Klinik für Hämatologie und Stammzelltransplantation
Universitätsmedizin Essen
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Therapie der Immunhämolysen – Aktuelle Empfehlung und Ausblick an Hand von Fallbeispielen

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THE DIFFERENTIAL DIAGNOSIS OF HAEMOLYTIC ANAEMIAS

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The differential diagnosis of haemolytic anaemias is difficult. It requires a wide clinical knowledge, complete command of a wide range of laboratory techniques and imagination. However, it is possible to base a system for differential diagnosis on no more than five basic tests. These are:—

1. Examination of a properly stained thin blood film, stained so that the cells are orange, but show polychromasia as a greyish tinge. This requires a buffered diluting fluid which has been carefully tested. Smears too thick, or stained dull grey, are quite useless, and it is usually much easier to obtain good staining with Leishman's stain (from British Drug Houses) than from any other brand, or from other Romanowsky stains such as Giemsa or Wright's stain (Discombe, 1950). A well-stained film may indicate spherocytosis, target cells, hypochromic cells, burr cells, or other odd forms. One should remember that severe carbon dioxide retention, or other acidosis, will make cells increase in diameter by as much as 1 μ, while obstructive jaundice causes target cells to appear.

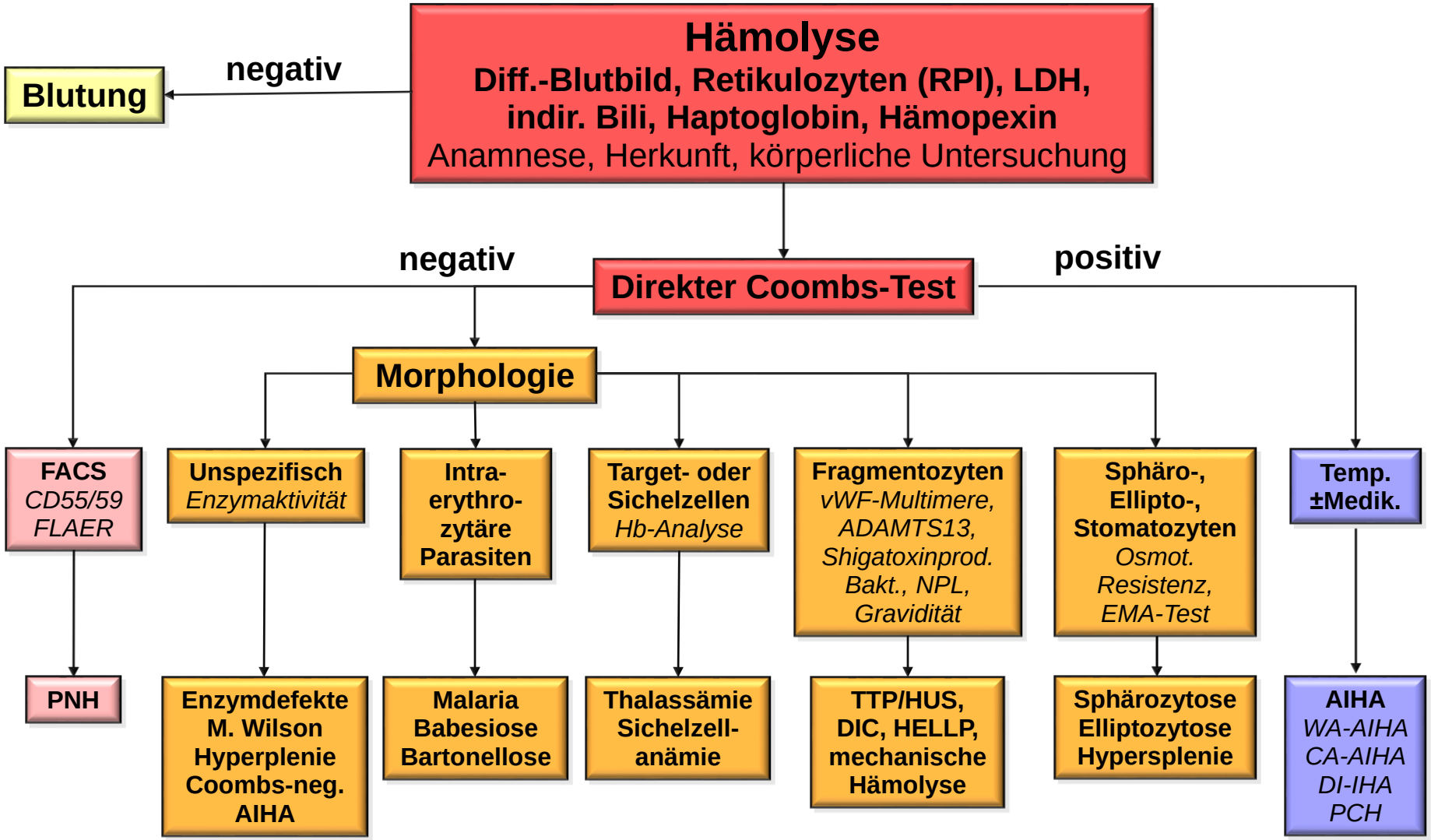
liberated into the blood stream and leaked into the urine; this is usually *paroxysmal nocturnal haemoglobinuria* (P.N.H.). Of course, stringent precautions must be taken against contamination, but contaminating iron is usually in irregular lumps, not the tiny spherical granules of haemosiderin.

4. The direct antiglobulin test should be performed on cells which have been allowed to cool to about 4°C. in contact with their serum, and the washed cells should be tested with antiglobulin serum at one, two, four and possibly eight times the concentration normally used for the demonstration of Rhesus antibodies. If positive, the test should be repeated using cells which have been taken in a warm syringe and at once washed with large volumes of saline previously warmed to 37°C., and with normal cells incubated in the patient's serum obtained from blood which has never been allowed to cool below 37°C., so that the quality and quantity of the antibody may be further assessed.

5. The only common haemoglobinopathies are those causing sickling and thalassaemia. The former is quickly detected by mixing cells with

Discombe, *Postgrad Med J*. 1959; 35:488-493.

DD hämolytische Anämie



Diagnostik hämolytischer Anämien

Differential-Blutbild mit Retikulozyten

- ***Erythrozytenmorphologie*** (z. B. Anisozytose, Polychromasie, Fragmentozyten, Sphärozyten, Target-Zellen, Sichelzellen, Parasiten, Erythrozyten-Agglutination)
- ***Normochrom, normozytär***; bei Retikulozytose, begleitendem Folsäure- oder Vitamin B_{12}-Mangel: MCV↑ (DD: Kälteagglutinine); bei Eisenmangel: MCV↓
- ***Zeitliche Verzögerung der Retikulozytose*** (~Tage), hämatopoetische Insuffizienz durch Grunderkrankung (Leukämie, NHL, PRCA, Parvovirus B19) oder laufende Chemotherapie

Lactatdehydrogenase (LDH) ↑

- Isoenzyme LDH-1 und LDH-2
- ***Korrelation mit Erythrozytendestruktion*** (500-1000 U/l: 3x; > 1000 U/l: 4x)

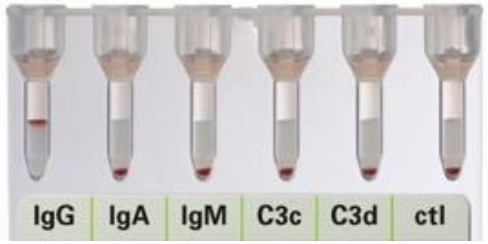
Bilirubin ↑

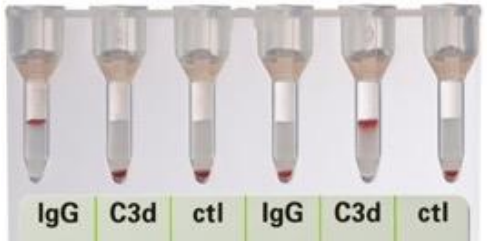
- Unkonjugiertes Bilirubin, Abhängigkeit von der Leberfunktion

Diagnostik hämolytischer Anämien

- **Haptoglobin ↓**
  - ***Sensitiver Parameter***, bindet freies Hb mit weiterem Abbau in der Leber, Abfall bei intravasaler Hämolyse oder Erschöpfung des RES
  - ***90%ige Spezifität für Hämolyse in Kombination mit LDH↑***
  - Akute-Phase-Protein → Korrelation mit CRP (Infektion, Infarkt, Tumore)
  - Erniedrigt bei Leberfunktionsstörungen, kongenitaler Hypo- oder Ahaptoglobinämie (1‰-30%)
  - Hämolyse transfundierter EKs intravasal innerhalb von 24h (bis zu 30%!)
- **Hämopexin ↓**
  - Bindet freie Häm-Gruppen und -Derivate; Abfall erst bei Erschöpfung von Haptoglobin → Hinweis auf ***Schwere der Hämolyse***
- **Direkter (monospezifischer) Antiglobulin-Test (Coombs)**
- **Spezialdiagnostik**
  - Nach Verdachtsdiagnose: z. B. freies Hämoglobin, Hämosiderinurie, Hämoglobinelektrophorese, Enzymanalysen, vWF-Multimere, ADAMTS13, PNH-Diagnostik (FACS), osmotische Resistenz, EMA-Test

(Monospezifischer) Coombs-Test (DAT)





- **Nachweis von:**
  - ***IgG, IgA,*** IgM
  - ***Komplement C3d/C3c***
- **Physiologisches Vorkommen von IgG auf Erythrozyten**
  - Wichtig für Transport von Immunkomplexen
- **0,3-8% hospitalisierter Patienten: *Falsch positiver DAT* !**
  - Mögliche Ursache z. B. Hypergammaglobulinämie
- **1-10% aller AIHA: *Falsch negativer DAT***
  - Durchflusszytometrie
- **Titer vs. Hämolyse, *Avidität***

Modifiziert nach *Wintrobe's Clinical Hematology*, 12th Edition. 2009.

Patientin #1, 39 Jahre

Hämatologie

Leukozyten	19.70
Erythrozyten	1.80
Hämoglobin	6.5
Hämatokrit	0.183
MCV	101.7
MCH	36.1
MCHC	35.5
Thrombozyten	129
Thrombozyten	129
Ery.verteilungsbreite (SD)	56.2
Ery.verteilungsbreite (VK)	26.9
Thromb.vert.breite	12.2
MPV	11.3
Thrombocyten >12fl	33.2
Thrombokrit	0.12
IPF(%)	3.9
IPF (#)	5.0
Retikulozyten-Parameter	
Retikulozyten%	15.64

Klinische Chemie

Natrium	141	mmol/l	136 - 145
Kalium	4.1	mmol/l	3,5 - 5,1
Chlorid	102	mmol/l	98 - 107
Calcium	2.27	mmol/l	2,08 - 2,65
Phosphat (anorg.)	4.4	mg/dl	2,7 - 4,5
S-Kreatinin (Jaffé)	1.30	mg/dl	0,9 - 1,3
S-Kreatinin (enzym.)	1.34	mg/dl	0,67 - 1,17
eGFR (CKD-EPI, Krea enzym.)	66.3	ml/min/1 ...	60
eGFR (MDRD, Krea enzym.)	59.0	ml/min/1 ...	60
eGFR (MDRD, Krea Jaffé)	>60.0	ml/min/1 ...	60
Harnstoff-N	17.3	mg/dl	6 - 19,8
Harnsäure	9.9	mg/dl	3,5 - 7,2
Eisen	210	µg/dl	60 - 175
CK	757	U/l	46 - 171
Bilirubin (gesamt)	2.0	mg/dl	0,3 - 1,2
Bilirubin (direkt)	0.44	mg/dl	<0,2
GOT (ASAT)	180	U/l	<50
GPT (ALAT)	38	U/l	<50
alkal. Phosphatase (AP)	53	U/l	40 - 130
		U/l	<55
		U/l	100 - 247
		U/ml	4,9 - 11,9
		U/l	12 - 53
		g/dl	6,4 - 8,3
		g/dl	3,2 - 4,8
		mg/dl	<0,5
		mg/l	1 - 2,4
		g/l	0,4 - 2,4
		µg/l	22 - 322
		g/l	2,15 - 3,65
Transfer.-Sättigung	70.9	%	16 - 45

