Case Discussions in Hematology

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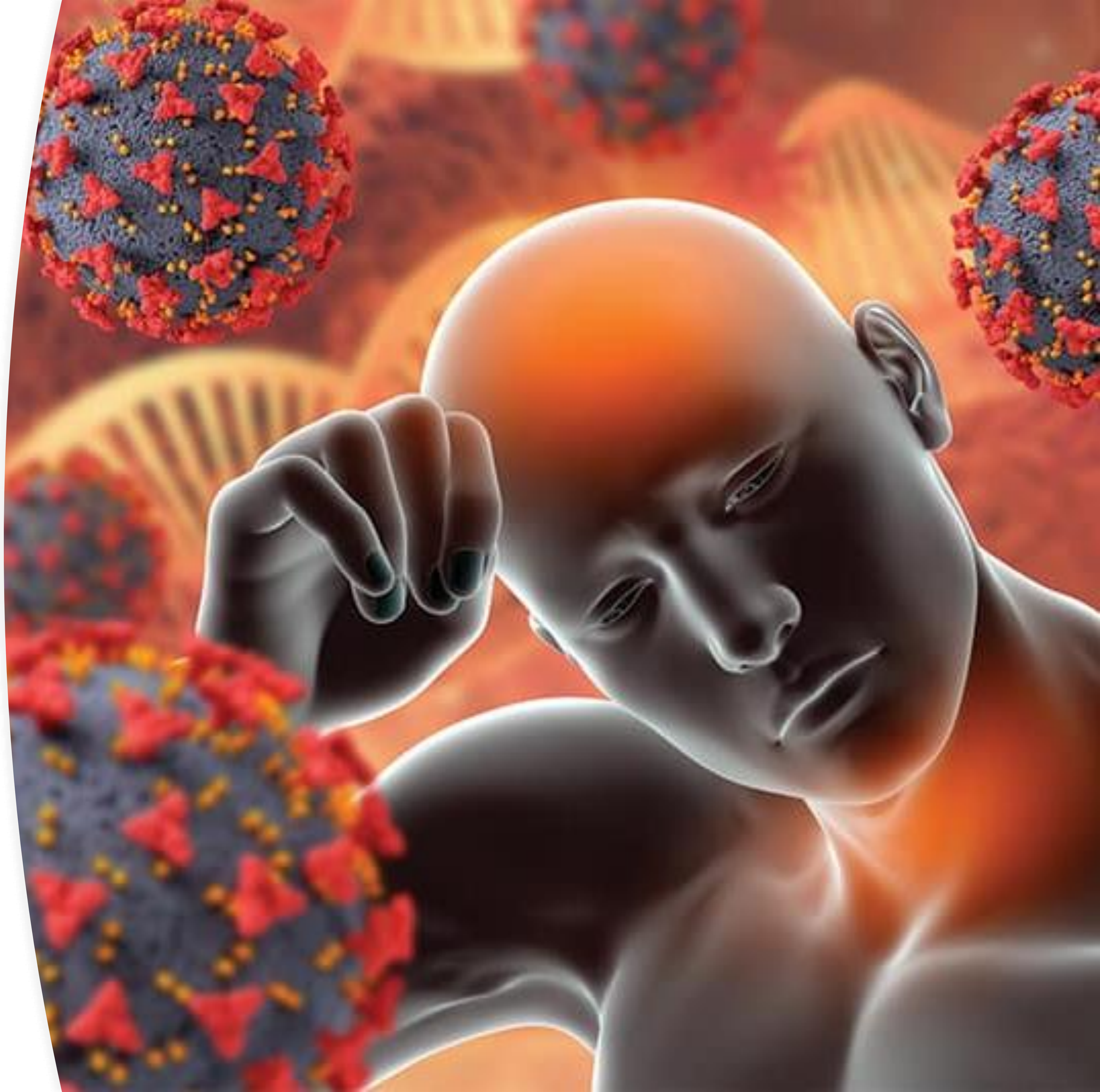
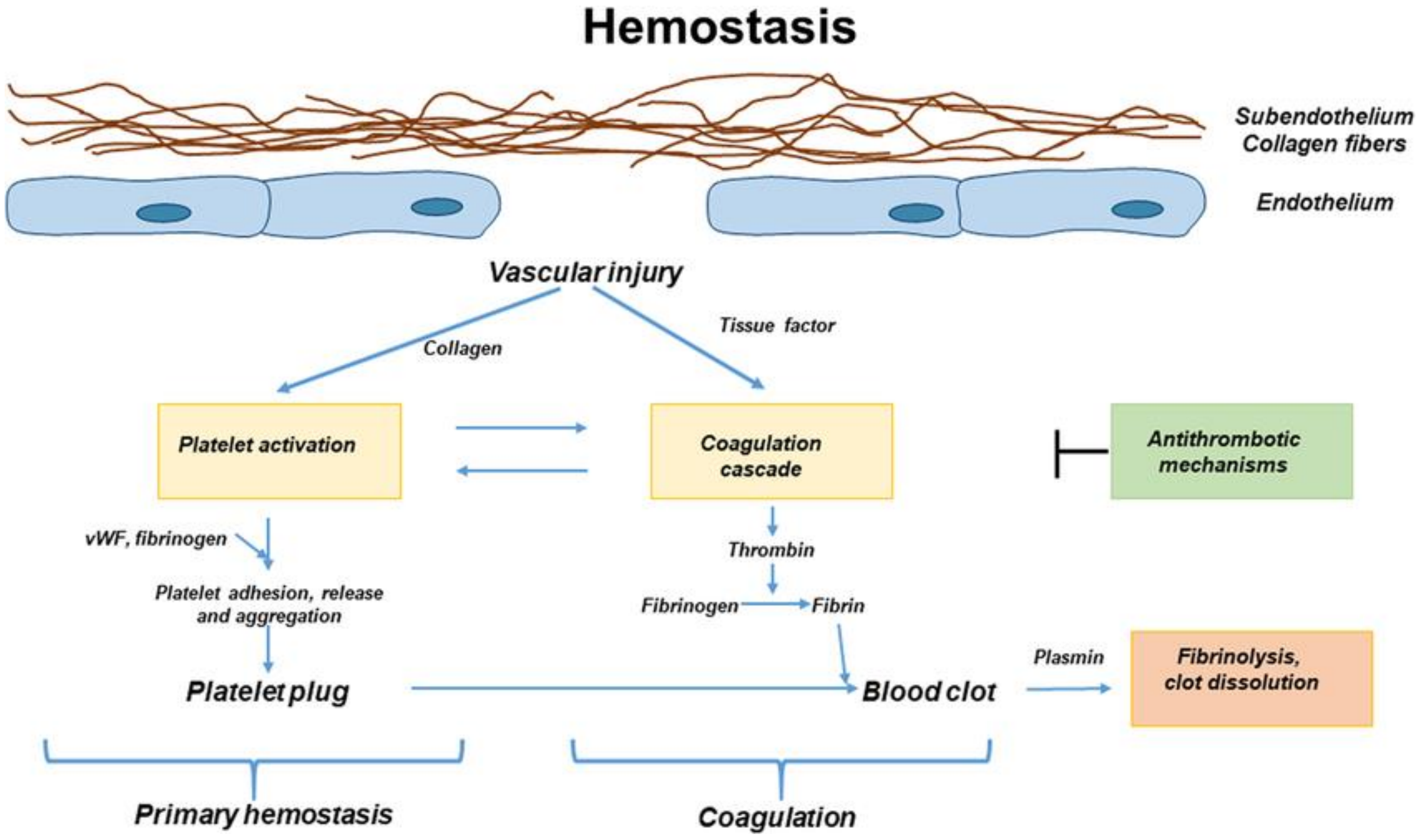


