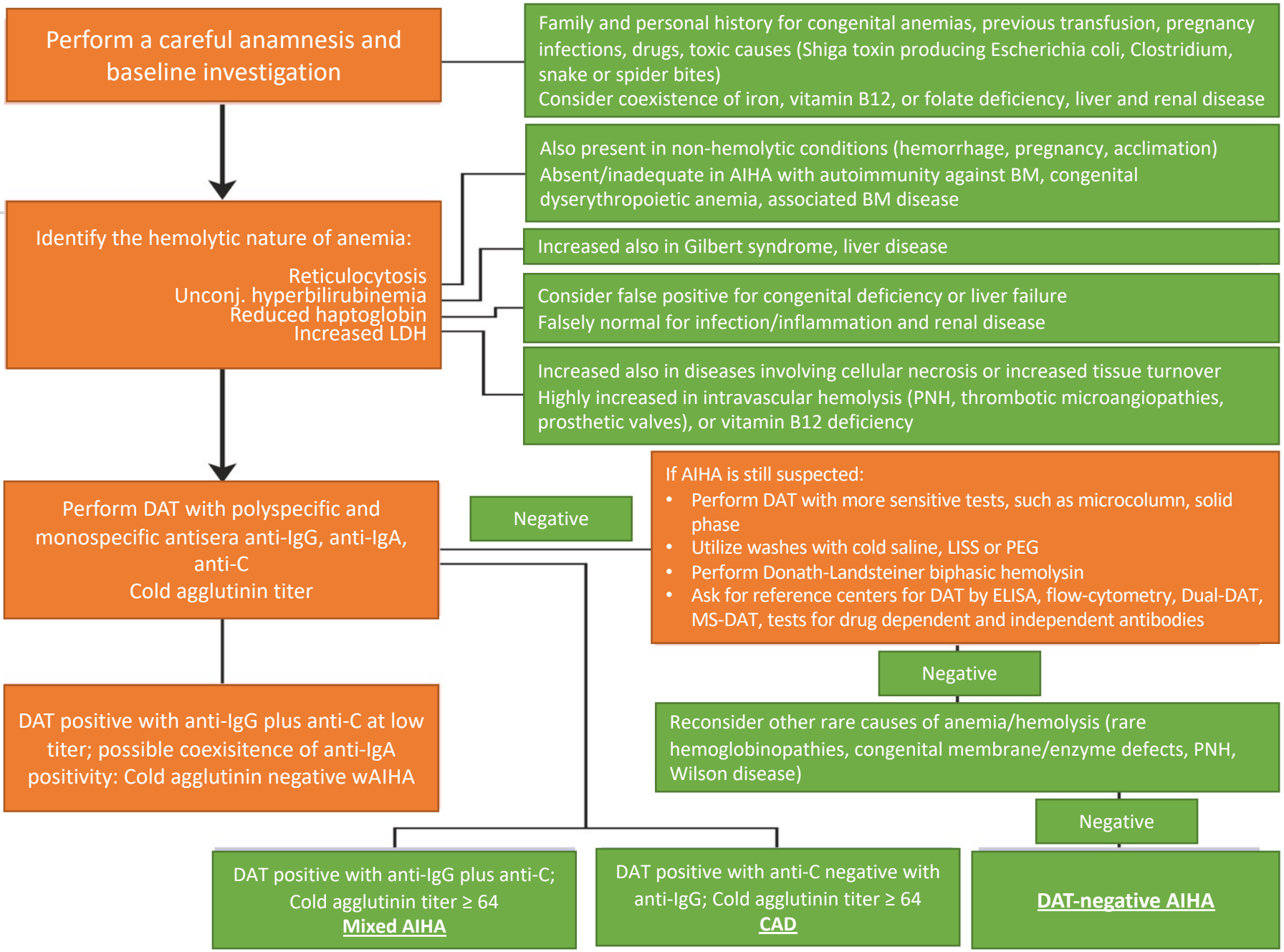
Diagnosing wAIHA

Symptoms of Autoimmune Hemolytic Anemia

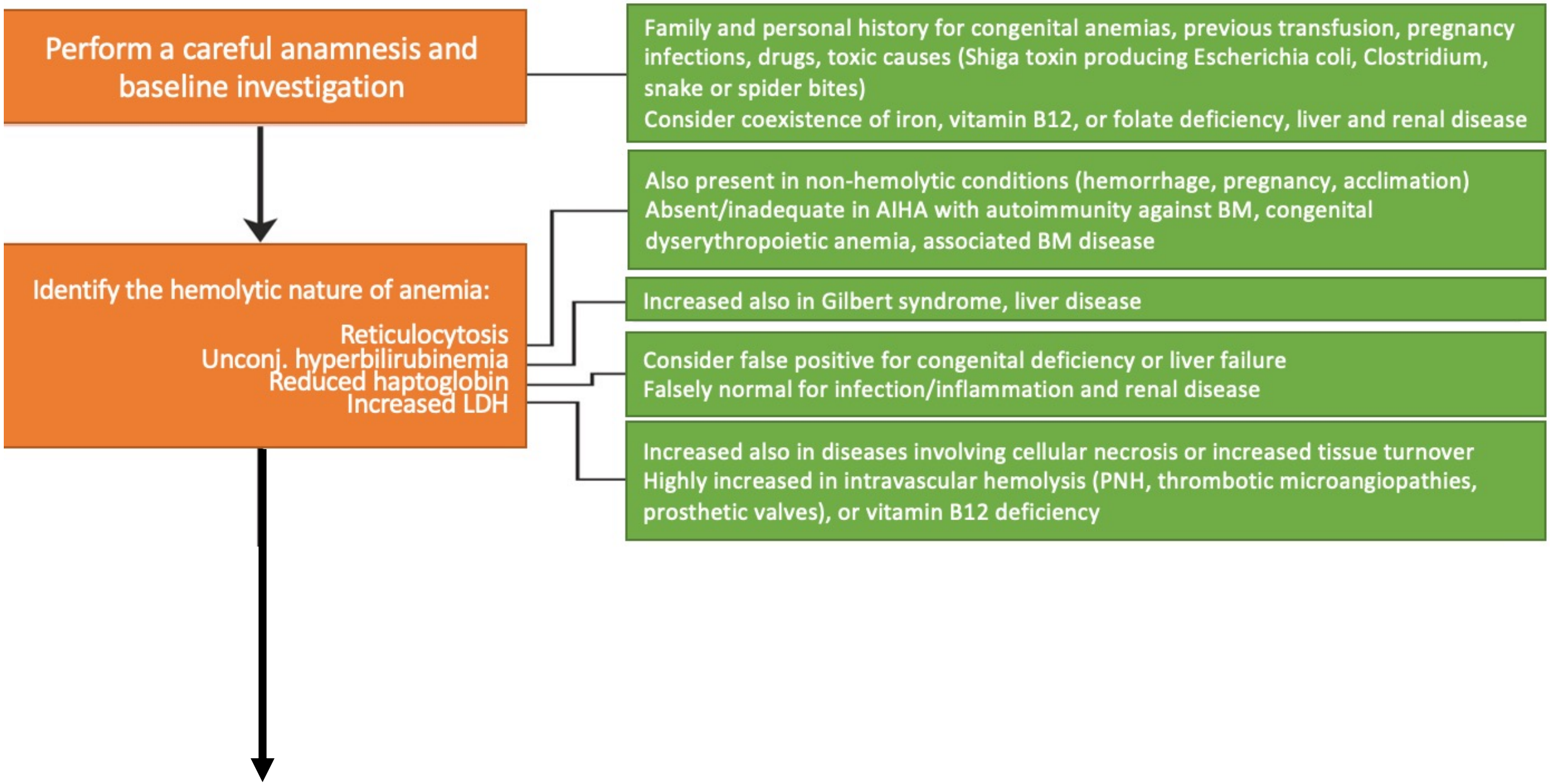


Fattizzo B et al, *J Clin Med.* 2020; 9: 3858.

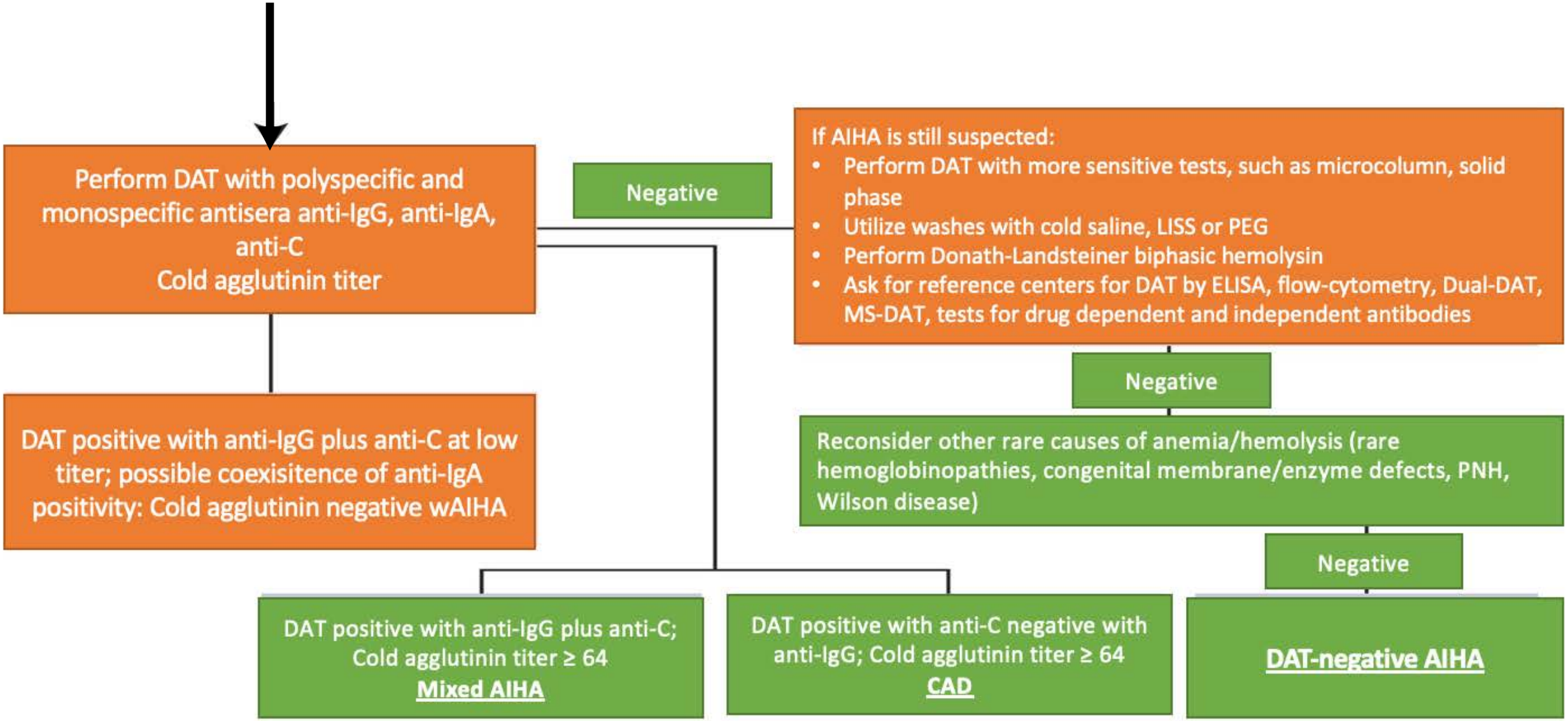
Diagnosis of AIHA



Barcellini W, Fattizzo B, *Blood.* 2021; 137: 1283-1294.



Barcellini W, Fattizzo B, *Blood.* 2021; 137: 1283-1294.