Immunhämatologischer Befund

Merkmal	Ergebnis
Blutgruppe	0 Rh positiv ccD.ee Kell negativ
Antikörpersuchtest	positiv
Antikörper	Anti-Wr(a)
Direkter Coombstest	positiv
Monospezifischer Direkter Coombstest	AHG ++++ algG ++++ aC3d -

Autoimmunhämolysen (AIHA)

Variable	Warm-Antibody Type (wAIHA)	Cold Agglutinin Disease (cAIHA/CAD)	Secondary Cold Agglutinin Syndrome (CAS)	Paroxysmal Cold Hemoglobinuria (PCH)	Mixed Type
Incidence and age at onset	5 to 10 cases/1 million persons/yr; occurs at any age but frequently in the elderly	0.45 to 1.9 cases/1 million persons/yr; occurs mainly in the elderly	Rare, any age	Rare in children, ultrarare in adults	Rare, depending on definition
Cause	Unknown in < 50% of cases; secondary in ≥ 50% of cases	Low-grade lymphoproliferative bone marrow disorder	Secondary	Postviral (in children); tertiary syphilis, hematologic cancers (in adults)	Unclear
Pathogenesis					
Autoantibody	Warm-reactive, panreactive, polyclonal	Cold agglutinin, anti-I (in rare cases, anti-Pr or anti-IH), monoclonal	Cold agglutinin, anti-I or anti-i, polyclonal or monoclonal	Non-agglutinating, biphasic anti-P, polyclonal	Both warm- and cold-reactive antibodies
Immunoglobulin class	IgG (in rare cases, IgM or IgA)	IgM (in rare cases, IgG)	IgM or IgG	IgG (in rare cases, IgM)	IgG plus IgM
Complement activation	Frequently none; Classical pathway (++), Terminal pathway (+)	Classical pathway (+++), Terminal pathway (+)	Classical pathway (+++), Terminal pathway (+)	Classical pathway (+++), Terminal pathway (+++)	Present, details not established
Predominant type of hemolysis	Extravascular (mainly in the spleen)	Extravascular (mainly in the liver); intravascular (in acute exacerbations)	Extravascular (mainly in the liver); intravascular (in acute exacerbations)	Intravascular	Not established
Typical findings					
Direct antiglobulin test	IgG positive; C3d negative or positive; In rare cases, IgA or IgM positive	C3d positive; In rare cases, IgG or IgM positive; IgA negative	C3d positive; IgG positive or negative; In rare cases, IgM positive; IgA negative	C3d positive; In rare cases, IgG or IgM positive; IgA negative	IgG and C3d positive; In rare cases, IgM positive; IgA negative
Cold agglutinin	Absent	High titer	High titer	Absent	High titer

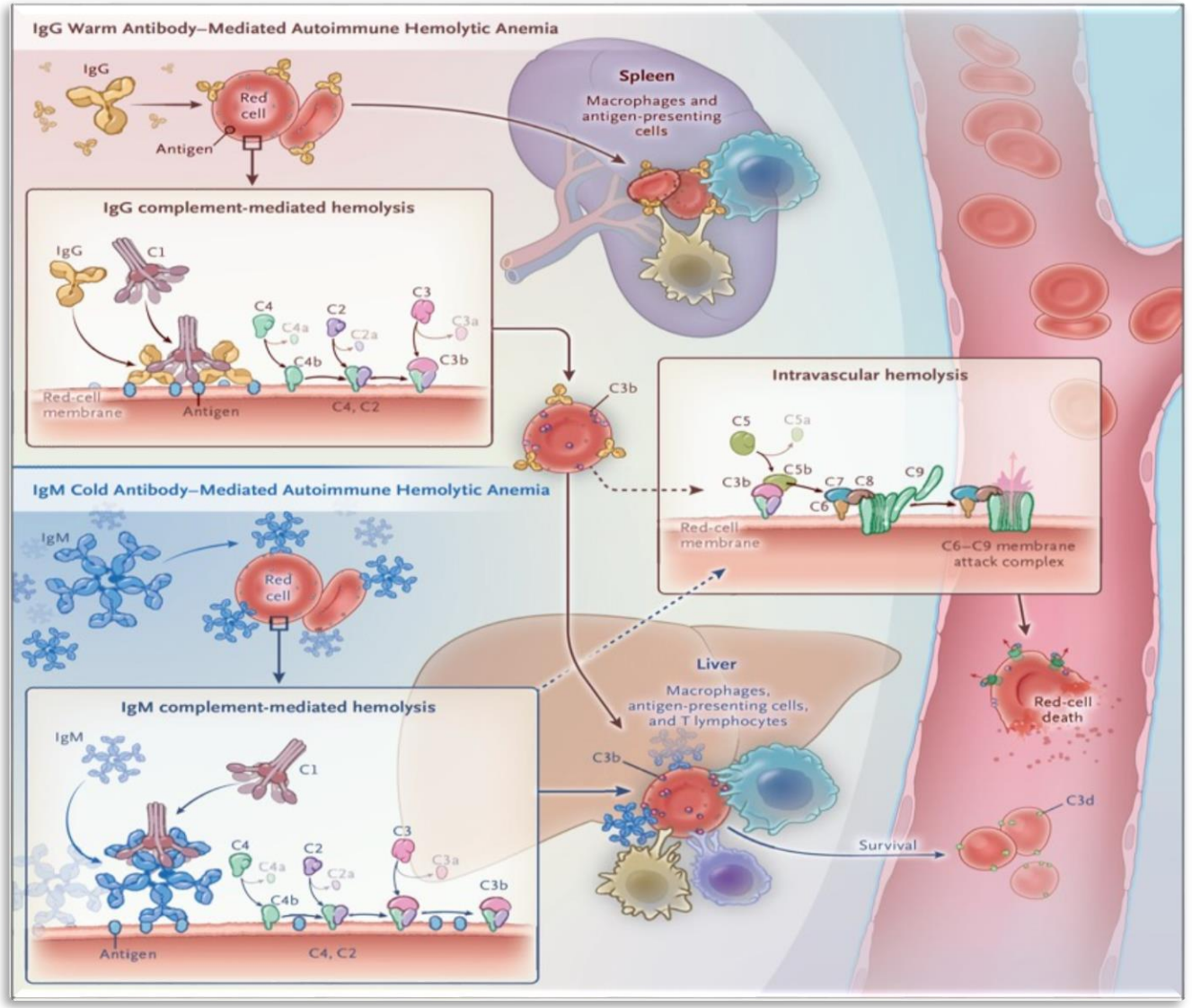
Berentsen S, et al. *N Engl J Med*. 2021;385:1407-1419.

Pathophysiologie von AIHA/Hämolysen

Extravasale Hämolyse
17 ml RBCs/h =
410 ml RBCs/24h

- ***Bilirubin***↑
- Retikulozyten↑
- Haptoglobin↓
- LDH↑

- Gallensteine
- Splenomegalie
- Eisenüberladung



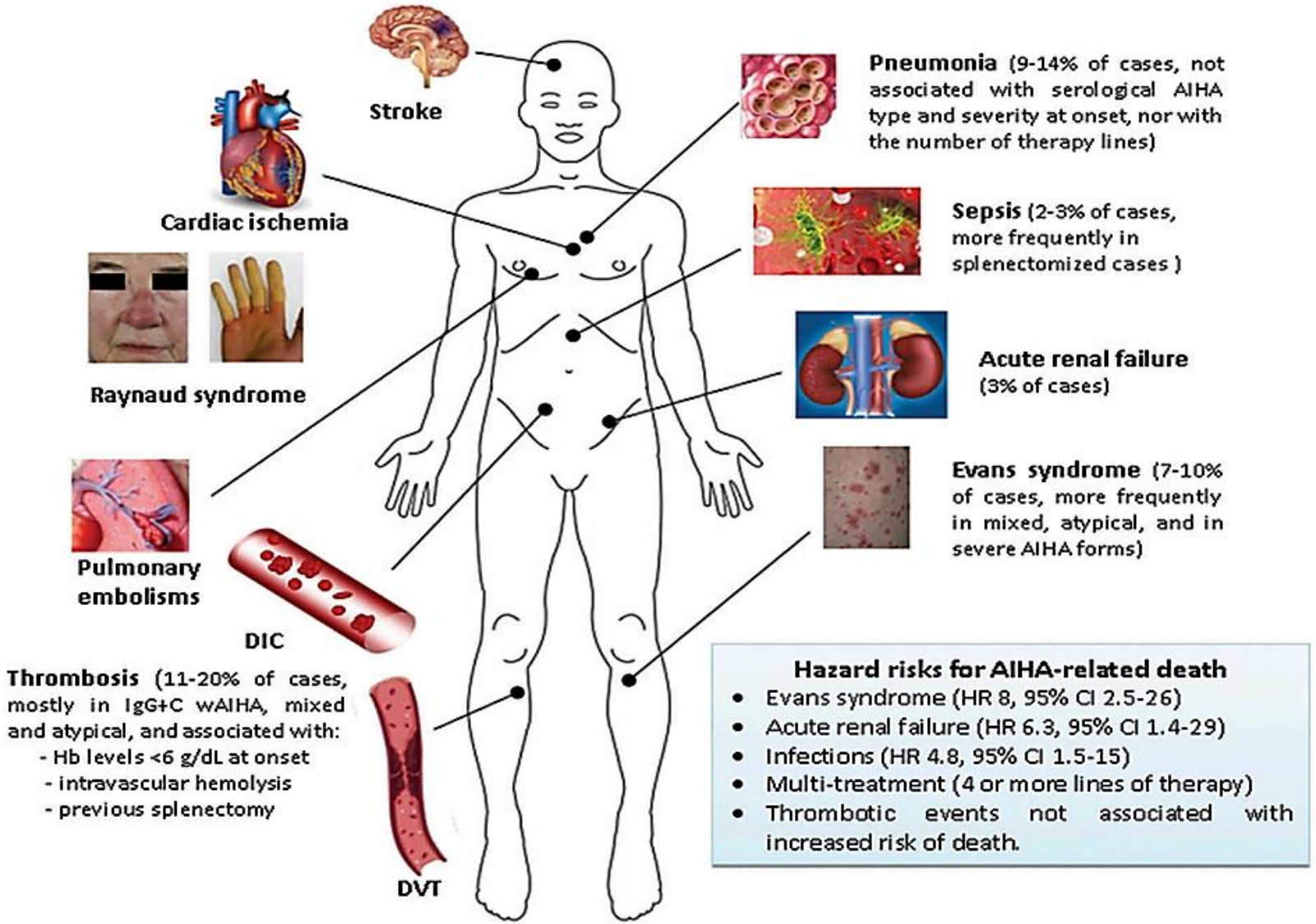
Intravasale Hämolyse
200 ml RBCs/h

- ***LDH***↑
- Freies Hämoglobin↑
- Haptoglobin↓
- Bilirubin↑
- Retikulozyten↑

- Hämoglobinurie/ Hämosiderinurie

Berentsen S, et al. *N Engl J Med*. 2021;385:1407-1419.