Disclosures

- None

Case 1: Multiple bruises of 6 months history



Noris M, Galbusera M. The complement alternative pathway and hemostasis. Immunol Rev. 2023

ISTH Bleeding Assessment Tool

SYMPTOMS (up to the time of diagnosis)	SCORE				
	0§	1§	2	3	4
Epistaxis	No/trivial	- > 5/year or - more than 10 minutes	Consultation only*	Packing or cauterization or antifibrinolytic	Blood transfusion or replacement therapy (use of hemostatic blood components and rFVIIa) or desmopressin
Cutaneous	No/trivial	For bruises 5 or more (> 1cm) in exposed areas	Consultation only*	Extensive	Spontaneous hematoma requiring blood transfusion
Bleeding from minor wounds	No/trivial	- > 5/year or - more than 10 minutes	Consultation only*	Surgical hemostasis	Blood transfusion, replacement therapy, or desmopressin
Oral cavity	No/trivial	Present	Consultation only*	Surgical hemostasis or antifibrinolytic	Blood transfusion, replacement therapy or desmopressin
GI bleeding	No/trivial	Present (not associated with ulcer, portal hypertension, hemorrhoids, angiodysplasia)	Consultation only*	Surgical hemostasis, antifibrinolytic	Blood transfusion, replacement therapy or desmopressin

Hematuria	No/trivial	Present (macroscopic)	Consultation only*	Surgical hemostasis, iron therapy	Blood transfusion, replacement therapy or desmopressin
Tooth extraction	No/trivial or none done	Reported in ≤25% of all procedures, no intervention**	Reported in >25% of all procedures, no intervention**	Resuturing or packing	Blood transfusion, replacement therapy or desmopressin
Surgery	No/trivial or none done	Reported in ≤25% of all procedures, no intervention**	Reported in >25% of all procedures, no intervention**	Surgical hemostasis or antifibrinolytic	Blood transfusion, replacement therapy or desmopressin
Menorrhagia	No/trivial	Consultation only* or - Changing pads more frequently than every 2 hours or - Clot and flooding or - PBAC score>100#	- Time off work/school > 2/year or - Requiring antifibrinolytics or hormonal or iron therapy	- Requiring combined treatment with antifibrinolytics and hormonal therapy or - Present since menarche and > 12 months	- Acute menorrhagia requiring hospital admission and emergency treatment or - Requiring blood transfusion, Replacement therapy, Desmopressin, or - Requiring dilatation & curretage or endometrial ablation or hysterectomy)
Post-partum hemorrhage	No/trivial or no deliveries	Consultation only* or - Use of syntocin or - Lochia > 6 weeks	- Iron therapy or - Antifibrinolytics	- Requiring blood transfusion, replacement therapy, desmopressin or - Requiring examination under anaesthesia and/or the use of uterin balloon/package to tamponade the uterus	- Any procedure requiring critical care or surgical intervention (e.g. hysterectomy, internal iliac artery legation, uterine artery embolization, uterine brace sutures)
Muscle hematomas	Never	Post trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion

Hemarthrosis	Never	Post trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring desmopressin or replacement therapy	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
CNS bleeding	Never	-	-	Subdural, any intervention	Intracerebral, any intervention
Other bleedings^	No/trivial	Present	Consultation only*	Surgical hemostasis, antifibrinolytics	Blood transfusion or replacement therapy or desmopressin