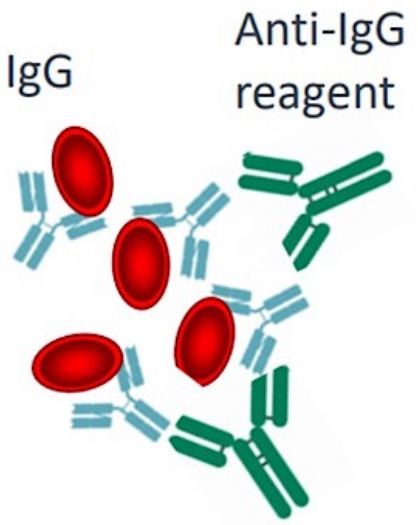


Barcellini W, Fattizzo B, *Blood.* 2021; 137: 1283-1294.

Direct Antiglobulin Test (Direct Coombs) Test

1945

Used rabbit anti-human globulin to identify autoantibodies on RBC surface



Agglutination with anti-IgG reagent
DAT + IgG (+/- C)

10% of AIHA are DAT negative:
IgA Abs
Low-affinity IgG
Low test sensitivity

Positive DAT in the absence of hemolysis:
0.1% healthy population
False positive:
Hypergammaglobinemia, IVIG

Next level testing:
Anti-IgA reagent
Cold wash solution
Low ionic solutions/PEG

<u>More sensitive testing</u>:
Microcolumn
Solid phase Agglutination
Flow cytometry
Mitogen-stimulated DAT

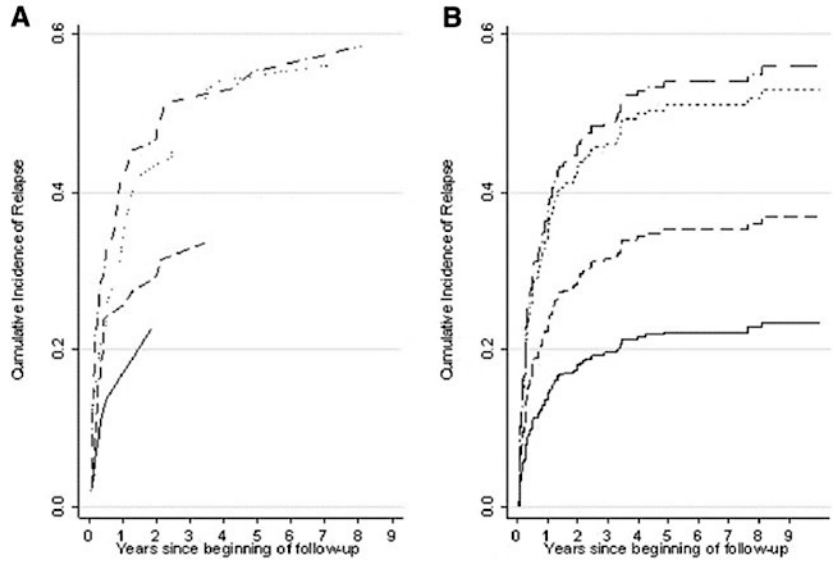
Barcellini W, Fattizzo B, *Blood.* 2021; 137: 1283-1294.

Clinical severity and predictors of relapse

	wAIHA (n=225)		CAD	Mixed AIHA	Atypical AIHA
	IgG (n=158)	IgG+C (n=67)	(n=107)	(n=24)	(n=22)
Median Age at diagnosis (yrs, range)	67 (5-94)	65 (21-92)	70 (28-94)	61 (20-86)	45 (25-78)
Hb (g/dL), median (range)	7.3 (2.1-14.1)	6.5 (2.0-11.5)	8.2 (4.0-13.5)	6.4 (4.3-10.7)	6.6 (3.0-10.9)
LDH (ULN), median (range)	1.7 (0.6-26.7)	1.8 (0.8-7.2)	1.4 (0.3-12.2)	1.7 (0.6-9.8)	2 (0.7-18.1)
Ret (x10⁹/L), median (range)	180 (22-644)	143 (53-641)	123 (13-644)	181 (45-576)	195 (29-780)
inadequate reticulocytosis, n of pts (%)	86 (54)	35 (52)	69 (64)	15 (62)	14 (64)
Therapy					
No therapy (%)	8 (5)	1 (1)	23 (22)	0 (0)	1 (5)
1 line of therapy, n of pts (%)	150 (95)	66 (98)	84 (79)	24 (100)	21 (95)
2 lines of therapy, n of pts (%)	60 (38)	39 (58)	51 (53)	16 (67)	8 (36)
3 lines of therapy, n of pts (%)	23 (15)	13 (19)	26 (24)	8 (33)	5 (22)
4 or more lines of therapy, n of pts (%)	6 (4)	2 (3)	10 (9)	2 (8)	2 (9)
Complications					
Infections, n of pts (%)	21 (13)	17 (25)	9 (8)	4 (17)	1 (5)
Thrombosis, n of pts (%)	21 (13)	18 (27)	14 (13)	1 (4)	4 (18)
Acute renal failure, n of pts (%)	5 (3)	3 (4)	1 (1)	1 (4)	1 (4)
Evans syndrome, n of pts (%)	11 (7)	5 (7)	1 (1)	4 (17)	2 (9)
Death, n of pts (%)	31 (19)	10 (15)	25 (23)	7 (29)	2 (9)
Death for AIHA, n of pts (%)	5 (3)	2 (3)	3 (3)	3 (13)	0 (0)

Risk of relapse

Hb levels	SHR	Robust Std. Err.	z	P>|z|	[95% Conf.	Interval]
8-10 g/dL	1.68	.685	1.19	0.234	.754	3.88
6.1-8 g/dL	2.82	1.09	2.77	0.006	1.34	5.98
≤ 6g/dL	3.08	1.24	2.98	0.003	1.54	6.57

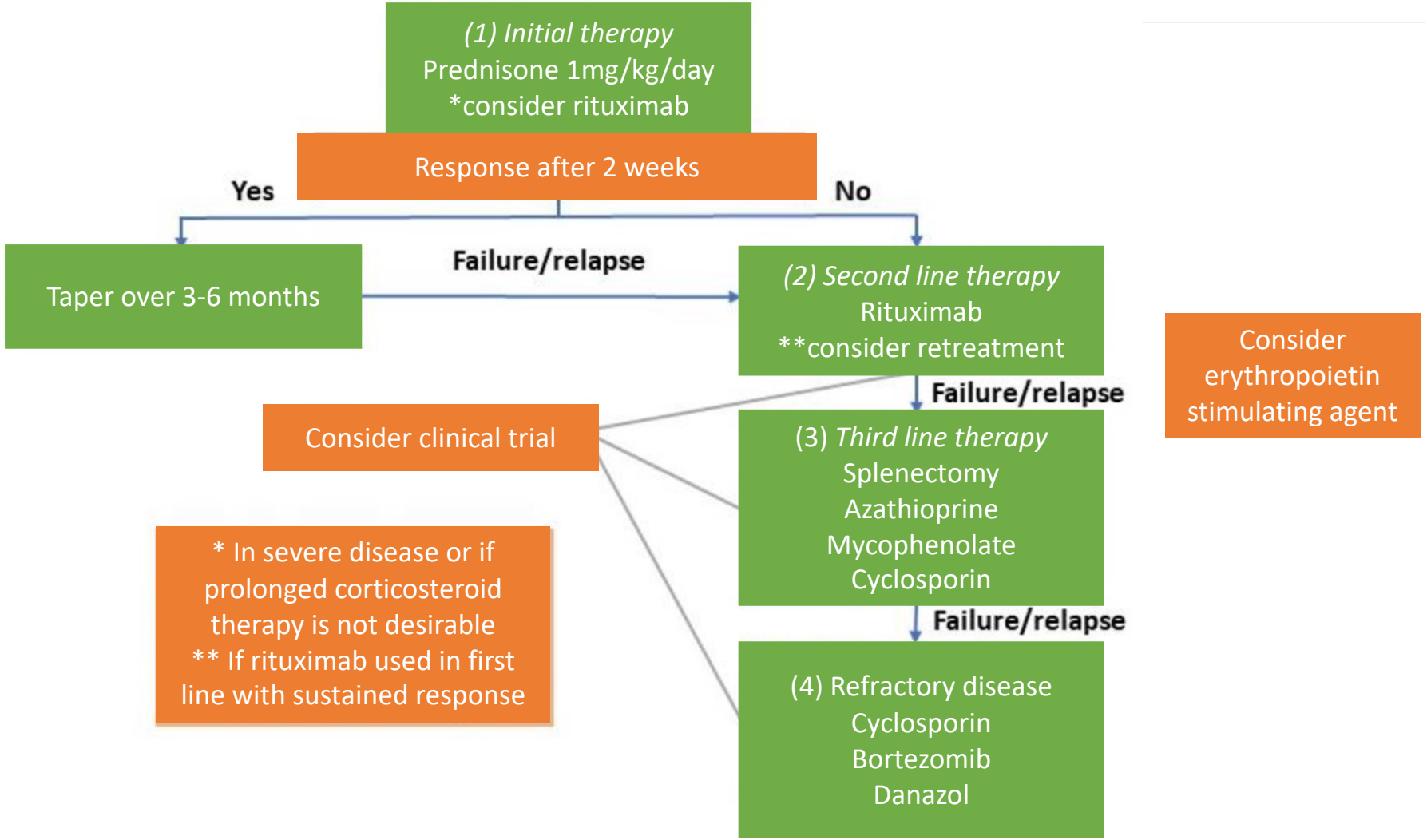


Low hgb at presentation associated with increased risk of multiple relapses and requirement of 2 or more therapy lines

Barcellini W et al. *Am J Hematol.* 2018; 93: E243-E246. Barcellini W et al. *Blood.* 2014; 6: 2930-2936. Tables and figures provided by authors.

Treating wAIHA

Treatment of wAIHA



Murakhovskaya I. *J Clin Med*. 2020; 9: 4034.

Steroids in wAIHA

- Prednisone: 1.0 to 2 mg/kg/day or 60-100 mg/day
- Maintain starting dose for at least 2 weeks and until Hgb >10 g/dL
  - reached in up to 80% of patients within 2 to 3 weeks
- Taper by 20 mg/wk over 4-6 wks until 20 mg daily, then slower taper 5mg/month (total duration of steroid therapy 4-6mo)
  - Relapse more common if steroids tapered to ≤10 mg in < 2 mo and if stopped in < 6 mo
- Goal hgb $\geq$ 10 g/dL with prednisone < 10mg/day by 3 mo after treatment
- Patients who *remain in remission after discontinuing prednisone: 20 - 30%*
- Second line therapy should be considered if:
  - No response to 1 mg/kg/day after 3 weeks
  - Relapse during or after steroid taper

Crowther M et al. *Blood.* 2011; 118: 4036-4040. Lechner K, Jäger U. *Blood.* 2010; 116: 1831-1838. Barcellini W et al. *Blood.* 2014; 124: 2930-2936. Roumier M et al. *Am J Hematol.* 2014; 89: E150-E155. Dussadee K, et al *J Med Assoc Thai.* 2010; 93 Suppl 1: S165-S170.