AIHA: Klinik und Komplikationen



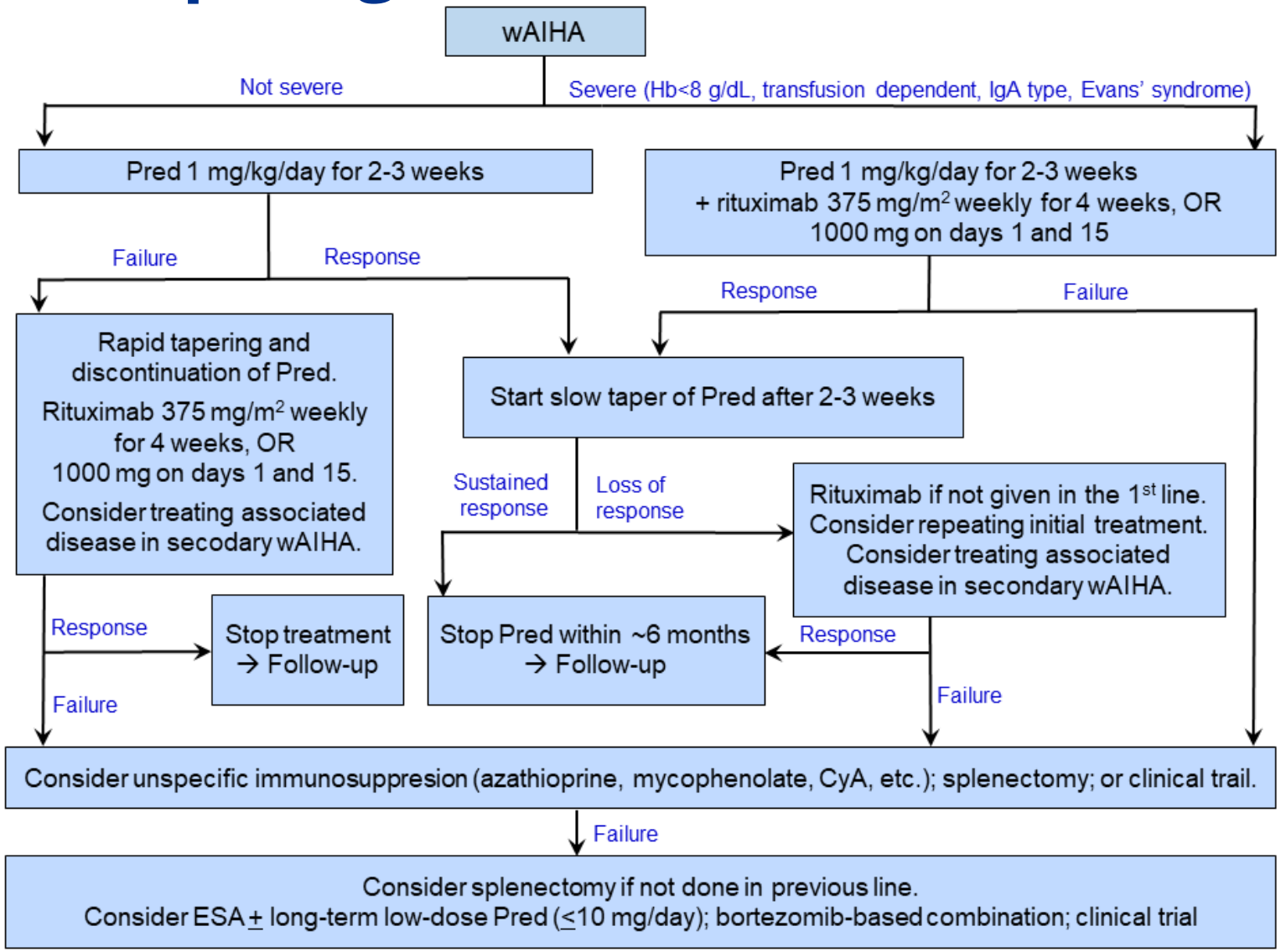
Barcellini W, et al. *Expert Rev Clin Immunol*. 2018;14:857-872.

Aktuelle Therapieoptionen der wAIHA

Treatment	Dose Schedule	Response Rate, %	Time to Response	Comments	Side Effects/Cons
Predniso(lo)ne	1 to 2 mg/kg per day for 3 to 4 wk	80 to 90 (estimated cure rate in 20 to 30 only)	7 to 25 d	▪ Gradual tapering during a period no shorter than 4 to 6 mo ▪ Steroid boluses may be used for acute severe forms (ie, methylprednisolone 250 mg IV daily for 3 d)	Diabetes mellitus, hypertension, peptic ulcer, osteoporosis, adrenal suppression, myopathy, psychosis, delayed wound healing, insomnia, menstrual irregularity, weight gain
IVIg	0.4 g/kg per day for 5 days	30 to 40	1 to 5 d	▪ Responses usually last for about 3 wk ▪ Advised in addition to steroids in critically ill patients, particularly during severe infections/sepsis	Infusion reactions particularly in patients with IgA deficiency, thromboembolic events, acute renal failure, increased serum viscosity
Rituximab	375 mg/m^2 per week for 4 wk	~80 (relapse-free survival of ~60 at 3 y)	3 to 6 wk	Other schedules include: ▪ low dose (100 mg weekly for 4 wk) in patients with nonsevere hemolytic anemia, and in the elderly ▪ 1 g days 1 and 15, particularly in wAIHA associated with other autoimmune diseases	▪ Infusion reactions, late-onset neutropenia, hypo-gammaglobulinemia, reactivation of underlying infections ▪ Regarding HBV reactivation, lamivudine prophylaxis up to 18 mo is recommended for anti-HBc Ab and/or anti-HBs Ab1 patients (if not vaccinated)
Splenectomy	n/a	~80 (curative rate 20 to 50)	7 to 10 d	Discouraged for patients older than 65 to 70 y with cardiopulmonary disorders, thrombotic risk, immunodeficiencies, lymphoproliferative diseases, and systemic autoimmune conditions	Possible complications include serious infections and thrombotic events
Azathioprine	2 to 4 mg/kg per day	~60 (usually with steroids)	1 to 3 mo	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 (50 mg daily, increase up to 150 mg in the absence of neutropenia), liver toxicity
Cyclosporine	2.5 mg/kg, twice per day	~60	1 to 3 mo	Advised as steroid-sparing agent, particularly in AIHAs secondary to autoimmune conditions, Evans syndrome, and in case of features of BMF	Kidney damage, hypertension, infections, nausea, excessive hair growth
Cyclo-phosphamide	50 to 100 mg per day or 800 mg/m^2 IV monthly, 4 to 5 cycles	50 to 70	2 to 6 wk	May be considered in cases of highly hemolytic disease, particularly if secondary to connective tissue disorders and lymphoproliferative diseases	Myelosuppression, infections, urotoxicity, secondary malignancy, teratogenicity, infertility
Mycophenolate	500 mg, twice per day	25 to 100 (small case series)	1 to 3 mo	Mainly used in the pediatric setting	Nausea, headache, diarrhea
Danazol	200 mg, 3 times per day	20 to 50	1 to 3 mo	Steroid-sparing properties	Androgenic effects (to be avoided in men with prostatic adenoma or carcinoma), liver toxicity

Barcellini W, et al. *Blood*. 2021;137:1283-1294.

wAIHA: Therapiealgorithmus



Jäger et al. *Blood Rev*. 2020 May;41:100648; Berentsen S et al. *Front Immunol*. 2023;14:1180509.

wAIHA: Therapie – Allgemeine Maßnahmen

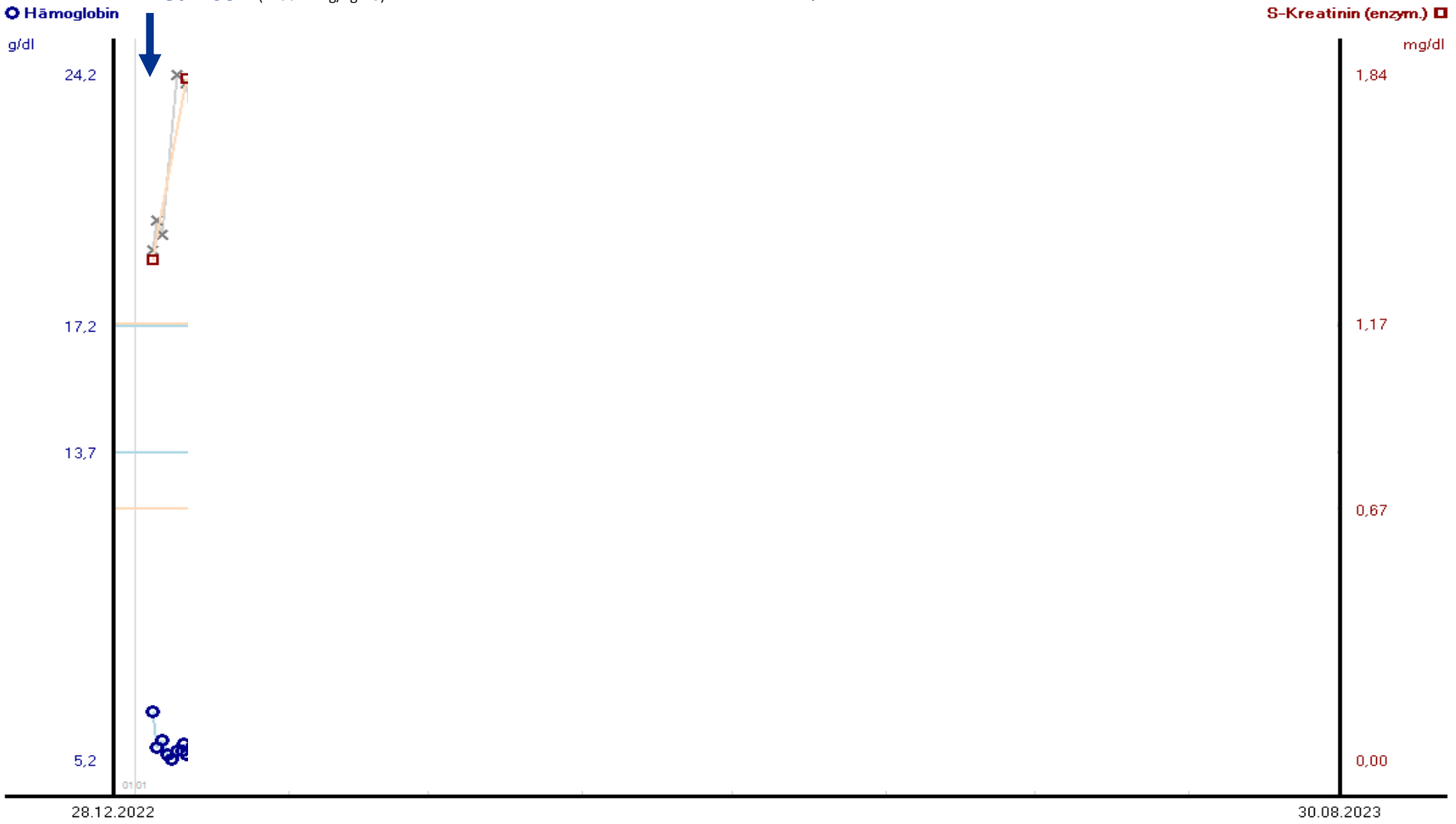
- ***Supplementierung mit Folsäure*** (5 mg/Tag); ggf. auch Vitamin B12 und Eisen (sofern Mangel)
- ***Prophylaxe einer Steroidtoxizität*** (Vitamin D, PjP-Prophylaxe, Antimykotika)
- ***Transfusionen*** (EKs) sofern klar indiziert, Risiko für Alloantikörper, Transfusionsreaktionen
- Ausreichende ***Hydration*** bei kritischer Hämolyse
- ***Konsequente Thromboseprophylaxe*** bei akuter (kritischer) Hämolyse, stationären Patienten, zusätzliche Risikofaktoren (z.B. Splenektomie, Immobilisation, fieberhafte Infektionen, hereditäre Thrombophilie, operative Eingriffe)
- Frühzeitige und konsequente ***Antibiose bakterieller Infektionen*** zur Vermeidung infektgetriggerter hämolytischer Krisen

Jäger et al. *Blood Rev*. 2020 May;41:100648; Berentsen S et al. *Front Immunol*. 2023;14:1180509.