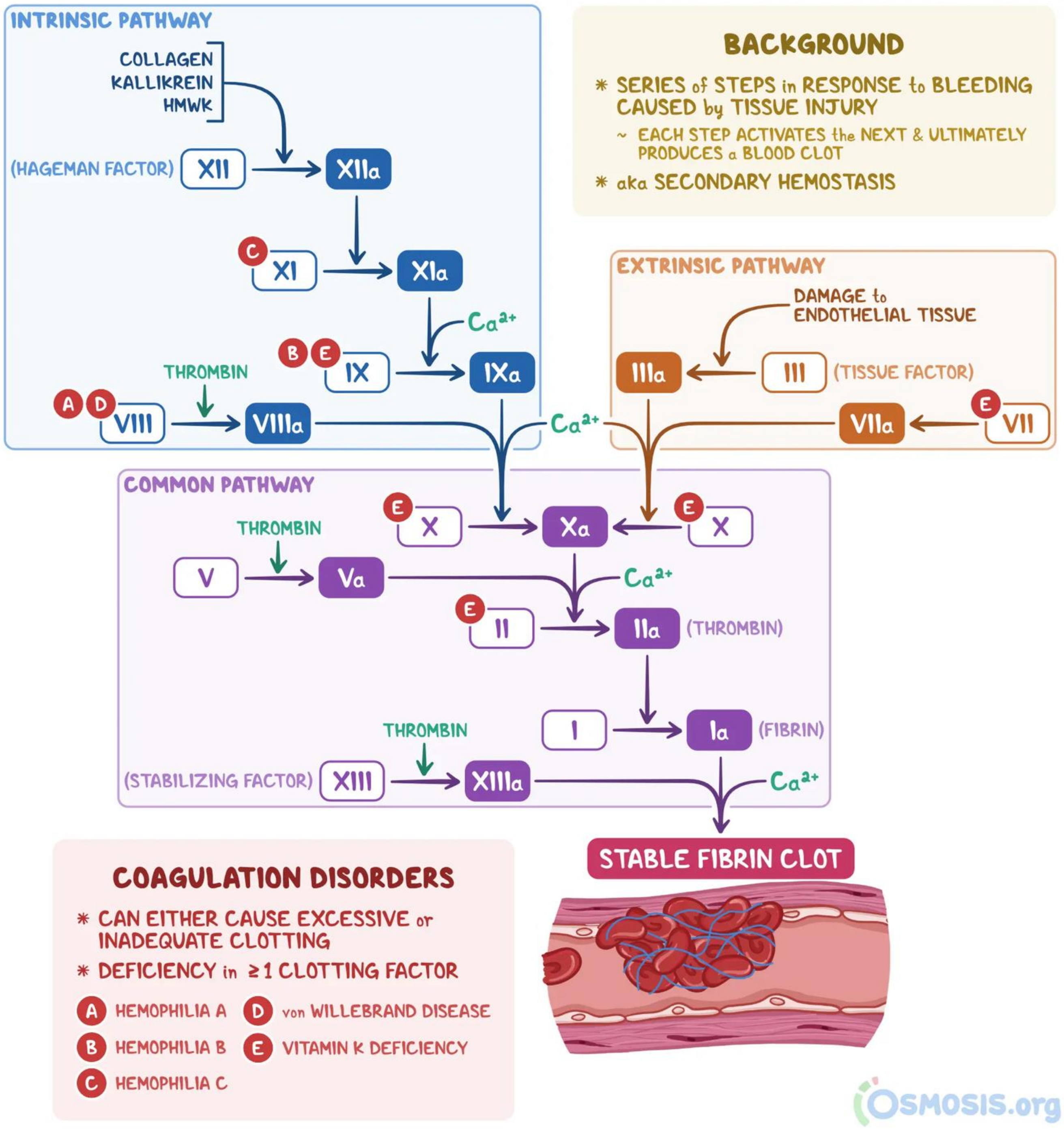
ISTH-SCC BAT Score		**Interpretation**
Adult males	0-3	Typical
	≥4	Atypical
Adult females	0-5	Typical
	≥6	Atypical
Children (<18 years)	0-2	Typical
	≥3	Atypical

Rodeghiero F, Tosetto A, Abshire T, et al. ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders. Journal of Thrombosis and Haemostasis. 2010;8(9):2063-2065.

WBC 4.2 - 10.0 x10exp9/L	6.2
RBC 3.80 - 5.10 x10exp12/L	3.57 ⌄
Hemoglobin 11.2 - 14.9 g/dL	10.2 ⌄
Hematocrit 36.0 - 48.0 %	33.0 ⌄
MCV 85.2 - 100.2 fL	92.4
MCH 27.0 - 32.4 pg	28.6
MCHC 29.5 - 34.2 g/dL	30.9
RDW 11.8 - 14.4 %	15.9 ^
Platelets 168 - 382 x10exp9/L	199
MPV 9.6 - 12.5 fL	9.5 ⌄
NRBC % -1.0 - 0.0 %	0.0
NRBC (absolute) x10exp9/L	0.0
Immature Granulocytes % %	0.3
Immature Granulocytes (absolute) 0.0 - 0.1 x10exp9/L	0.0
Seg Neutrophil % %	69.1
Seg Neutrophil (absolute) 1.9 - 6.7 x10exp9/L	4.3
Lymphocyte % %	10.6
Lymphocyte (absolute) 1.0 - 3.3 x10exp9/L	0.7 ⌄
Monocyte % %	12.8
Monocyte (absolute) 0.3 - 0.9 x10exp9/L	0.8
Eosinophil % %	6.4
Eosinophil (absolute) 0.0 - 0.4 x10exp9/L	0.4
Basophil % %	0.8
Basophil (absolute) 0.0 - 0.1 x10exp9/L	0.1