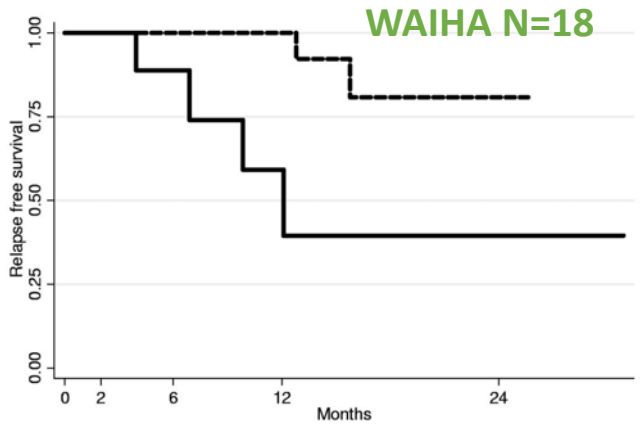
Rituximab for Relapsed/Refractory wAIHA

Retrospective trials of rituximab in R/R wAIHA					
First Author (Year)	**Number of Pts**	**Splenectomy (N)**	**ORR/CR (%)**	**Duration of Response (mo)**	**Comment**
Narat (2006)	11	5	64/27	2-20	
D'Arena (2007)	11	1	100/73	1-96+	All primary AIHA pts received 3 additional monthly doses of maintenance rituximab; 1 additional pt had rituximab retreatment for ITP
Bussone (2009)	27	6	93/30	NR	5 (18%) relapses after median f/u 20.9 mo, 3 retreated with rituximab and responded
Dierickx (2009)	36	10	83/50	1 yr PFS 72% 2 yr PFS 56%	
Penaiver (2010)	27	13	77/61	Duration of response > 6 mo in pts in CR	
Maung (2013)	34	3	71/27	9-60	50% relapse; median time to next treatment 16.5 mo; 28.5% maintained response at 3 yrs
Roumier (2014)	25	2	80/NR	50% relapse after mean of 14 mo ± 8	62% secondary wAIHA
Barcellini (2014)	32	NR	81/56		Primary AIHA only; low dose rituximab
Jaime-Perez (2019) First-line Relapsed	 18 8	 N/A 7	 100/83 100/63	 Median 16.5 Mean maintained response 82 ± 18	 Low dose rituximab + high dose dexamethasone (40 mg/day) for 4 days

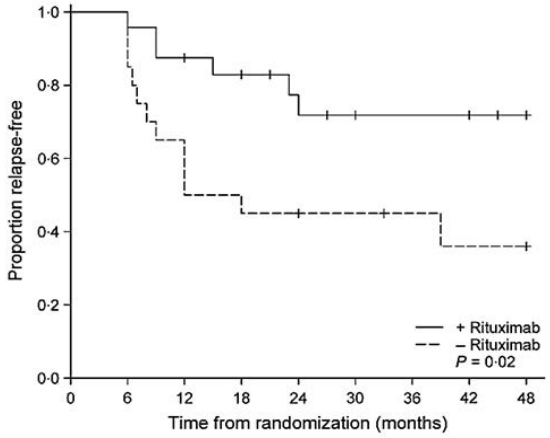
Murakhovskaya I. *J Clin Med*. 2020; 9: 4034.

Rituximab: What dose?

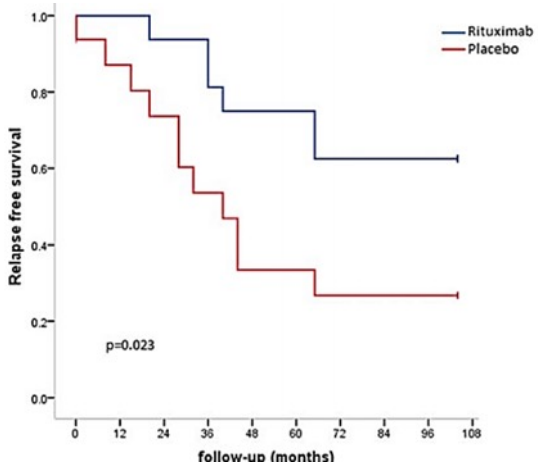
Rituximab 100 mg IV weekly x 4



Rituximab 375 mg/m^2 weekly x 4

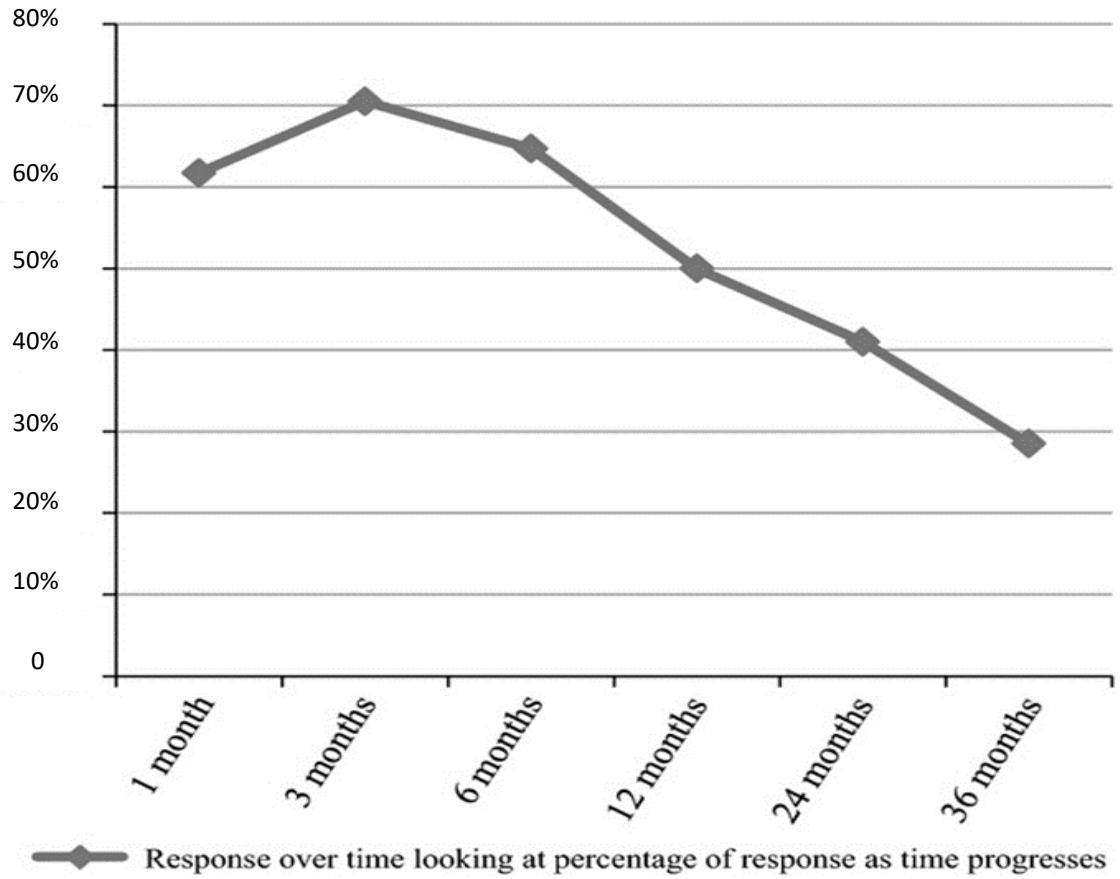


Rituximab 1000 mg, on day 1, 15



Barcellini W et al. *Blood.* 2012; 119; 3691-3697.
Birgens H et al. *Br J Haematol.* 2013; 163; 393-399.
Michel M et al. *Am J Hematol.* 2017; 92: 23-27

Percentage of patients responding to rituximab over time

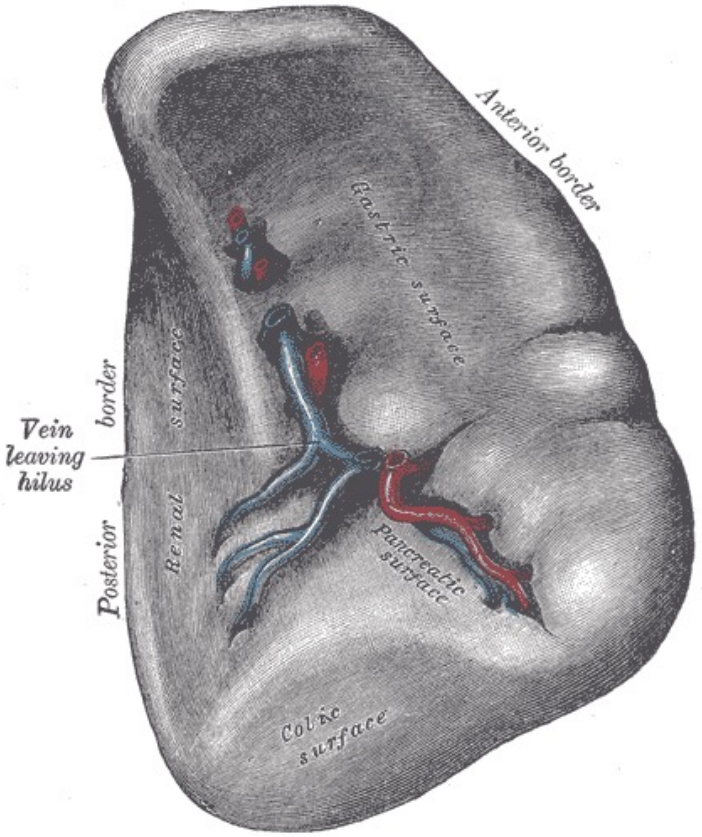


- Median time to response: 4 - 6wks
- Responses within the first week seen
- 87.5% response within 4 wks, 100% response by 3 months.
- Relapse at 1 - 2 years 25 -50%

Maung S et al. *Br J Haematol.* 2013; 163; 118-122.

Splenectomy

- Response 60-70%; long-term remission ~20%
- Surgical mortality rate of 0.8%
- Infectious complications:
  - Overwhelming sepsis 3-5% with mortality rate 50%
    - Even with vaccinations
- Thrombotic events
  - 1.86% risk within 90 days HR 3.2
  - 1.9% risk within 1 year HR 2.8



Lechner K, Jäger U. *Blood.* 2010; 116: 1831-1838.
Thomsen RW et al *Ann Intern Med*. 2009; 151: 546-555.
Roumier M et al *Am J Hematol*. 2014; 89: E150-E155.
Balagué C et al *Surg Endosc*. 2004; 18: 1931-1933.
Thomsen RW et al *J Thromb Haemost*. 2010; 8: 1413-1416.

Current treatments of wAIHA

Treatment	Dose schedule	Response rate	Time to response	Comments	Side effects/cons
Prednis(lo)ne	1-2 mg/kg/day for 3-4 weeks	80-90% (estimated cure rate 20-30%)	7-25 days	Gradual tapering during a period no shorter than 4-6 months Steroid boluses may be used for acute severe forms (i.e., methylprednisone 250 mg iv daily for 3 days)	Diabetes mellitus, hypertension, peptic ulcer, osteoporosis, adrenal suppression, myopathy, psychosis, delayed wound healing, insomnia, menstrual irregularity, weight gain
Rituximab	375 mg/sqm/wk for 4 weeks	~80% (relapse free survival of ~60% at 3 years)	3-6 weeks	Other schedules include: • Low dose (100 mg weekly for 4 weeks) in pts with non-severe hemolytic anemia and in the elderly • 1 g Day 1 and 15, particularly in wAIHA associated with other autoimmune diseases	Infusion reactions, late-onset neutropenia, hypo-gammaglobulinemia, reactivation of underlying infections (HBV, HCV, HIV, tuberculous, etc.)
Splenectomy		~80% (curative rate 20-50%)	7-10 days	Discouraged in pts older than 65-70 years, with cardiopulmonary disorders, thrombotic risk, immunodeficiencies, lymphoproliferative diseases, and systemic autoimmune diseases	Possible complications include serious infectious (vaccinations warranted against Neisseria meningitidis ACWY and B type, pneumococcal, and Haemophilus influenzae type B; annual flu vaccine, variable schedule for 5 yearly boosters) and thrombotic events
Azathioprine	2-4 mg/kg/day	~60% (usually with steroids)	1-3 months	Advised as steroid sparing agent in AIHAs secondary to systemic autoimmune conditions, inflammatory bowel diseases, and autoimmune hepatitis	Myelotoxicity, particularly in case of thiopurine methyltransferase deficiency (start with 50 mg daily, increase up to 150 mg in absence of neutropenia), liver toxicity
Cyclosporine	2.5 mg/kg twice daily	~60%	1-3 months	Advised as steroid sparing agent, particularly in AIHA secondary to autoimmune conditions, Evan's syndrome, and in case of features of bone marrow failure	Kidney damage, hypertension, infections, nausea, excessive hair growth
Cyclophosphamide	50-100 mg/day or 800 mg/sqm IV monthly for 4-5 cycles	50-70%	2-6 weeks	May be considered in highly hemolytic disease, particularly if secondary to connective tissue disorders and lymphoproliferative diseases	Myelosuppression, infections, urotoxicity, secondary malignancy, teratogenicity, and infertility
Mycophenolate	500 mg twice daily	25-100% (small case series)	1-3 months	Mainly used in the pediatric setting	Nausea, headache, diarrhea

Barcellini W, Fattizzo B. *Blood.* 2021; 137: 1283-1294..