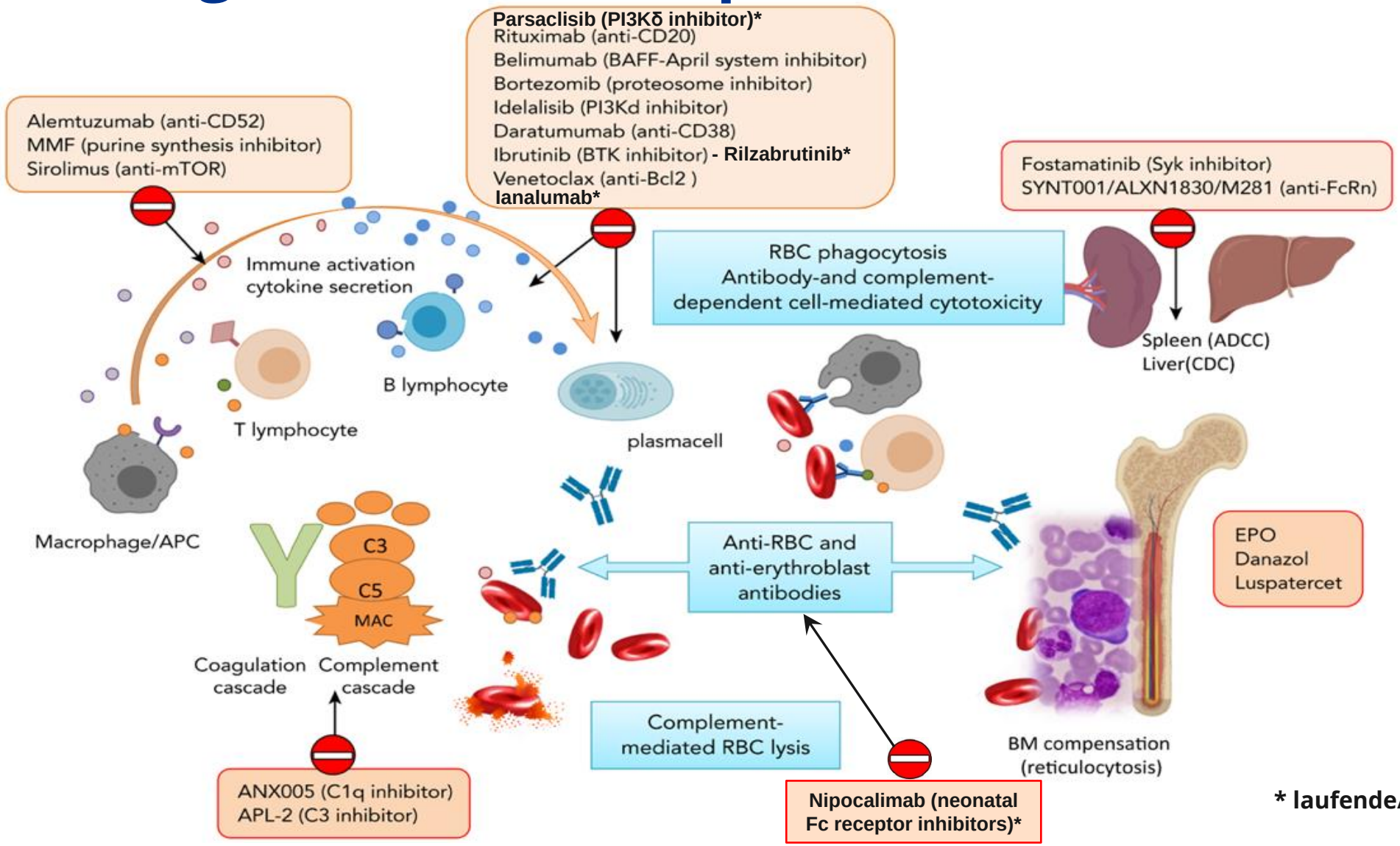
Patientin #1, 39 Jahre

Prednison (initial 1 mg/kg KG) →

LDH_{max} 3550 U/l



(Neue) zielgerichtete Therapien der wAIHA



*** laufende/geplante Studien**

Barcellini & Fattizzo, *Blood*. 2021;137:1283-1294;
Barcellini & Fattizzo, *Transfusion Medicine Reviews*. 2022;35:175-180.

Patientin #2, 61 Jahre

Hämatologie

Leukozyten	8.41		
Erythrozyten	3.01		
Hämoglobin	10.4		
Hämatokrit	0.297		
MCV	98.7		
MCH	34.6		
MCHC	35.0		
Thrombozyten	396		

Kapillarzonenelektrophorese

Albumin (Elektrophorese)	68.6	%	55,8 - 66,1
Alpha 1-Globulin	4.5	%	2,9 - 4,9
Alpha 2-Globulin	5.4	%	7,1 - 11,8
Beta-Globulin	10.6	%	8,4 - 13,1
Gamma-Globulin	10.9	%	11,1 - 18,8

Immunglobuline

IgA-Serum	1.6	g/l	0,4 - 3,5
IgG-Serum	7.4	g/l	6,5 - 16
IgM-Serum	3.07	g/l	0,5 - 3
IgE-Serum	36.5	IU/ml	<158
Monokl. IgG (S)	negativ		negativ
Monokl. IgA (S)	negativ		negativ
Monokl. IgM (S)	+		negativ
Monokl. geb./freies Kappa	+		negativ
Monokl. geb./freies Lambda	negativ		negativ
Freie Leichtkette Kappa	8.71	mg/l	3,3 - 19,4
Freie Leichtkette Lambda	10.7	mg/l	5,71 - 26,30
Ratio Kappa/Lambda	0.814		0,26 - 1,65

Klinische Chemie

Natrium	143	mmol/l	136 - 145
Kalium	4.5	mmol/l	3,5 - 5,1
Calcium	2.20	mmol/l	2,08 - 2,65
Phosphat (anorg.)	3.8	mg/dl	2,7 - 4,5
S-Kreatinin (Jaffé)	0.79	mg/dl	0,6 - 1,1
S-Kreatinin (enzym.)	0.73	mg/dl	0,51 - 0,95
eGFR (CKD-EPI, Krea enzym.)	85.5	ml/min/1 ...	60
eGFR (MDRD, Krea enzym.)	>60.0	ml/min/1 ...	60
	>60.0	ml/min/1 ...	60
	16.0	mg/dl	6 - 19,8
	6.1	mg/dl	2,6 - 6,0
	180	µg/dl	45 - 170
	35	U/l	34 - 145
	4.9	mg/dl	0,3 - 1,2
	1.04	mg/dl	<0,2
	39	U/l	<35
	19	U/l	<35
	84	U/l	55 - 105
	22	U/l	<35
	702	U/l	120 - 247
	7.54	U/ml	4,9 - 11,9
	49.0	U/l	12 - 53
	6.75	g/dl	6,4 - 8,3
	4.7	g/dl	3,2 - 4,8
	<0.4	mg/dl	<0,5
	108	pg/ml	125
Beta 2-Mikroglobulin	1.3	mg/l	1 - 2,4
Haptoglobin	<0.01	g/l	0,4 - 2,4
Hämopexin	0.51	g/l	0,5 - 1,15
Ferritin	319	µg/l	10 - 291
Transferrin	2.0	g/l	2,5 - 3,8
Transfer.-Sättigung	63.8	%	16 - 45
sTFR (lösl. Transferrinrezeptor)	4.27	mg/l	0,76 - 1,76

Patientin #2, 61 Jahre

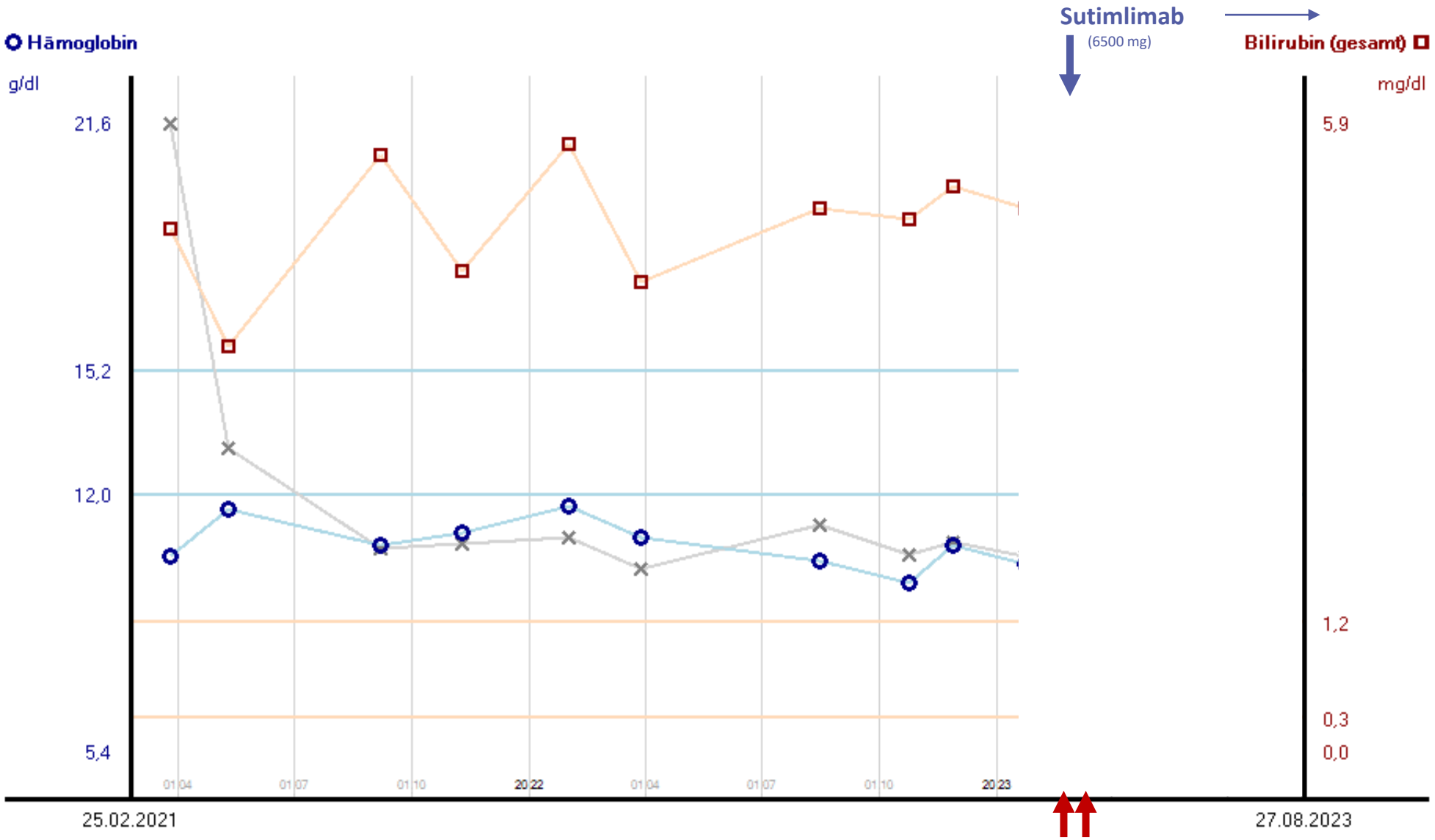
Immunhämatologischer Befund

Merkmal	Ergebnis
Blutgruppe	unklar Rh unklar Kell unklar
Antikörpersuchtest	positiv
Direkter Coombstest	unklar
Monospezifischer Direkter Coombstest	aC3c entfällt aC3d entfällt aIgA entfällt aIgG entfällt aIgM entfällt
Rh-Formel	unklar