Glucose 67 - 99 MG/DL	134 ^
BUN 6 - 24 MG/DL	34 ^
Creatinine 0.44 - 1.03 MG/DL	1.73 ^
Sodium 135 - 145 MEQ/L	137
Potassium 3.6 - 5.1 MEQ/L	4.5
Chloride 98 - 110 MEQ/L	106
CO2 22 - 32 MEQ/L	22
Anion Gap 3 - 13	9
Calcium 8.5 - 10.5 MG/DL	9.1
eGFR Abnormal <60 ML/MIN/1.73M	27 ⌄

Prothrombin Time	12.3
INR	1.0
PTT	
PTT	135.0 ^



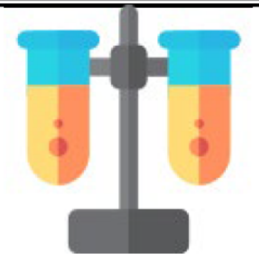
INTRINSIC PATHWAY
COLLAGEN
KALLIKREIN
HMWK
(HAGEMAN FACTOR) XII
XIIa
C XI
XIa
Ca^{2+}
B E IX
IXa
THROMBIN
A D VIII
VIIIa
Ca^{2+}
BACKGROUND
* SERIES of STEPS in RESPONSE to BLEEDING CAUSED by TISSUE INJURY
~ EACH STEP ACTIVATES the NEXT & ULTIMATELY PRODUCES a BLOOD CLOT
* aka SECONDARY HEMOSTASIS
EXTRINSIC PATHWAY
DAMAGE to ENDOTHELIAL TISSUE
IIIa
III (TISSUE FACTOR)
VIIa
E VII
COMMON PATHWAY
E X
Xa
E X
THROMBIN
V
Va
Ca^{2+}
E II
IIa (THROMBIN)
I
Ia (FIBRIN)
THROMBIN
(STABILIZING FACTOR) XIII
XIIIa
Ca^{2+}
STABLE FIBRIN CLOT
COAGULATION DISORDERS
* CAN EITHER CAUSE EXCESSIVE or INADEQUATE CLOTTING
* DEFICIENCY in ≥ 1 CLOTTING FACTOR
A HEMOPHILIA A
B HEMOPHILIA B
C HEMOPHILIA C
D von WILLEBRAND DISEASE
E VITAMIN K DEFICIENCY
OSMOSIS.org

Workup of a Prolonged PT or aPTT

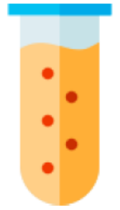
Investigations

To distinguish between a single factor deficiency and inhibitor, an immediate 50:50 mix is performed when the prolongation is greater than 4 seconds from the upper limit of normal .

Control plasma



Patient plasma



This test is performed by combining one part patient's plasma with one part normal plasma.

An aPTT or a PT is then performed on the 50:50 mix

Interpretation

The mixture "corrects" if the aPTT is within 3-4 seconds of normal and the PT is within 2 seconds of normal.

- 50:50 mix
  - Does not correct
    - Specific inhibitor
    - Non-specific inhibitor
    - Multiple factor deficiencies
  - Corrects
    - Suggests single factor deficiency

Caution

The 50:50 mix may not completely correct in the case of multiple factor deficiencies

Caution

Autoimmune FVIII inhibitors cause acquired hemophilia A. Alloimmune FVIII inhibitors occur in patients with congential hemopiliha A and render the replaced FVIII less or not effective. These are the most common specific factor inhibitors.

Control plasma

Patient plasma

37°C

2 hours

Acquired hemophilia: the autoantibodies are temperature and time sensitive.

When the mix is incubated at 37° Celsius for two hours, the 50:50 aPTT remains prolonged (i.e. does not correct)

Specific factor levels are more informative than the 50:50 mix.