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Rituximab	375 mg/sqm/wk for 4 weeks	~80% (relapse free survival of ~60% at 3 years)	3-6 weeks	Other schedules include: • Low dose (100 mg weekly for 4 weeks) in pts with non-severe hemolytic anemia and in the elderly • 1 g Day 1 and 15, particularly in wAIHA associated with other autoimmune diseases	Infusion reactions, late-onset neutropenia, hypo-gammaglobulinemia, reactivation of underlying infections (HBV, HCV, HIV, tuberculous, etc.)

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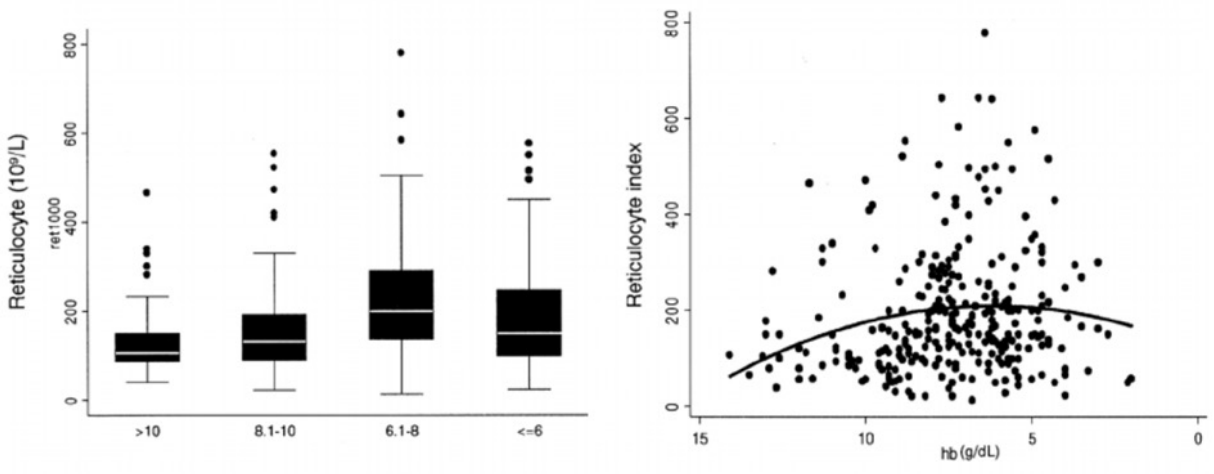
Barcellini W, Fattizzo B. *Blood.* 2021; 137: 1283-1294..

Erythropoietin in AIHA

Predictors of refractoriness to therapy and healthcare resource utilization in 378 patients with primary autoimmune hemolytic anemia from eight Italian reference centers

Wilma Barcellini MD, Anna Zaninoni BS, Bruno Fattizzo MD, Juri Alessandro Giannotta MD, Monia

Absolute reticulocyte count as a function of hemoglobin at onset



- Reticulocytopenia in 20% adults and 39% children
- Inadequate reticulocytosis in > 50% patients, particularly with Hgb < 6g/dL

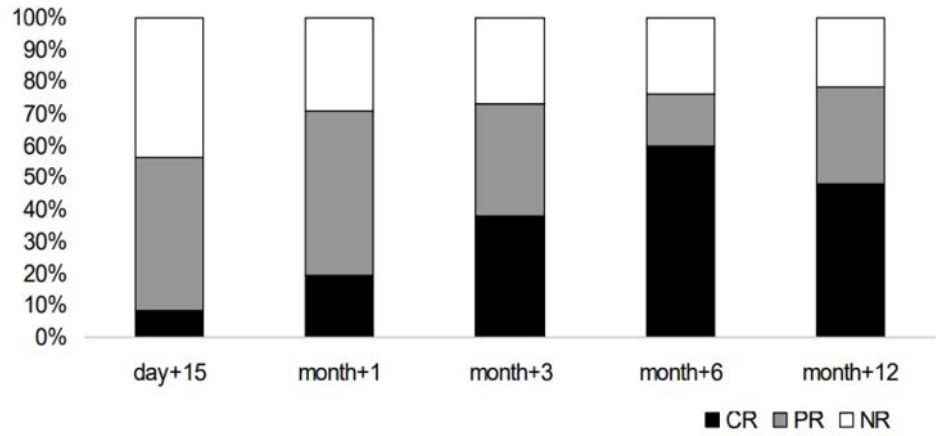
Barcellini W et al. *Am J Hematol.* 2018; 93: E243-E246. Figure used with permission from Author.

Fattizzo B et al. *Haematologica* 2021; 106: 622-625. Creative commons figure.

Efficacy of recombinant erythropoietin in autoimmune hemolytic anemia: a multicenter international study

Bruno Fattizzo, Marc Michel, Anna Zaninoni, Juri Giannotta, Stephanie Guillet, Henrik Frederiksen, Josephine M.I. Vos,

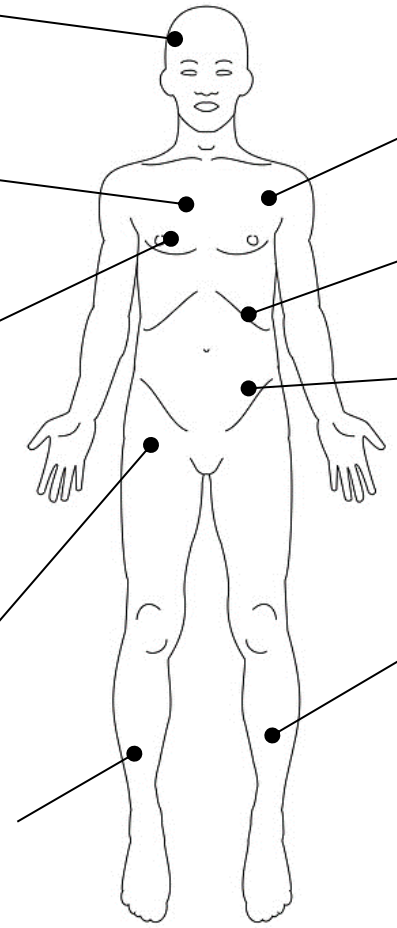
Response to erythropoietin



- 48 cases AIHA treated for a median of 7 months
- Epo α 40,000 U/wk or Darbepoetin α 20-300 mcg/wk
- Response ~70% in refractory AIHA
  - Esp severe anemia, low endogenous epo, use early in disease

Complications

AIHA: Potential Life-Threatening Complications



Stroke

Cardiac ischemia

Raynaud syndrome (typical of CAD)

Pulmonary embolisms

Thrombosis (11-20% of cases, mostly in IgG+C wAIHA, mixed and atypical, and associated with:

- Hb levels <6 g/dL at onset
- intravascular hemolysis
- previous splenectomy

DIC

DVT

Pneumonia (9-14% of cases)

Sepsis (2-3% of cases, more frequently in splenectomized cases)

Acute renal failure (3% of cases)

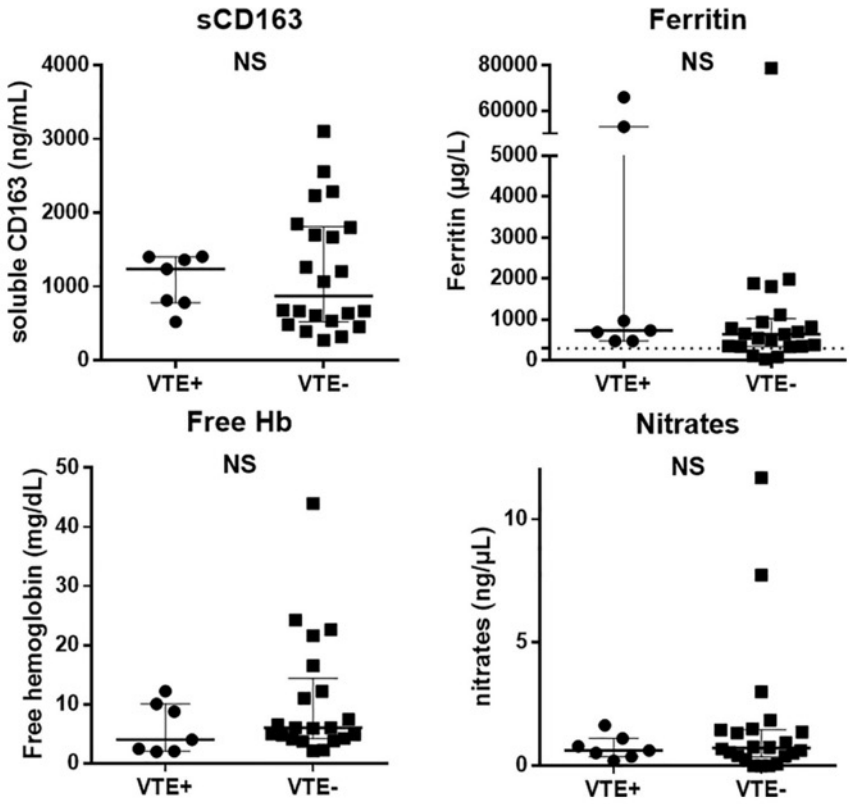
Evans syndrome (7-10% of cases, more frequently in mixed, atypical, and in severe AIHA forms)

Hazard risks for AIHA-related death (3-4% of cases)

- **Evans syndrome** (HR 8, 95% CI 2.5-26)
- **Acute renal failure** (HR 6.3, 95% CI 1.4-29)
- **Infections** (HR 4.8, 95% CI 1.5-15)
- **Multi-treatment** (4 or more lines of therapy)
- Thrombotic events not associated with increased risk of death

Barcellini W et al. Expert Rev Clin Immunol. 2018; 14: 857-872.

Thrombosis and wAIHA



Thrombotic events 11-20% of patients

Lecouffe-Desprets M, et al *Autoimmun Rev.* 2015; 14: 1023-1028.
Barcellini W et al. *Blood. 2014;* 124: 2930-2936.
Audia S et al *PLoS One.* 2018; 13: 3020718
Berentsen S, Barcellini W. *N Engl J Med.* 2021; 385: 1407-1419.