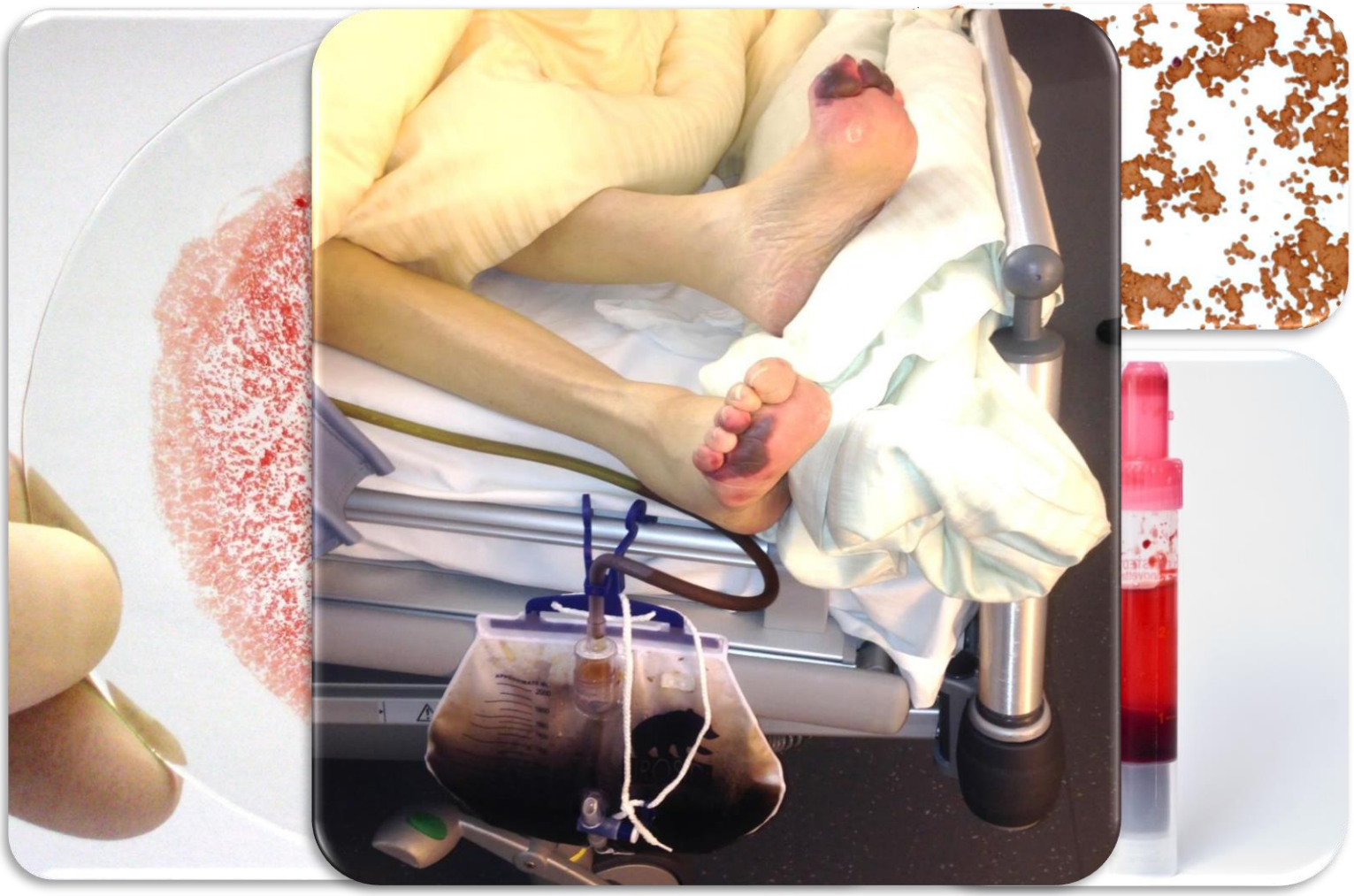
Immunhämatologischer Befund

Merkmal	Ergebnis
Direkter Coombstest	positiv
Monospezifischer Direkter Coombstest	aC3c + aC3d ++++ aIgA - aIgG - aIgM +++
Kälte Agglutinine (4°C)	Titer: 128
Kälte Agglutinine (30°C)	Titer: 2
Kälte Agglutinine (37°C)	Titer: 0

Patientin #2, 61 Jahre



Kälteagglutininerkrankung (CAD)



Röth et al., *Transfusion*. 2022;62:51-59.

Röth & Dührsen. *Eur J Haematol*. 2010;84(1):91.

Kälteagglutininerkrankung (CAD)

- ***Primär (CAD):*** ***Autoimmunerkrankung*** mit zugrunde liegender ***lympho-proliferativer B-Zell-Erkrankung*** (MYD88 L265P negativ)[1–4]
- ***Sekundär:*** ***Kälteagglutininsyndrom (CAS)*** – *bei* ***malignen Erkrankung oder akuten Infektionen***[1,2]
- ***90%*** der Kälteagglutinine sind ***IgM-kappa*** und binden an Oberflächenantigene (I) von Erythrozyten bei ***≤37°C***[2,4,5]
- ***„Kälte“*** bezieht sich primär auf die ***Biologie/Bindungseigenschaft der Antikörper*** und nicht auf die Klinik der Patienten
- ***IgM-Antigenkomplex aktiviert den klassischen Reaktionsweg des Komplementsystems***[2]

1. Berentsen S et al. *Hematology*. 2007;12(5):361-370. 2. Berentsen S, et al. *Hematol Oncol Clin North Am*. 2015;29(3):455-471. 3. Randen U et al. *Haematologica*. 2014;99(3):497-504. 4. Röth A et al. *Eur J Haematol*. 2010;84(1):91. 5. Gertz MA. *Br J Haematol*. 2007;138(4):422-429.

CAD: Pathophysiologie

Eigenständige lymphoproliferative B-Zell-Erkrankung

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Leukemia

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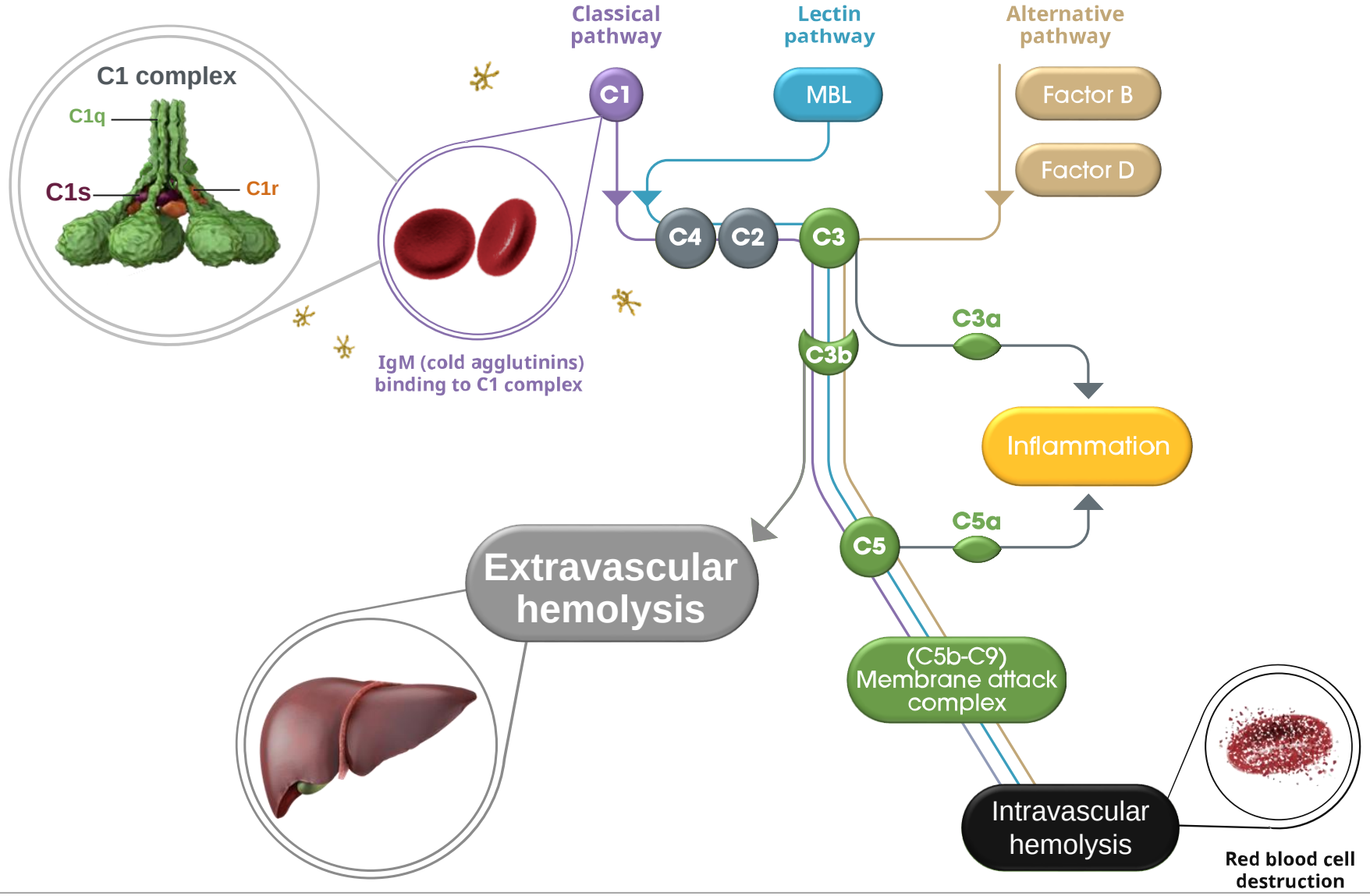
LYMPHOMA

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

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*

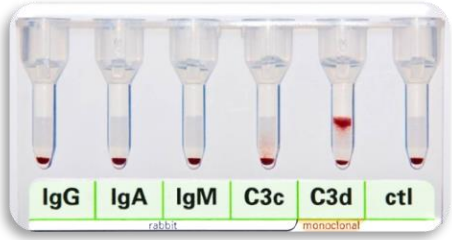
Randen U et al. *Haematologica*. 2014;99(3):497-504; Alaggio et al. *Leukemia* (2022) 36:1720-1748.

CAD: Pathophysiologie



Röth et al., *N Engl J Med*. 2021;384(14):1323-1334.

CAD: Diagnosestellung



Zwingend erforderlich:

- ***Chronische Hämolyse***
- ***Monospezifischer DAT***

  stark positiv für C3d
- ***Titer ≥ 1:64 bei 4 °C***
- ***Kein Anhalt für eine maligne***

  Erkrankung

Ergänzend sinnvoll:

- ***Monoklonales IgMκ*** im Serum (selten IgG, IgA oder λ)
- ***κ/λ-Ratio > 3,5*** (selten <0,9) der B-Lymphozytenpopulation (KM)
- ***Nachweis einer lymphoproliferativen B-Zell-Erkrankung*** (Histologie)
- ***C4-Spiegel***

Probenmaterial muss bis zur Analyse bei 37°C bis 38°C gehalten werden!

Berentsen et al. *J Blood Med*. 2019;10:93-103.

Röth & Dührsen. *Eur J Haematol*. 2010;84(1):91.