Specific factor levels are performed by combining one part patient's sample with commercial factor deficient plasma.

Factor deficient plasma: Commercial plasma completely deficient in a factor relevant to the PT (e.g. FVII, X) or aPTT (e.g. FVIII, IX, XI, XII).

Patient plasma

An aPTT or PT is performed on the mix and factor levels are derived from a calibration curve

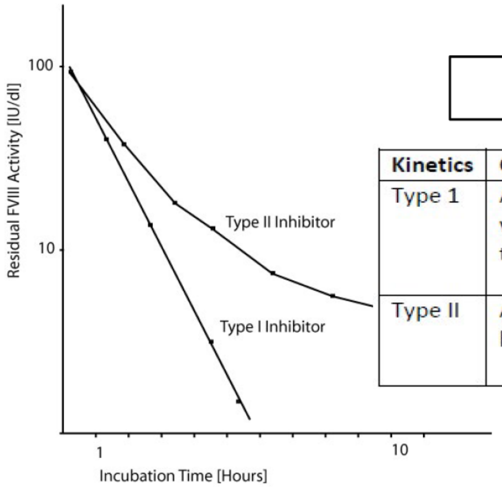
The Bethesda assay is used to quantitate specific factor inhibitors.

One Bethesda unit is defined as that amount of inhibitor that results in 50% residual FVIII:C activity after incubation at 37° Celsius for two hours.

No incubation is needed for factor inhibitors that are not time sensitive (i.e. FIX)

The inhibitor concentration is derived from a graph depicting factor VIII (Y axis) activity versus inhibitor units (x axis).

When defining a patient's inhibitor titer, derive the inhibitor titer from the graph and multiply by the dilution to obtain the final titer.



Types of inhibitors

Kinetics	Clinical syndrome
Type 1	Alloantibodies arising in a person with congenital haemophilia treated with FVIII concentrates
Type II	Autoantibodies as seen in acquired haemophilia A

Elbaz C, Sholzberg M. An illustrated review of bleeding assessment tools and common coagulation tests. Res Pract Thromb Haemost. 2020

BLEEDING AND BRUISING

@rav7ks

DISORDERS OF HEMOSTASIS

Quantitative or Qualitative defect in platelets

Mucosal bleeding of the gums and gastrointestinal tract is more characteristic of a platelet disorder than of a coagulopathy

Bleeding gums can also arise from gingivitis or gingival leukemic infiltration

Deficiency or an inhibitor of a coagulation factor

NORMAL PT/NORMAL PTT:

- Von Willebrand's disease
- Factor XIII deficiency
- Disorders of fibrinolysis
- Disorders of vascular integrity

Clotting cascade is intact- test for Von Willebrand disease

- Von Willebrand factor Ag
- Von Willebrand factor activity (also called ristocetin cofactor activity)
- factor VIII level

NORMAL PT/ABNORMAL PTT:

Abnormality in the intrinsic pathway
Perform a PTT mixing study to distinguish abnormalities in the clotting factors (VIII, IX, and XI) vs. clotting factor inhibitors- factor VIII inhibitor and lupus anticoagulant

Inherited

- Deficiency of factor VIII, IX, or XI
- Deficiency of factor XII, prekallikrein, or HMW kininogen (not associated with a bleeding diathesis)
- von Willebrand disease

Acquired

- Heparin, dabigatran, argatroban, direct factor Xa inhibitors (variable)*
- Acquired inhibitor of factor VIII, IX, XI, or XII
- Acquired von Willebrand syndrome
- Lupus anticoagulant (more likely to be associated with thrombosis than bleeding)

ABNORMAL PT/NORMAL PTT

Suggests an abnormality in the extrinsic pathway.
If the PT remains prolonged after Vitamin K administration, evaluation of factor VII should be undertaken.