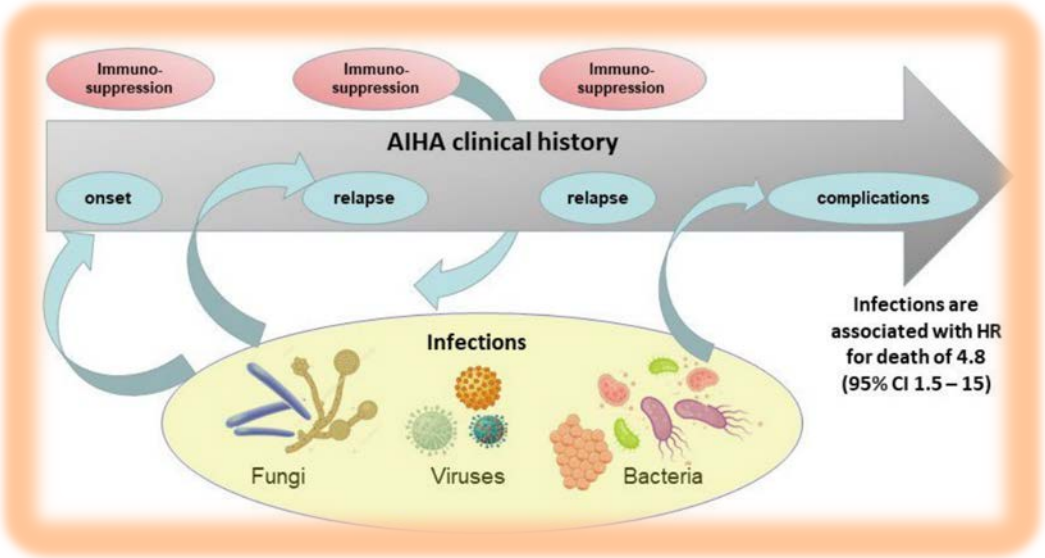
Cumulative incidence of thrombosis (continuous line) and of mortality (dashed line).

Thrombotic Events in 30 of 287 Patients with AIHA

Fattizzo B, et al. *J Thrombo Haematol.* 2022; 20: 1852-1858.

Infections

Infections may trigger AIHA reactivations but may also be consequent to long-term immunosuppressive therapy



Pathogen	Screening Test	Risk Factors	Prophylaxis
HBV	HBsAg, antiHBs, antiHBc, antiHBe, HBeAg, HBV-DNA when indicated	Steroids Rituximab Immunosuppressors Bortezomib	- Lamivudine, entecavir, tenofovir or pre-emptive therapy according to EASL or AGA guidelines - HBV vaccination of seronegative patients
HCV	Anti-HCV (HCV-RNA if Ab positive)	Long-term steroids Rituximab	- No drugs approved for prophylaxis - Eradication therapy in HCV-RNA+
Mycobacterium tuberculosis	tuberculin skin test or serum interferon gamma release assays +/− chest X-ray	Long-term steroids	Isoniazid (or rifampicin) in latent TB, polichemotherapy in active TB
Pneumocystis jirovecii	No screening tests available	Steroids >10 mg/day + age >65 or pulmonary disease or therapy with rituximab/CTX	TMP-SMX (atovaquone, pentamidine, dapsone if not tolerated/contraindicated)
Encapsulated bacteria	No screening tests available	Splenectomy Complement inhibitors	- ACWY and B group meningococcal vaccines - 23-valent and 13-valent pneumococcal vaccines - Haemophilus influenzae type B vaccine

Giannotta JA et al. *J Clin Med.* 2021; 10: 164.

Pathogen	Screening Test	Risk Factors	Prophylaxis
HBV	HBsAg, antiHBs, antiHBc, antiHBe, HBeAg, HBV-DNA when indicated	Steroids Rituximab Immunosuppressors Bortezomib	- Lamivudine, entecavir, tenofovir or pre-emptive therapy according to EASL or AGA guidelines - HBV vaccination of seronegative patients
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Giannotta JA et al. *J Clin Med.* 2021; 10: 164.

Evans Syndrome

- Evans syndrome (ES) is a rare disease characterized by the association of multiple autoimmune cytopenias, usually **AIHA** and immune thrombocytopenia (**ITP**) (and occasionally autoimmune neutropenia)
- Risk factors for developing ES: infections, malignancies, autoimmune diseases, recent vaccinations, drugs or a **family history** of immune disorders
- Clinical features: palor, weakness, fatigue, jaundice, petechiae, ecchymosis, gingivorrhagia and epistaxis. **Risk of 66.6% of patients developing respiratory tract infections (prolonged immunosuppressive therapy +associated underlying immune deficit)**

In adult patients, Michel et al. have shown that ES was a secondary condition in 56% of cases (mainly as a results of malignancies and autoimmune diseases)

Evans R et al, *AMA Arch Intern Med.* 1951; 87: 48-65. Michel M et al. *Blood.* 2009; 114: 3167-3172. Fattizzo B et al. *Blood Adv.* 2021; 5: 5468-5478.

Evans Syndrome

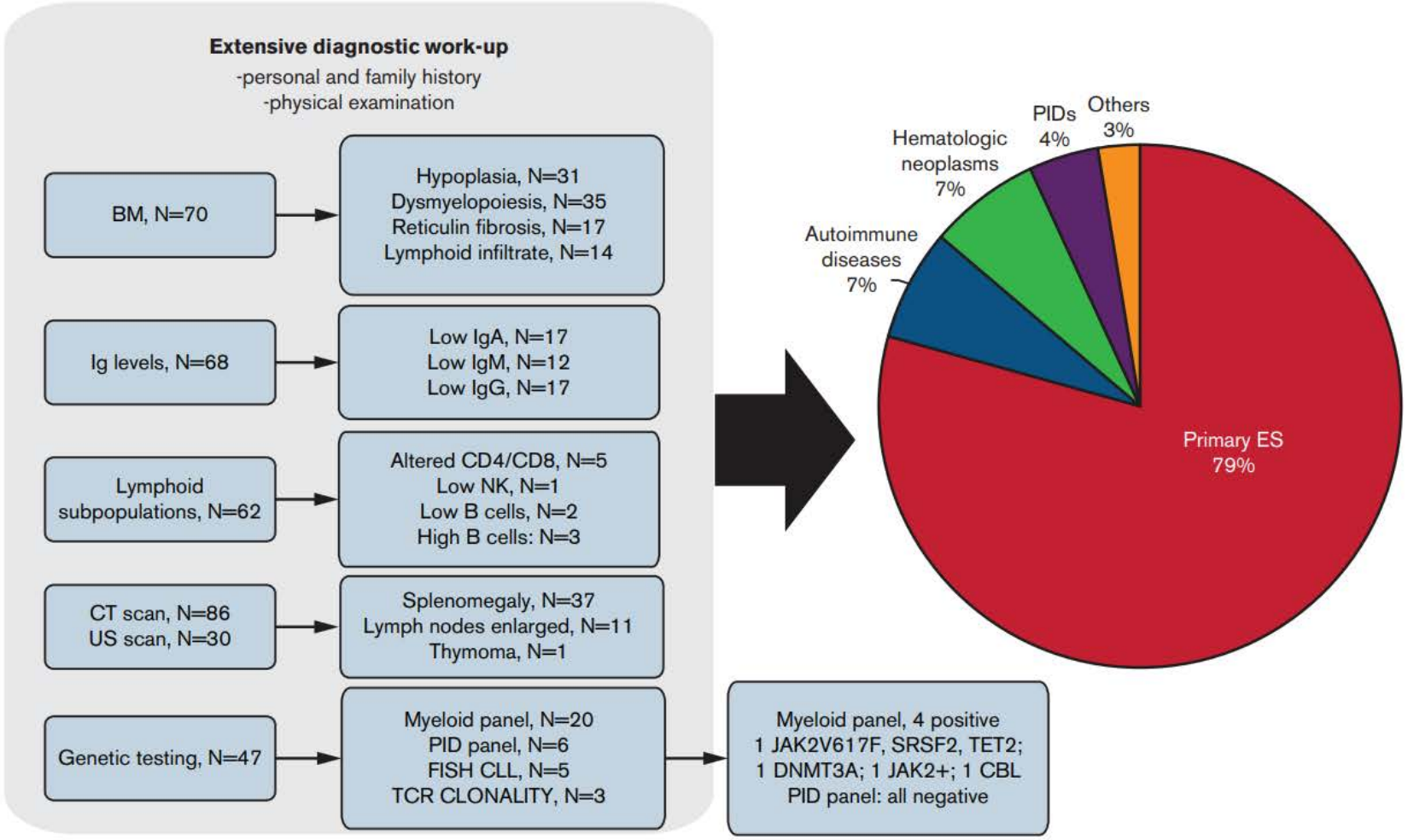
Diagnosis

- Exhaustive **clinical history** including risk factors for developing ES: infections, malignancies, autoimmune diseases, recent vaccinations, drugs or a **family history** of immune disorders
- Thorough **physical examination** focused on signs of anemia or thrombocytopenia
- Complete blood count and smear
- Markers of hemolysis
- Positive direct anti-human globulin test (DAT) test confirming ongoing immune hemolysis
- Additional studies
  - Antibodies against platelets→ 35% of individuals, mostly type anti-IIb-IIIa
  - Anti-granulocyte antibodies
  - Others to identify connectivitis, LAC,ACA,anti-beta2 glycoprotein 1 if **history of thrombosis**

Primary ES is a diagnosis of exclusion and secondary ES must be searched because treatment and responses are different!

Evans R et al, *AMA Arch Intern Med* 1951; 87: 48-65. Michel M et al. *Blood.* 2009; 114: 3167-3172. Fattizzo B et al. *Blood Adv.* 2021; 5: 5468-5478.

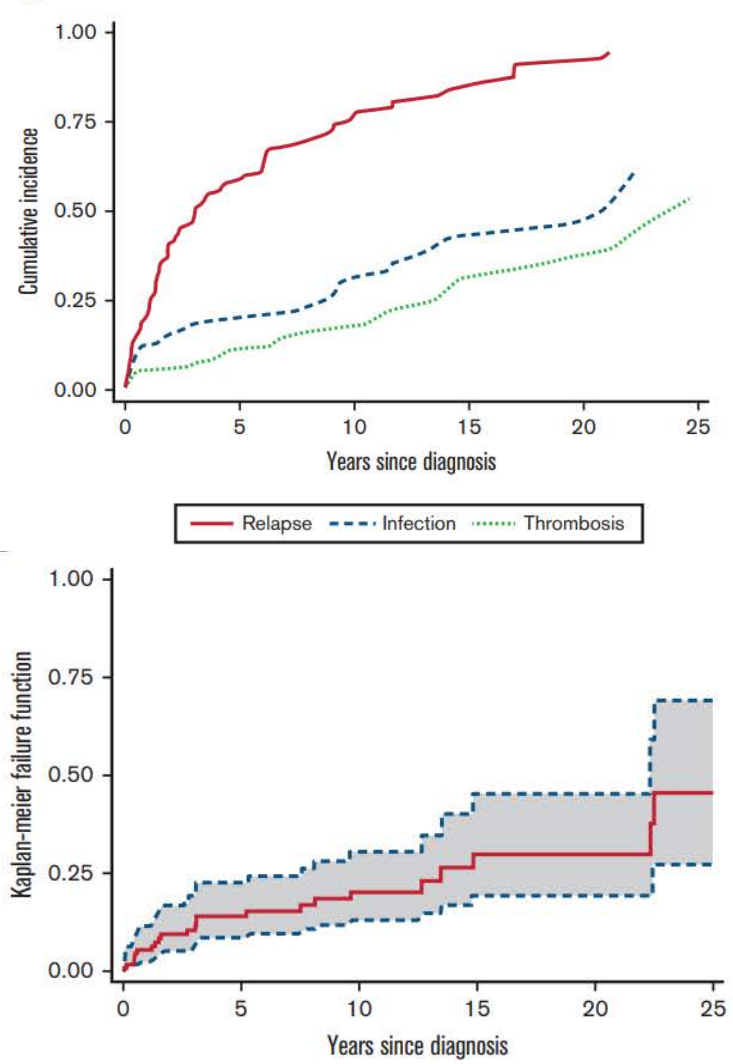
Evans Syndrome: Primary vs Secondary



Fattizzo B et al. *Blood Adv* 2021; 5: 5468-5478.