CAD: Klinische Präsentation

- **Hämolyse/Hämolytische Anämie**
- **Fatigue**
- **Dyspnoe**
- **Hämoglobinurie**
- **Ikterus**

Komplement-vermittelte Symptome[1-4]

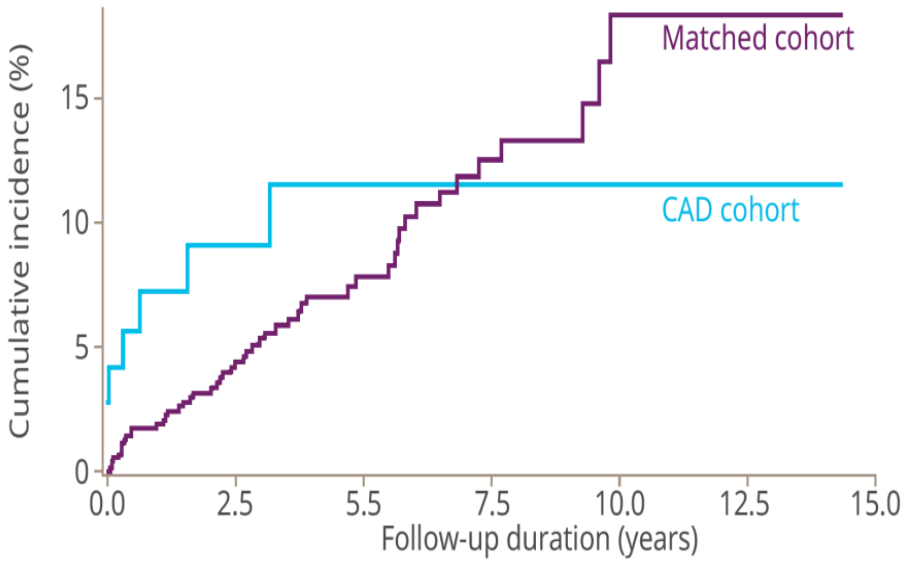
- **Akrozyanose**
- **Raynaud-Phänomen**
- **Livedo reticularis**
- **Gangrän**

Kälteagglutinin-vermittelte Symptome[5-7]

1.Berentsen S. *Br J Haematol*. 2018;181(3):320-330. 2. Röth A and Dührsen U. *Eur J Haematol*. 2010;84(1):91. 3. Onishi S, et al. *J Cardiol Cases*. 2016;15(2):43-45. 4. Jäger U, et al. *Blood*. 2019 Feb 28; 133(9): 893–901. 5. Kohlert S, et al. *J Otolaryngol*. 2019;48(1):52. 6. Jeskowiak A and George T. *N Engl J Med.* 2013; 369:e1. 7. Sharma K and Patel A. *N Engl J Med.* 2019;381:e27.

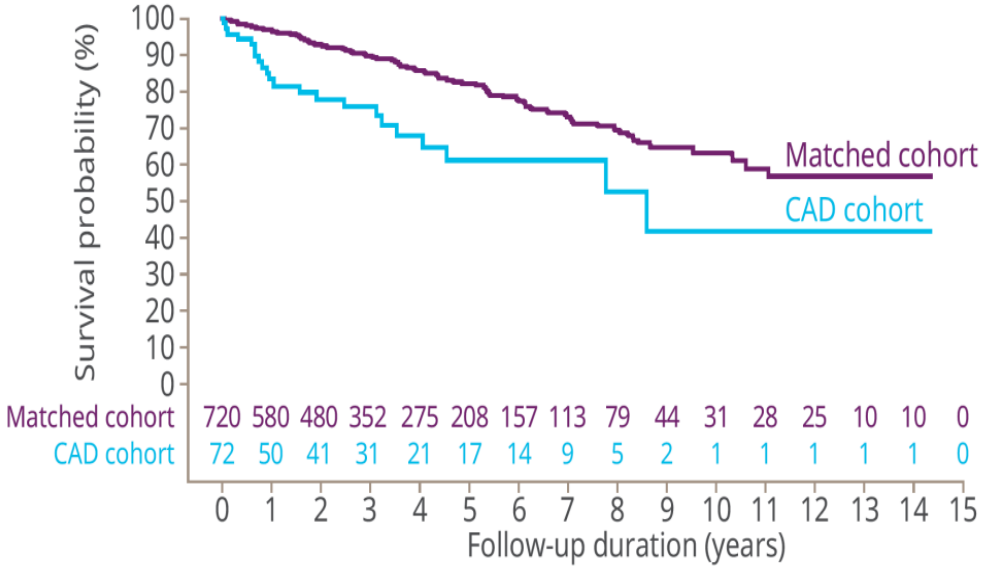
CAD: Thrombosen und Mortalität

Cumulative incidence of TE among patients with CAD and the matched comparison between 1999–2013



Years after diagnosis/ cohort entry	Cumulative incidence (95% CI)	
	CAD cohort	Matched cohort
1	7.22 (2.66–14.89)	1.90 (1.07–3.14)
3	9.06 (3.66–17.50)	5.33 (3.65–7.44)
5	11.54 (4.92–21.28)	7.80 (5.53–10.55)

Kaplan-Meier survival curve for patients with CAD and the matched comparison between 1999–2013



Years after diagnosis/ cohort entry	Survival probability	
	CAD cohort	Matched cohort
1	83.15%	97.71%
3	75.67%	89.83%
5	60.95%	82.11%

In 2013, the *prevalence of CAD was 1.26 per 100,000* and the *incidence rate was 0.18 per 100,000 person-years*

Bylsma et al. *Blood Adv*. 2019;3(20):2980-2985.

Novel Management of CAD/CAS…

TRANSFUSION MEDICINE ILLUSTRATED

Novel management of cold agglutinin disease

Paul M. Ness, William R. Bell, and R. Sue Shirey

Cold agglutinin disease is an uncommon form of autoimmune hemolytic anemia. In contrast to warm autoimmune hemolytic anemia, where patients typically respond to immunosuppressive drugs or splenectomy, the response of cold agglutinin disease to therapy is less predictable. Some cases of cold agglutinin disease result from an underlying lymphoproliferative disorder; the hemolytic anemia will sometimes respond to chemotherapy targeted to destroy the malignant clone in these cases. The majority of cases of cold agglutinin disease arise following an infection with *Mycoplasma pneumoniae* or a virus, such as Epstein-Barr virus. In these cases, the best therapy is to keep the patient warm until the disease remits spontaneously.

We took care of a patient with postviral cold agglutinin disease whom we wanted to keep in an environment heated to near body temperature; however the patient was unwilling to stay in the hospital (Bartholomew JR, Bell WR, Shirey RS. Ann Intern Med 1987;106:243–4). One of us (W.R.B.) solved this problem by procuring an environmental suit from the National Aeronautics and Space Administration. The suit maintains a warm environment by recirculating the patient's body heat. Filtered air is provided by either a bottled external source or a compressor; carbon dioxide diffuses through the chlorinated polyethylene wall of the suit. The suit allows ambulation and stair climbing. When necessary, a bed pan or urine bottle can be used inside the suit. In the figure, Dr. Bell is accompanying the patient out of the hospital. The patient was followed at home, and wore the suit for several days until the hemolysis abated.

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TRANSFUSION 2003;43:839.

SUBMISSION OF IMAGES

See Instructions for Authors for submission instructions. Submit images to:

Paul M. Ness, MD
Editor, **TRANSFUSION**
email: pness@jhmi.edu
Articles can be submitted directly online at:
http://transfusion.manuscriptcentral.com

Ness PM et al. *Transfusion.* 2003;43:839.

CAD: Therapie – Allgemeine Maßnahmen

- ***Vermeidung kalter Temperaturen*** (warme Bekleidung, Vermeidung von kalten Getränken, Eis, kalte Luft, kalte Infusionen/Transfusionen etc.)
- ***Supplementierung mit Folsäure*** (5 mg/Tag); ggf. auch Vitamin B12 und Eisen (sofern Mangel)
- Frühzeitige und konsequente ***Antibiose bakterieller Infektionen*** zur Vermeidung infektgetriggerter hämolytischer Krisen
- ***Transfusionen*** (EKs, kein Plasma) sofern indiziert (Extremität mit Zugang warm halten; Blut- bzw. Infusionswärmer)
- Ausreichende ***Hydration*** bei kritischer Hämolyse
- ***Konsequente Thromboseprophylaxe*** bei (kritischer) Hämolyse
- ***Steroide, Alkylantien, Interferon, Splenektomie nicht wirksam!***

Gertz. *Br J Haematol*. 2007;138:422-29; Berentsen et al. Hematology. 2007;12:361-70; Petz. *Blood Reviews*. 2008;22:1-15; Röth et al. *Eur J Haematol*. 2010;84:91; Berentsen et al. *Hematol Oncol Clin N Am*. 2015;29:455-71; Wouters et al. *Haemtologica*. 2015;100: 1388-95.

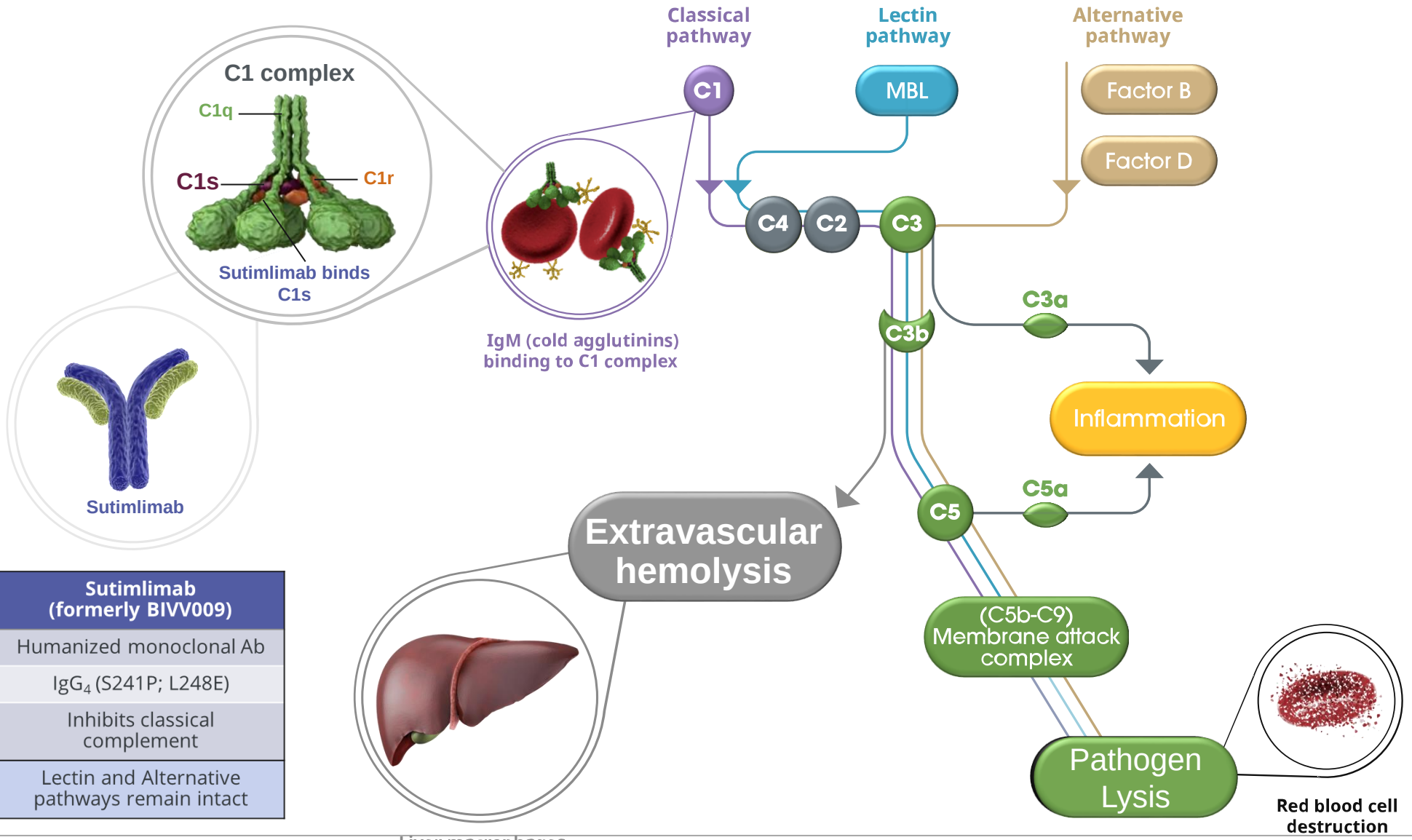
CAD: B-Zell-gerichtete Immunchemotherapien

Study/ publication	Drug(s) studied	Study design	Patients/ Courses of therapy, N	OR %	CR %	Hb increase, g/dL	Median response duration, Months	Toxicity
Berentsen et al. 2004	**Rituximab***	Prospective, non-randomized	27/37	**54**	**4**	**4.0**	**11 (observed)**	Low
Schöllkopf et al. 2006	**Rituximab***	Prospective, non-randomized	20/20	**45**	**5**	**3.1**	**6.5 (observed)**	Low
Berentsen et al. 2010	**Fludarabine* + Rituximab***	Prospective, non-randomized	29/29	**76**	**21**	**3.1**	**>66 (estimated)**	Significant
Berentsen et al. 2017	**Bendamustine* + Rituximab***	Prospective, non-randomized	45/45	**71**	**40**	**4.0**	**>>32 (observed)**	Relatively low, manage-able
Rossi et al. 2018	**Bortezomib***	Prospective, non-randomized	19/19	**32**	**16**	**2.9**	**16 (observed)**	Low
Berentsen et al. 2020	**Bendamustine* + Rituximab***	Follow-up, part of a larger study	45/45	**78**	**53**	Not re-evaluated	**>88 (estimated)**	Long-term: Low

*Off-Label bei CAD

Berentsen S. *Blood*. 2021;137:1295-1303.