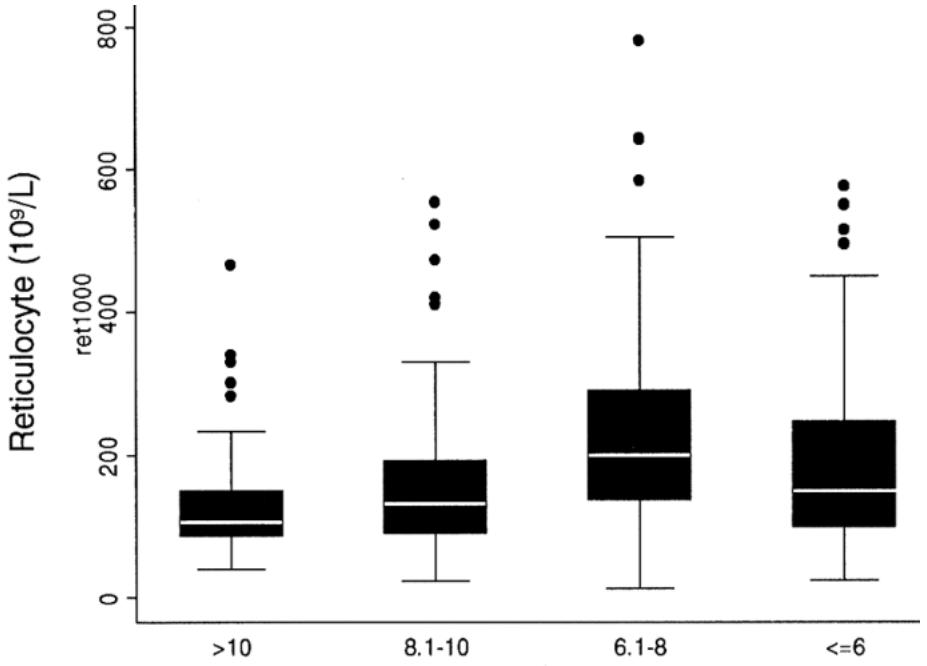
Evans Syndrome: Risk of Thrombosis, Relapse, Death

- Bleeding occurred in 42% of patients
  - Mainly low grade and at ITP onset
- All patients received first-line steroids+/- IVIG
- 23% needed early additional therapy "primary refractoriness"
- 2nd line included rituximab, splenectomy, immunosuppressants, thrombopoietin receptor agonists, and others, with response rates > 80%
- 70% relapsed and 54% required ≥ 3 therapy lines
- Infections in 33% and thrombosis in 21% of patients, mainly grade > 3, correlated with n. therapy lines
- Mortality of 2.4 per 100 persons year
  - Associated with anemia at onset and occurrence of relapse, infection, and thrombosis
- **Risk of death in patients with AIHA and ES: (HR 6.8; 95% CI, 1.99-23.63; *P* = .0074)**



Fattizzo B et al. *Blood Adv.* 2021; 5: 5468-5478. Barcellini W et al. *Blood* 2014; 124: 2930-2936.

Reticulocytopenia: A Medical Emergency

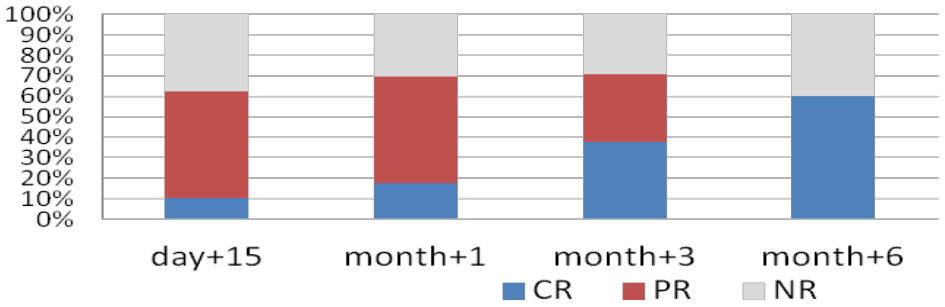


- Reticulocytopenia is present in 20% of adults and 39% of children
- Reticulocytopenia is present in severe cases
- Due to autoimmune reaction against BM erythroid? precursors?

EUROPEAN HEMATOLOGY ASSOCIATION

AMSTERDAM 24TH CONGRESS JUNE 13 - 16 | 2019 European Hematology Association

Evidence Based **Use of Erythropoietin in Patients with Autoimmune Hemolytic Anemia**: A Multicenter International Study



rEPO (i.e. epoetin alpha 40,000 IU/week sc)→ 70% ORR associated with:

- **primary AIHA** (73% vs 33% in secondary)
- **inadequate reticulocytosis** (76% vs 50% with adequate reticulocytosis)

Liesveld JL et al. *Blood*. 1987; 69: 820-826. Aladjidi N et al. *Haematologica.* 2011: 96: 655-663. Barcellini W et al. *Blood.* 2014; 6: 2930-2936. Barcellini W et al. Am J Hematol. 2018; 93: E243-E246. Fattizzo B et al. *Haematologica*. 2021; 106: 622-625.

AIHA in ICU: diagnostic delay (i.e. warm IgM and DAT negative) and high mortality

Characteristics and outcome of adults with severe autoimmune hemolytic anemia admitted to the intensive care unit: Results from a large French observational study

Clara Pouchelon, Charlotte Lafont, Antoine Lafarge, Thibault Comont, Etienne Riviere, David Boutboul, Claire Fieschi, Antoine Dossier, Sylvain Audia, Julien Vaidie, Marc Ruivard ... See all authors

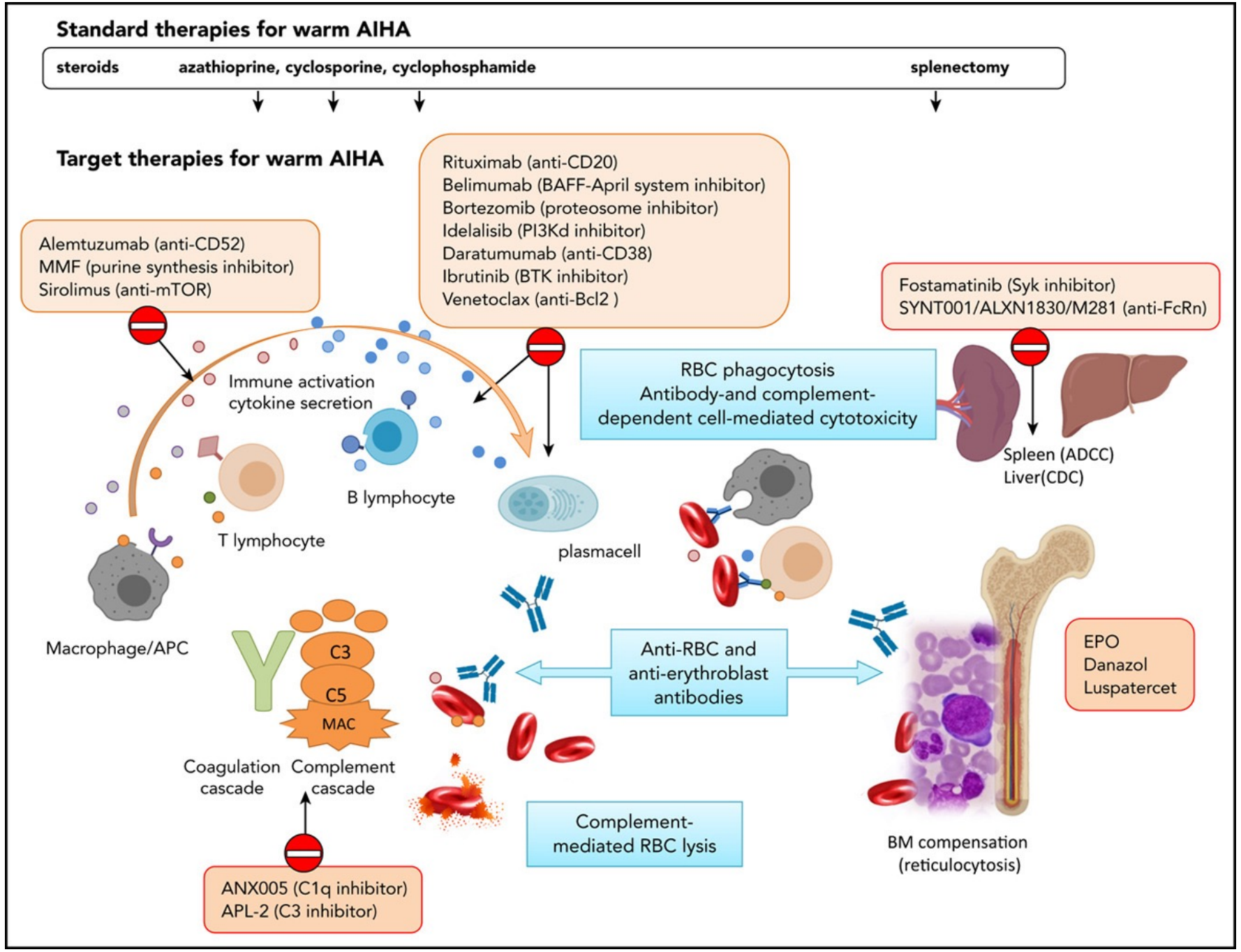
First published: 24 July 2022 | https://doi.org/10.1002/ajh.26665

- **62 patients (median age 55 years)**
- mostly **warm (79%),** newly diagnosed (69.3%),
- **secondary AIHA (64.5%).**
- Median hemoglobin level 4.3 g/dL [3.7–5.1];
- **92% of patients had a low (< 121) BMRI**.
- Despite enoxaparin **9.7% DVT**
- **16% severe infectious**
- **8 (12.9%) patients died after a median of 3.5 [1–9] days**
- 90.3% required transfusions → 1.5 units per day [1.0–2.5].
- **Recombinant erythropoietin** was given to 14 (**22.6%**) patients.
- 16.1% IV Ig and 8.1% plasma exchange.

	Clinical presentation	Diagnostic issues	Therapeutic hints
AIHA in the intensive care unit 0.05% of primary AIHA cases	Very severe anemia Massive hemolysis Unresponsiveness to transfusion MOF	Factors associated with severity are concomitant ITP, severe infections, and thrombosis	Intensive support with transfusion, along with steroid boli, iv Ig, rituximab, erythropoietin, and plasma-exchange

Pouchelon C et al. *Am J Hematol.* 2022; 97: E371-E373.

Treatments in Development



Barcellini W, Fattizzo B, *Blood.* 2021; 137: 1283-1294.