CAD: Sutimlimab



Sutimlimab (formerly BIVV009)
Humanized monoclonal Ab
IgG_4 (S241P; L248E)
Inhibits classical complement
Lectin and Alternative pathways remain intact

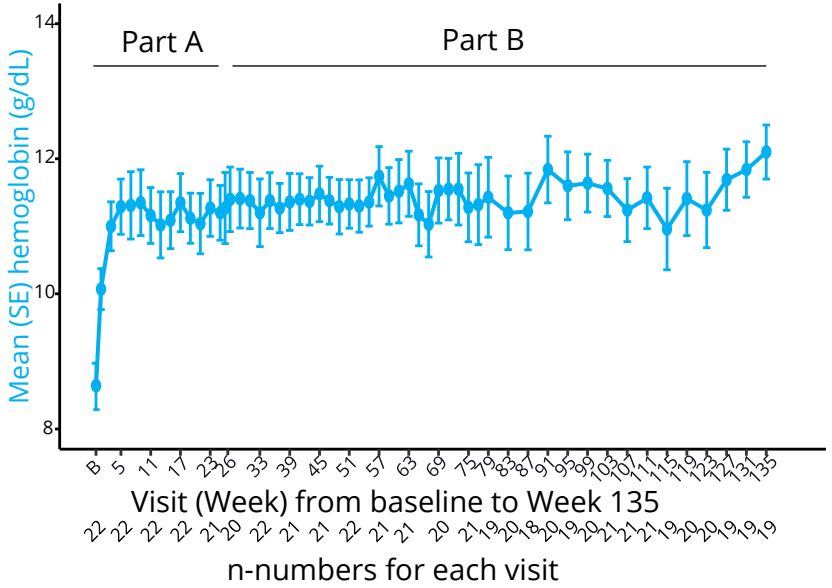
Röth et al., *N Engl J Med*. 2021;384(14):1323-1334.

Sutimlimab bei CAD

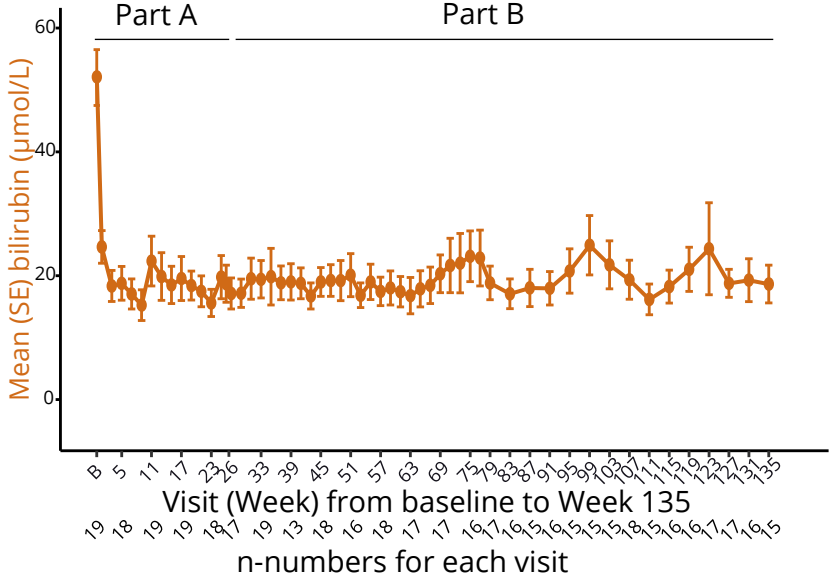
Phase III CARDINAL results from baseline to Week 135[1]

Data for the combined study period up to 135 weeks' follow-up for all ongoing patients[a,b]

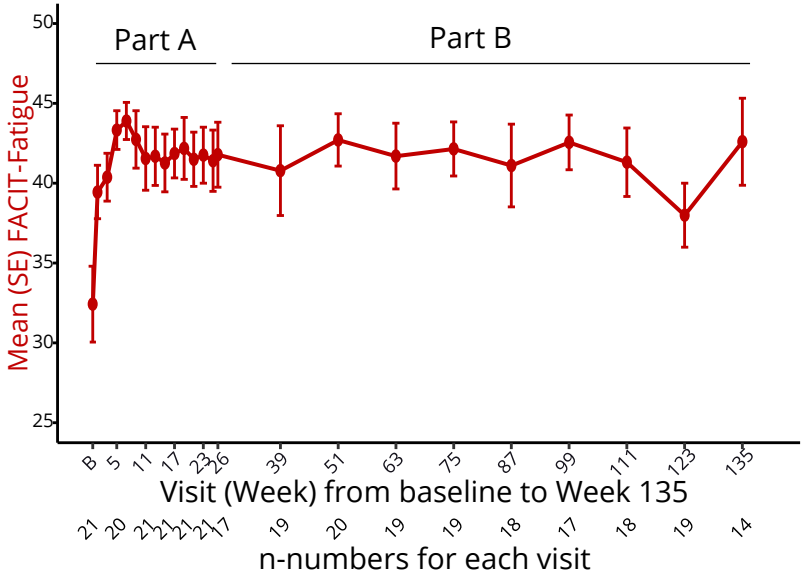
Haemoglobin (g/dL)



Bilirubin (µmol/L)



FACIT-Fatigue score



Mean Hb increase >1 g/dL from baseline by Week 1 and maintained stable and durable ***Hb levels >11 g/dL*** while patients remained on sutimlimab

Mean total bilirubin normalised within 1–3 weeks (after 1–2 doses of sutimlimab) and was ***maintained from Week 3-131*** *with occasional excursions*

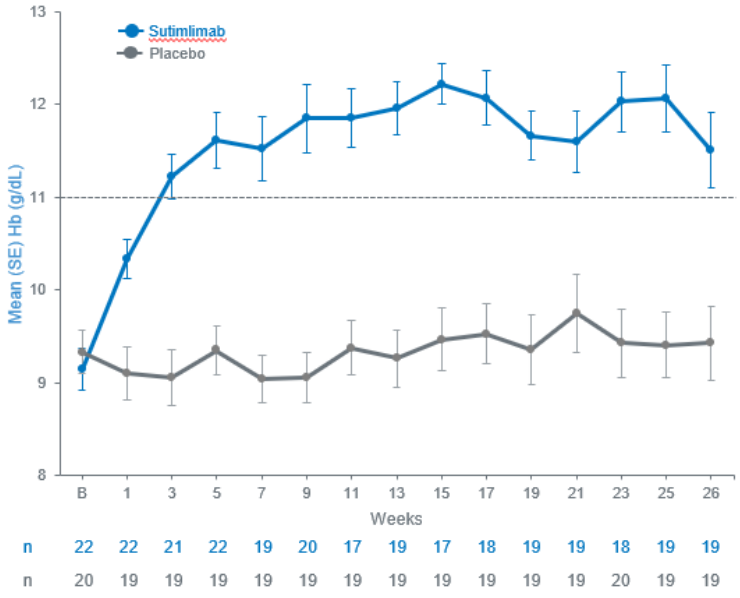
7-point mean improvement in FACIT-Fatigue by Week 1, and improvements were consistent with a clinically meaningful change (≥5)[c]

Röth A, et al. *N Engl J Med.* 2021;384:1323–34; Röth A, et al. *Am J Hematol.* 2023;98:1246-1253.

Sutimlimab bei CAD

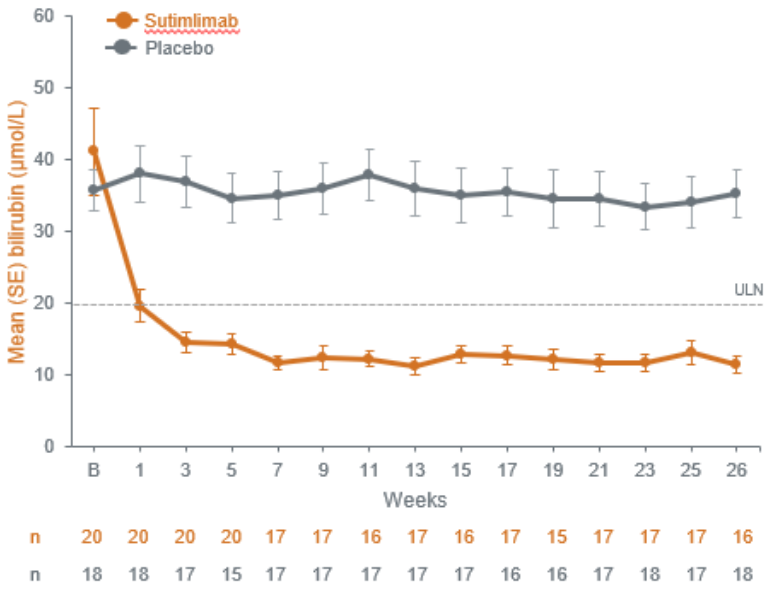
Phase III CADENZA results from baseline to Week 26 compared with placebo[1]

Haemoglobin (g/dL)



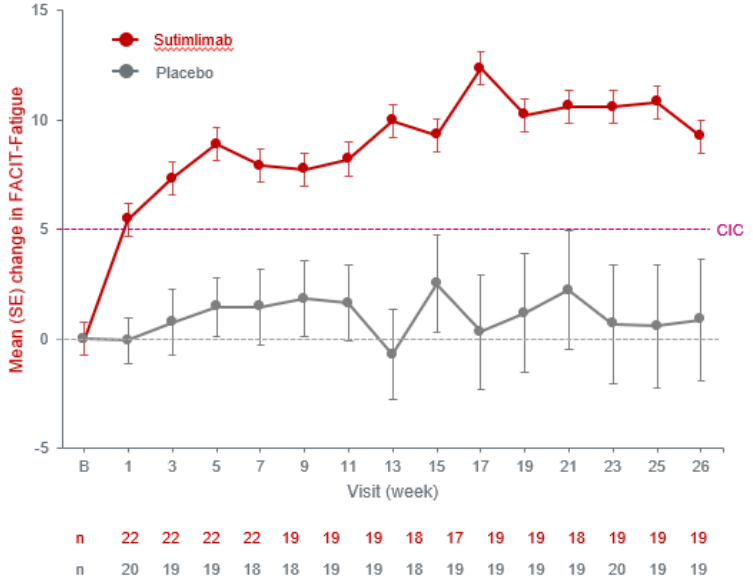
At the treatment assessment timepoint,[a] the LS mean difference between sutimlimab and placebo groups was ***2.6 (SEM, 0.4); p<0.001***

Bilirubin (µmol/L)