Novel agents in treatment of wAIHA

Drug/Class	Mechanism	Indication	Study
Monoclonal Antibodies			
Alemtuzumab	Anti-CD52	Secondary AIHA	Case reports
Daratumumab	Anti-CD38	HSCT-AIHA	Case reports
Ofatumumab	Anti-CD20	Secondary AIHA	Case reports
Ianalumab	Anti-BAFF	Primary of secondary wAIHA	Phase 3
Povetacicept	Anti-APRIL/BAFF	Primary wAIHA, CAD, ITP	Phase 1b
Obexelimab	Anti-CD19	Primary or secondary wAIHA	Phase 3
B-cell receptor pathway and FcγR signaling **inhibitors**			
Ibrutinib	BTKi	Secondary AIHA	Case reports
Rilzabrutinib	BTKi	Primary, secondary wAIHA	Phase 2
Venetoclax	Bcl2	Secondary AIHA	Case reports
IgG-mediated Phagocytosis Inhibitors			
Fostamatinib	Syk inhibitor	wAIHA	**Phase 2,3**
Sovleplenib	Syk inhibitor		**Phase 2/3**
Nipocalimab	FcRn MoAB	wAIHA	**Phase 2/3**
Orilanolimab	FcRn MoAB	wAIHA	Phase 2
Complement inhibitors			
Annexion-005	C1q inhibitor	wAIHA, CAD	Phase 1/2
Eculizumab	C5 inhibitor	CAD/Mixed AIHA	Case reports, Phase 2
Pegcetacoplan	C3/C3b inhibitor	wAIHA, CAD	Phase 1/2
Bortezomib	Proteosome Inhibitor	WAIHA, CAD	Case reports, Phase 2

Novel agents in treatment of wAIHA

Drug/Class	Mechanism	Indication	Study
Monoclonal Antibodies			
Alemtuzumab	Anti-CD52	Secondary AIHA	Case reports
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Ofatumumab	Anti-CD20	Secondary AIHA	Case reports
Ianalumab	Anti-BAFF	Primary of secondary wAIHA	Phase 3
Povetacicept	Anti-APRIL/BAFF	Primary wAIHA, CAD, ITP	Phase 1b
Obexelimab	Anti-CD19	Primary or secondary wAIHA	Phase 3

Novel agents in treatment of wAIHA

Drug/Class	Mechanism	Indication	Study
B-cell receptor pathway and FcγR signaling inhibitors			
Ibrutinib	BTKi	Secondary AIHA	Case reports
Rilzabrutinib	BTKi	Primary, secondary wAIHA	Phase 2
Venetoclax	Bcl2	Secondary AIHA	Case reports

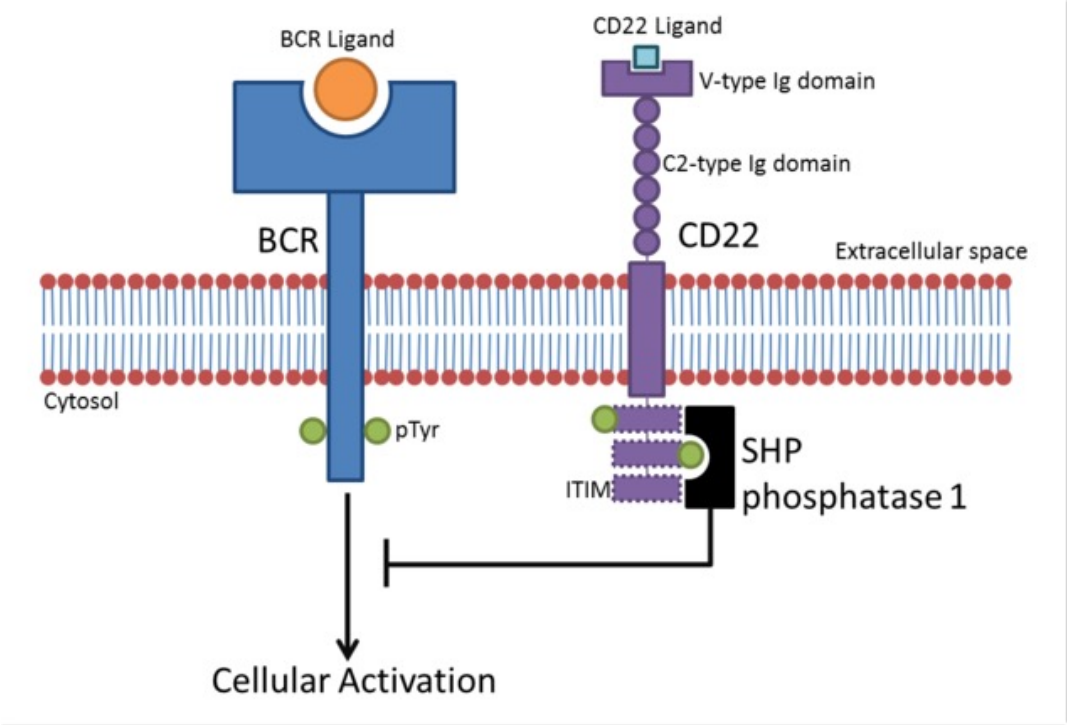
Novel agents in treatment of wAIHA

Drug/Class	Mechanism	Indication	Study
IgG-mediated Phagocytosis Inhibitors			
Fostamatinib	Syk inhibitor	wAIHA	**Phase 2,3**
Sovleplenib	Syk inhibitor		**Phase 2/3**
Nipocalimab	FcRn MoAB	wAIHA	**Phase 2/3**
Orilanolimab	FcRn MoAB	wAIHA	Phase 2

Novel agents in treatment of wAIHA

Drug/Class	Mechanism	Indication	Study
Complement inhibitors			
Annexion-005	C1q inhibitor	wAIHA, CAD	Phase 1/2
Eculizumab	C5 inhibitor	CAD/Mixed AIHA	Case reports, Phase 2
Pegcetacoplan	C3/C3b inhibitor	wAIHA, CAD	Phase 1/2
Bortezomib	Proteosome Inhibitor	WAIHA, CAD	Case reports, Phase 2

BCR pathway

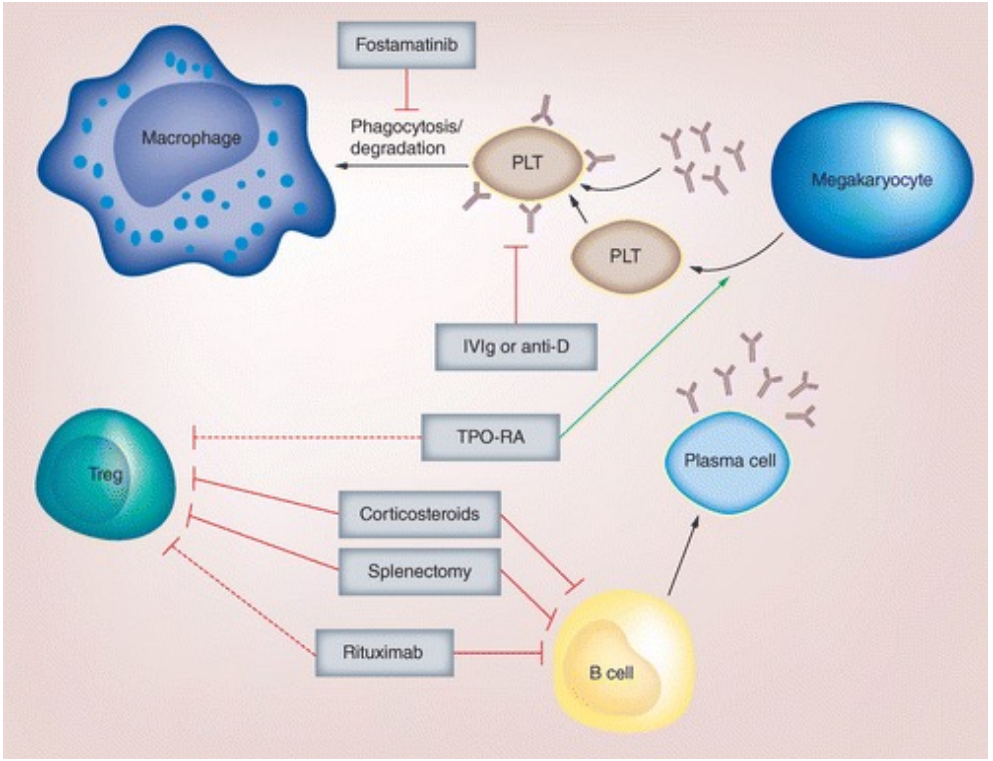


- Essential for normal B-cell development, selection, survival, proliferation, and differentiation into antibody-secreting cells.
- Dysregulation in congenital immunodeficiencies, autoimmunity, and leukemia and lymphoma
- Controlled by several key enzymes, PI3Kδ, Syk, and Btk, expression is limited mostly to hematopoietic cells and essential functions mostly in B-cells

Puri KD et al. *Int Rev Immunol* 2013; 32: 397-427.
Avalos Am et al. *Adv Immunol*. 2014; 123: 1-49.

Syk inhibition

- Syk: cytoplasmic tyrosine kinase activated by binding of Ag to the BCR
  - Required for signaling downstream of the BCR
  - Activation leads to phosphorylation of Syk
  - FcγR phagocytosis of the antibody coated RBCs is dependent upon Syk signaling.
- Syk inhibition:
  - blocks B-cell activation, reduces ability of B cells to serve as APCs to T-cells and elicit the T-cell help required for antibody secretion, antibody affinity maturation, and Ig class switching
  - inhibits FcR-triggered, Syk-dependent cytoskeletal rearrangement during phagocytosis



Podolanczuk A et al. *Blood* 2009; 113: 3154-3160.
Newland A et al. *Immunotherapy*. 2018; 10: 9-25. Creative commons figure

Fostamatinib

Phase 3, Randomized, Double-Blind, Placebo-Controlled, Global Study (FORWARD) of Fostamatinib for the Treatment of Warm Antibody Autoimmune Hemolytic Anemia

David J. Kuter, Caroline I. Piatek, Khalil Saikali, Wolfgang Dummer

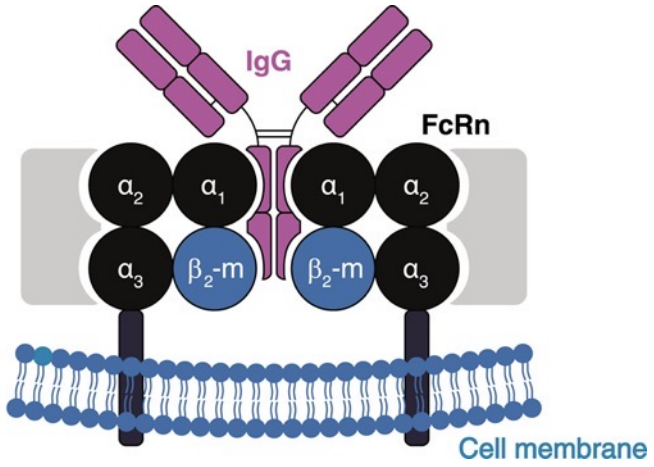
- Approved for ITP April 17, 2018
- AIHA Orphan Drug designation

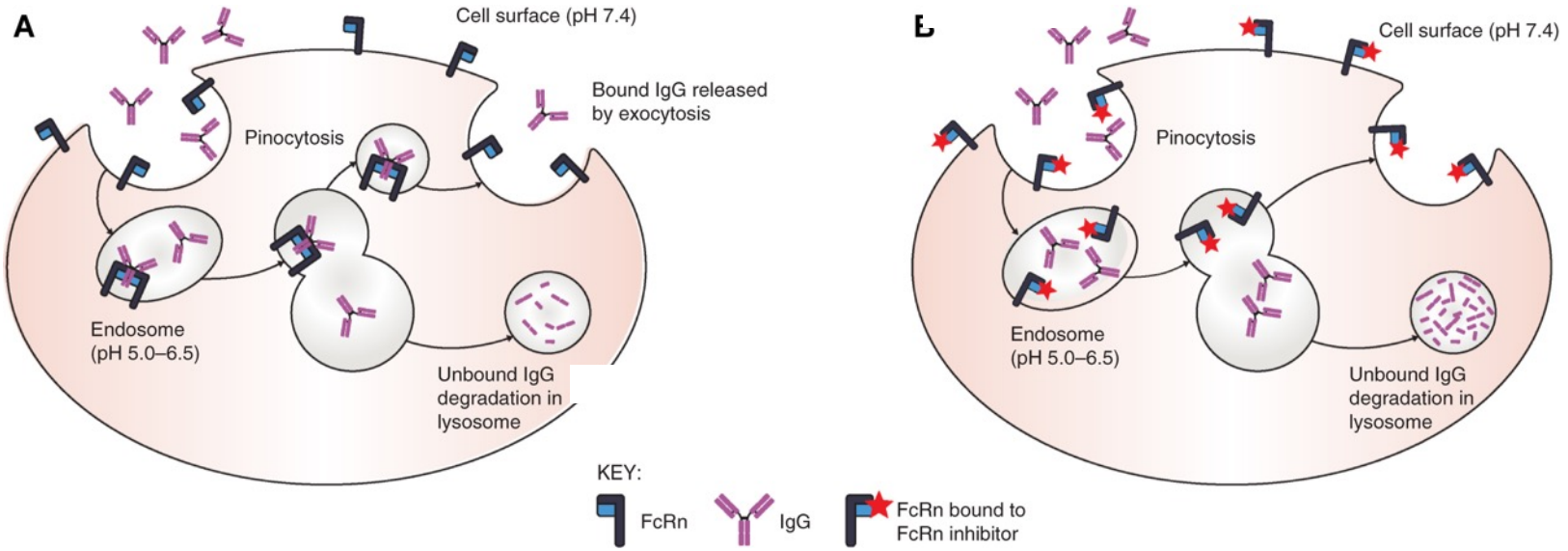
- FORWARD study is 24-week Phase 3 RCT (N=90)
- Primary endpoint: Hgb > 10 g/dL and ≥ 2 g/dL from baseline
- Overall response rate: 35.8% in fostamatinib group vs 26.7% in placebo group.
- Reanalysis: 33% in fostamatinib group vs 14.0% in placebo group. (Two patients removed from placebo group who did not have evidence of hemolysis)
- High placebo response rate observed (esp in Eastern Europeans)

Regions	**Durable hemoglobin response, n (%)**	
Treatment group	Fostamatinib	Placebo	p-value
Overall population – prespecified analysis	16/45 (35.6%)	12/45 (26.7%)	P=0.398
Overall population, n (%) – reanalysis	15/45 (33.3%)	6/43 (14.0%)	P=0.0395
U.S., Canada, Australia, Western Europe – reanalysis	8/25 (32.0%)	0/28 (0)	P=0.021
Eastern Europe – reanalysis	7/20 (34.0%)	6/15 (40.0%)	NS

Kuter D et al. *Blood.* 2022; 140 (suppl 1): 2438-2439.

FcRn Inhibition





- MHC class I FcγR
- IgG transplacental transport
- IgG recycling and transport
- Albumin recycling and transport

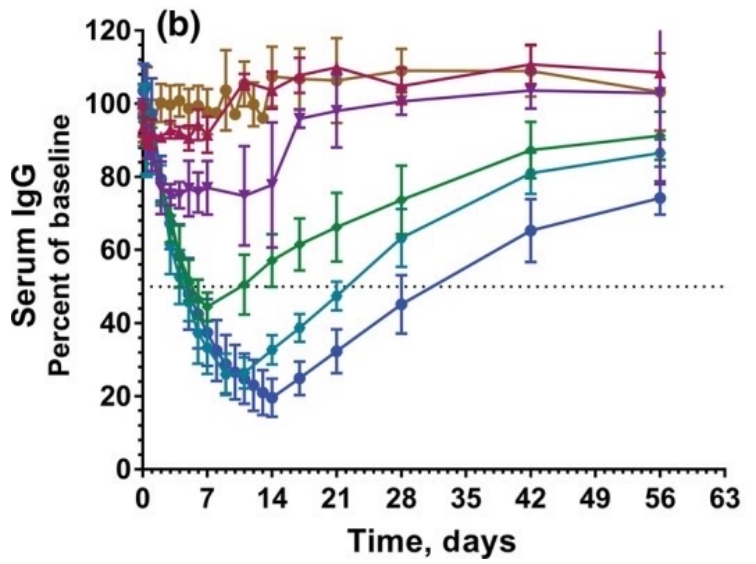
Ling LE et al. Clin Pharmacol Ther. 2019; 105: 1031-1039.
Patel DD, Bussel JB. J. Allergy Clin. Immunol. 2020; 146(3): 467-478.

Nipocalimab

Energy Trial in Warm Autoimmune Hemolytic Anemia (wAIHA): Design of a Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Nipocalimab, an FcRn Blocker

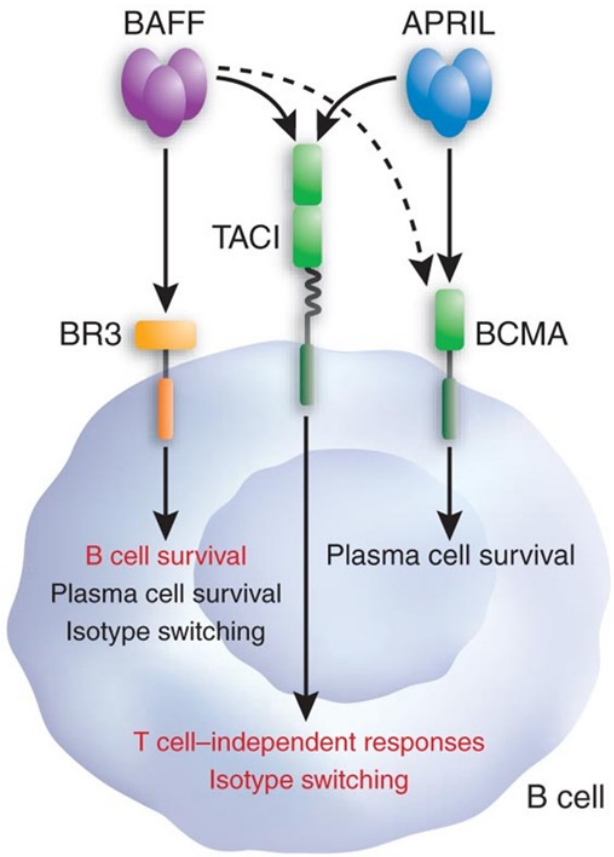
Irina Murakhovskaya, Bruno Fattizzo, Tarek Ebrahim, Kristen Sweet, Cathye Shu

- AIHA Orphan Drug designation
- **Vivacity-MG: Phase 2 trial in myasthenia gravis**
  substantial and rapid reductions in serum total and pathogenic IgG autoantibodies which were correlated statistically significantly with symptom improvement (P<0.0001).
- Open-label phase 2 UNITY trial
  positive results from the treatment of pregnant adults at high risk for severe hemolytic disease of the fetus and newborn (HDFN).
- ENERGY trial is 24-week Phase 2/3 RCT (N=111)
- Primary endpoint: durable response of improvement in Hgb
- Enrolment is ongoing.



Murakhovskaya I et al. *Blood.* 2022; 140 (suppl 1): 2443-2444.
Murakhovskaya et al *EHA 2021, NORD 2021*. Figure provided by Author.

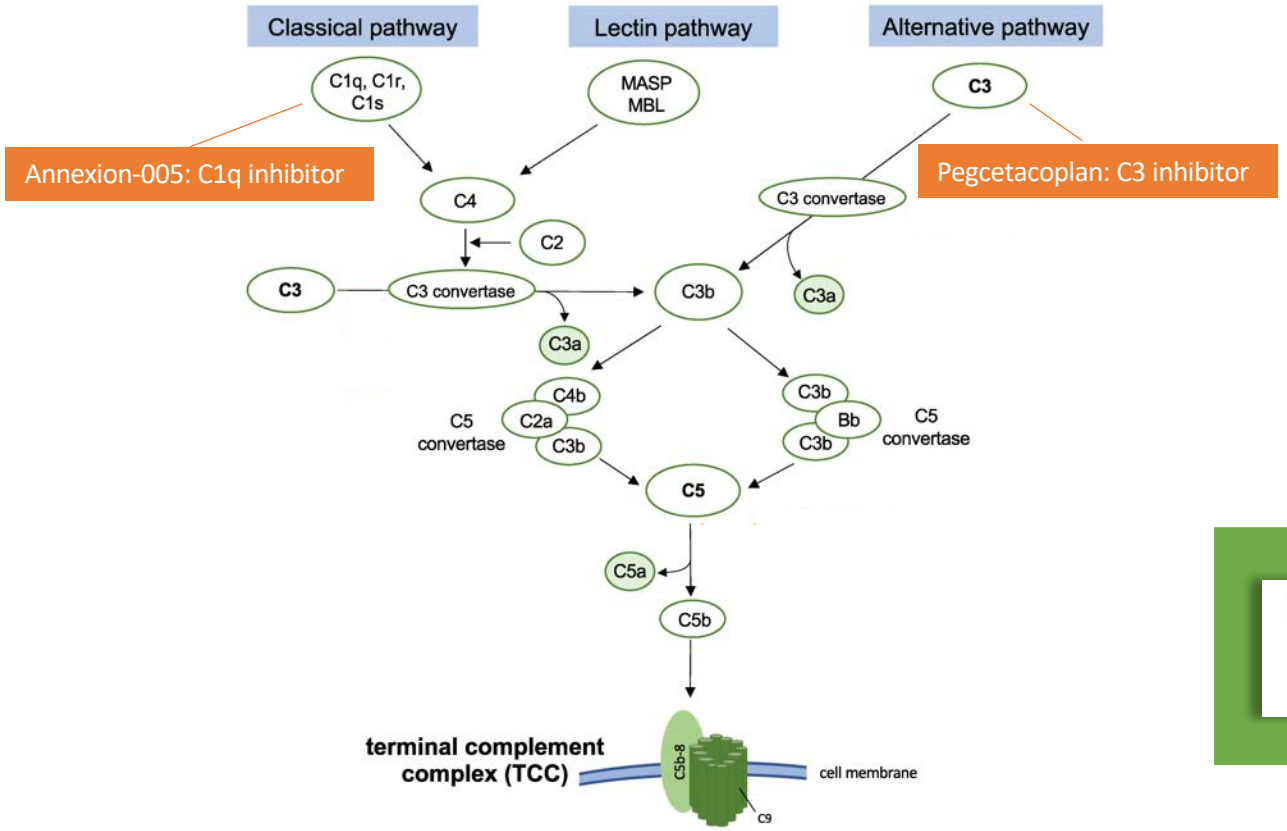
BAFF inhibition



- BAFF-mediated signaling needed for B-cell maturation, proliferation, and survival
- Ianalumab:
  - Monoclonal antibody against the BAFF receptor
  - B cell depletion via direct lysis of B cells
  - BAFF receptor blockade
- Povetacicept:
  - inhibits of BAFF and a proliferation inducing ligand APRIL
  - Reduces Antibody-Secreting Cells

Bowman SJ et al. Lancet 2021; 399; 161-171.
https://www.alpineimmunesciences.com/alpn-303/

Complement Inhibition in wAIHA



- ~20-50% wAIHA have complement involvement
- Complement involvement associated with lower hemoglobin and need for second- and third-line therapies

Inhibition of C3 with APL-2 Results in Normalisation of Markers of Intravascular and Extravascular Hemolysis in Patients with Autoimmune Hemolytic Anemia (AIHA)

Federico Grossi, MD, Merrill Kingman Shum, MD, Morie A. Gertz, MD, Eloy Roman, MD, Pascal Deschatelets, PhD, Mohamed Hamdani, MS, Frank Stout, Cedric G Francois, MD PhD

Grossi F et al. *Blood* 2018; 132 (suppl 1): 3623.
Barcellini W et al. *Blood* 2014; 124: 2930-2936.
Kuhn A et al. *Cells* 2023; 12(6): 887.

Clinical Pearls

- Clinical severity of wAIHA is influenced by antibody class, ability of antibodies to activate complement, and adequacy of bone marrow compensatory response
- DAT is cornerstone of diagnosis but can be negative in 5-10% cases
- Identification of secondary etiologies is essential as therapy can be different

Clinical Pearls

- First line therapy includes steroids with slow taper to prevent relapse
- Rituximab is the preferred second line therapy and should be considered in first line in select cases
- Erythropoietin can be effective therapy in patients with inadequate erythropoietic response

Clinical Pearls

- Many complications associated with AIHA
- Thrombosis is common and thromboprophylaxis is important in high-risk situations
- Infectious complications are often iatrogenic and should be attentioned
- New therapeutic agents directed at pathogenic mechanism of the disease (B-cell and plasma directed therapy, IgG reduction, phagocytosis inhibition) are in progress