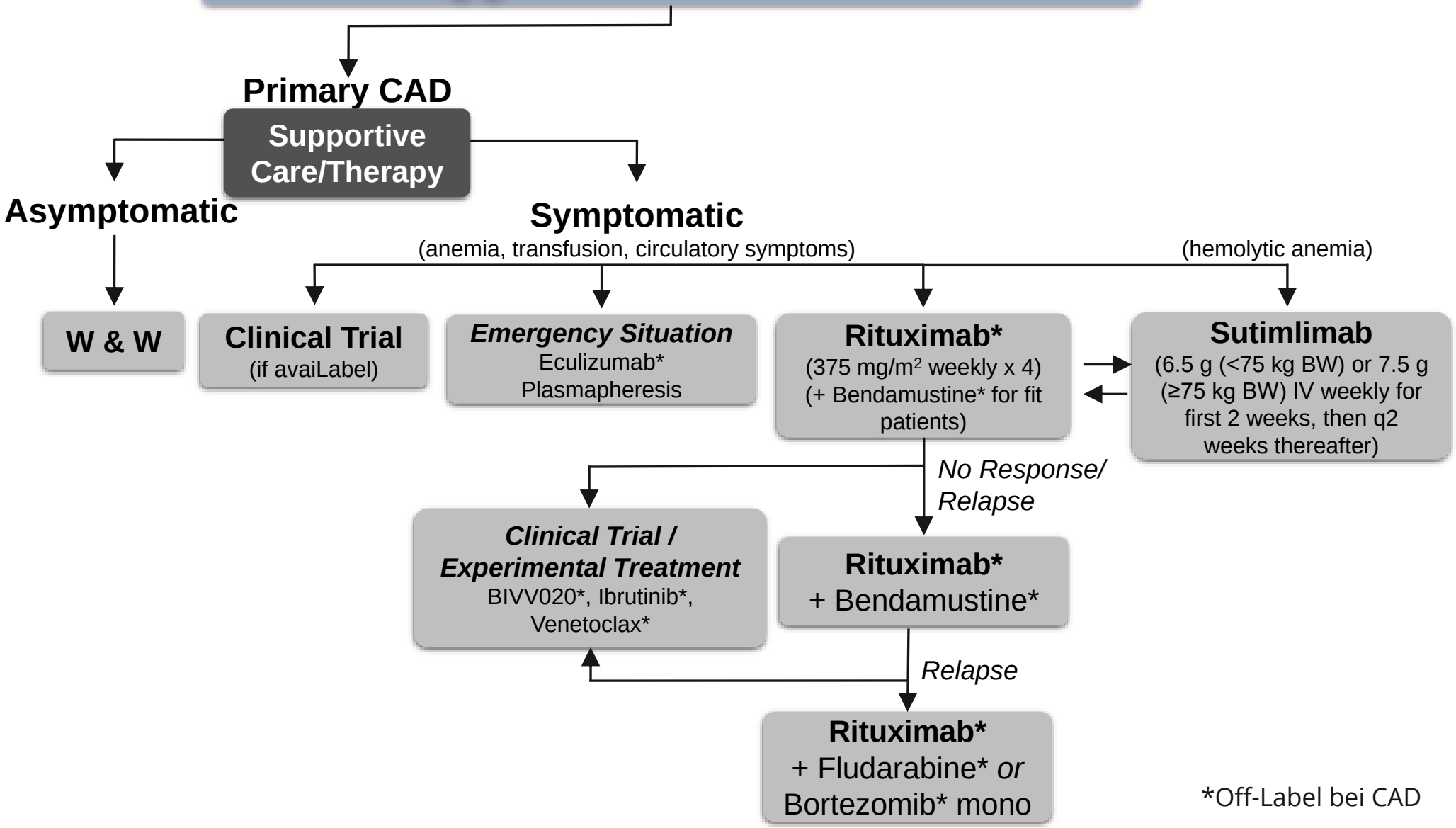
Mean (SE) change from baseline in total bilirubin was ***-22.1 (2.5) µmol/L*** in the sutimlimab group, representing a clinically meaningful decrease, and -1.3 (3.3) µmol/L in the placebo group, representing no meaningful impact on haemolysis[b]

FACIT-Fatigue score



At the treatment assessment timepoint,[a] the LS mean difference between sutimlimab and placebo groups was ***8.9 points (SEM, 2.5); p<0.001***[c]

Cold agglutinin mediated AIHA



*Off-Label bei CAD

Modifiziert nach Jäger et al. *Blood Rev*. 2020 May;41:100648 und Röth. *Blood*. 2020 Jul 23;136(4):380-381.

Sutimlimab: Therapieschema Essen

Neueinstellung

Schutzimpfungen
MCV-ACWY (Nimenrix® oder Menveo®)
Men-B (Trumenba® *oder* Bexsero®)
PCV-13 (Prevenar®)
HiB-Mono (ActHib®)

Schutzimpfungen
MCV-ACWY (Nimenrix® oder Menveo®)nach 2 Monaten als Auffrischung
Men-B nach 1-6 Monaten (nach Impfstoff, Grundimmunisierung)
PPSV-23 (Pneumovax®) nach 2-6 Monaten als Auffrischung

Auffrischimpfungen
alle 5-6 Jahre
je nach Impfstoff!

Bei Neueinstellung:
Penicillin V 2 x 1 Mio IE
pro Tag für 2 Wochen

Bei Verdacht auf Meningokokkeninfektion:
Ciprofloxacin 750 mg stand-by oder
Amoxicillin/Clavulansäure stand-by
und sofortige Diagnostik und ggf. weitere Therapie

1 Woche

6500 mg oder
7500 mg nach KG
≥39kg-75kg KG = 6500mg
≥75kg KG = 7500 mg

6500 mg oder
7500 mg nach KG

6500 mg oder
7500 mg nach KG

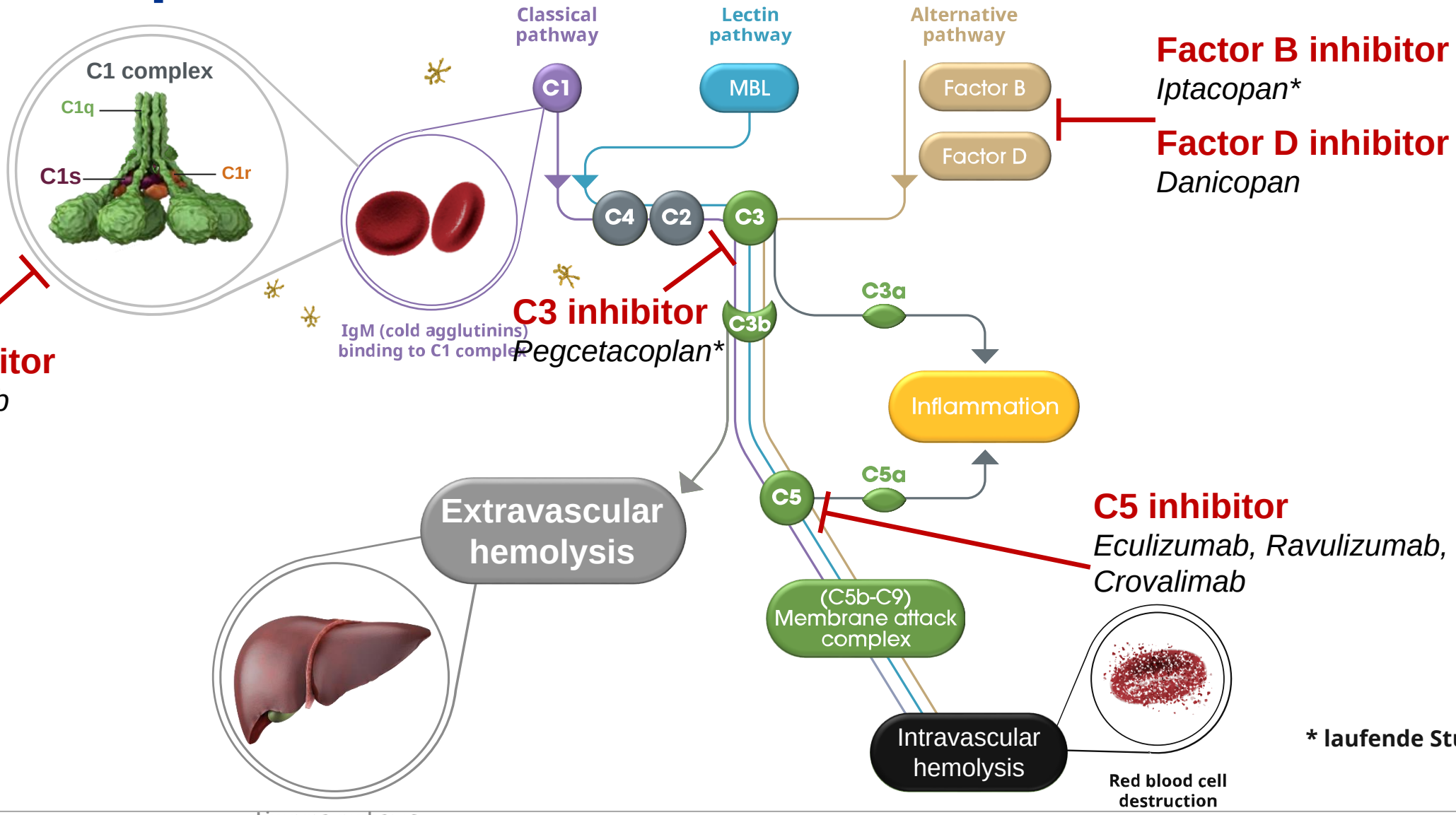
Aufsättigung → **Erhaltung** →

- ***Gewichtsabhängige Dosierung***
- Keine Verdünnung notwendig
- Haltbarkeit angebrochen 72 Stunden im Kühlschrank,16 Stunden bei Raumtemperatur
- Intravenöse Infusion bei Raumtemperatur mit 0,22 µm-Filter über 1 (-2) Stunden

- ***Nachspülung***, Nachbeobachtung 1 Stunde (bei Erstgabe 2 Stunden)
- Halbwertszeit 21 Tage
- ***Erhaltung alle 2 Wochen ± 2 Tage***
- Nach längerer Pause > 17 Tage erneute Aufsättigung
- Wechselwirkung mit IVIG beachten

1. Röth A, et al. *N Engl J Med.* 2021;384:1323–34; 2. Röth A, et al. *Blood*. 2022;140:980-991; ENJYAMO Fachinformation 11/2022; www.asplenie-net.org; Epidemiologisches Bulletin 2018; 34: 335–383.

CAD: Komplementinhibition



Factor B inhibitor
*Iptacopan**

Factor D inhibitor
Danicopan

C1 inhibitor
Sutimlimab
ANX005
C1-INH

C3 inhibitor
*Pegcetacoplan**

C5 inhibitor
Eculizumab, Ravulizumab, Crovalimab

*** laufende Studien**

Röth et al., *N Engl J Med*. 2021;384(14):1323-1334.

C A D E N C E

Cold Agglutinin Disease Real World EvidENCE Registry

Globale, multinationale, prospektive, longitudinale Registerstudie, welche Daten zum ***klinischen Verlauf, Therapien und Lebensqualität*** erfasst bei:

- Individuen mit CAD oder CAS
- Geplant sind 400 Patienten an 90 Zentren

Für weitere Informationen kontaktieren Sie mich bitte unter:

Prof. Dr. Alexander Röth

alexander.roeth@uk-essen.de

Cadence
REGISTRY
COLD AGGLUTININ DISEASE
Real World evidENCE Registry

ZUSAMMENFASSUNG

- AIHAs ***keine harmlose Erkrankungen.***
- ***wAIHA – Standardtherapie: Steroide ± Rituximab***
- ***cAIHA/CAD – Standartherapie Sutimlimab, ggf. Rituximab ± Bendamustin*** je nach Klinik
- Risiko für ***thromboembolische Komplikationen*** bei AIHAs
- Bedeutung allgemeiner ***supportiver Maßnahmen***
- Berücksichtigung/Evaluation relevanter ***Belastungen durch die Symptome der Erkrankung*** und ***der verfügbaren Behandlungsmöglichkeiten.***
- ***Klinische Studien*** entscheidend für Etablierung neuer Therapie!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Essen-
Holsterhausen
E-Zentrum
400 m
800 m
800 m