Inherited

- Factor VII deficiency

Acquired

- Mild vitamin K deficiency
- Liver disease
- Warfarin
- Acute DIC

ABNORMAL PT/ABNORMAL PTT

Prolongation of the PT and the PTT suggests liver failure, disseminated intravascular coagulation, or defects in the common pathway to the intrinsic and extrinsic pathways. The appropriate evaluations to discern these causes are liver function tests (if not already performed), fibrinogen levels, and testing factor assays

Inherited

- Deficiency of prothrombin, fibrinogen, factor V, or factor X
- Combined factor deficiencies

Acquired

- Liver disease
- Acute DIC
- Severe vitamin K deficiency
- Anticoagulants (warfarin, direct thrombin inhibitors, others)*
- Acquired inhibitor of prothrombin, fibrinogen, factor V, or factor X
- Amyloidosis-associated factor X deficiency
- Anticoagulant rodenticide poisoning

Disruption in vascular integrity

- Vasculitis
- Amyloidosis
- Scurvy

Connective Tissue disorders

- Ehlers Danlos

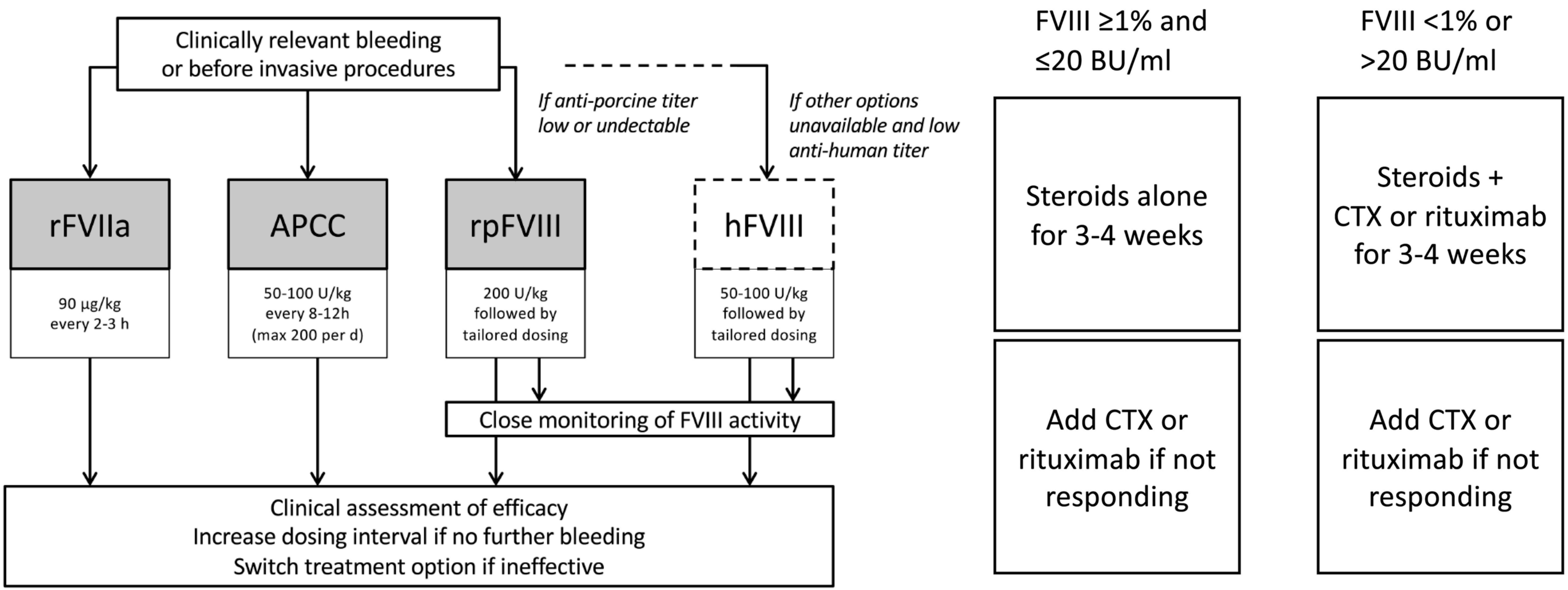
Nutrition:

- Vitamin C

What is the diagnosis?

Factor VIII Activity 50 - 150 %	<1 ⩔
Factor VIII Inhibitor Assay <1.0 B.U.	450.0 ⩓

Acquired Hemophilia A management



Tiede A et al International recommendations on the diagnosis and treatment of acquired hemophilia A. Haematologica. 2020

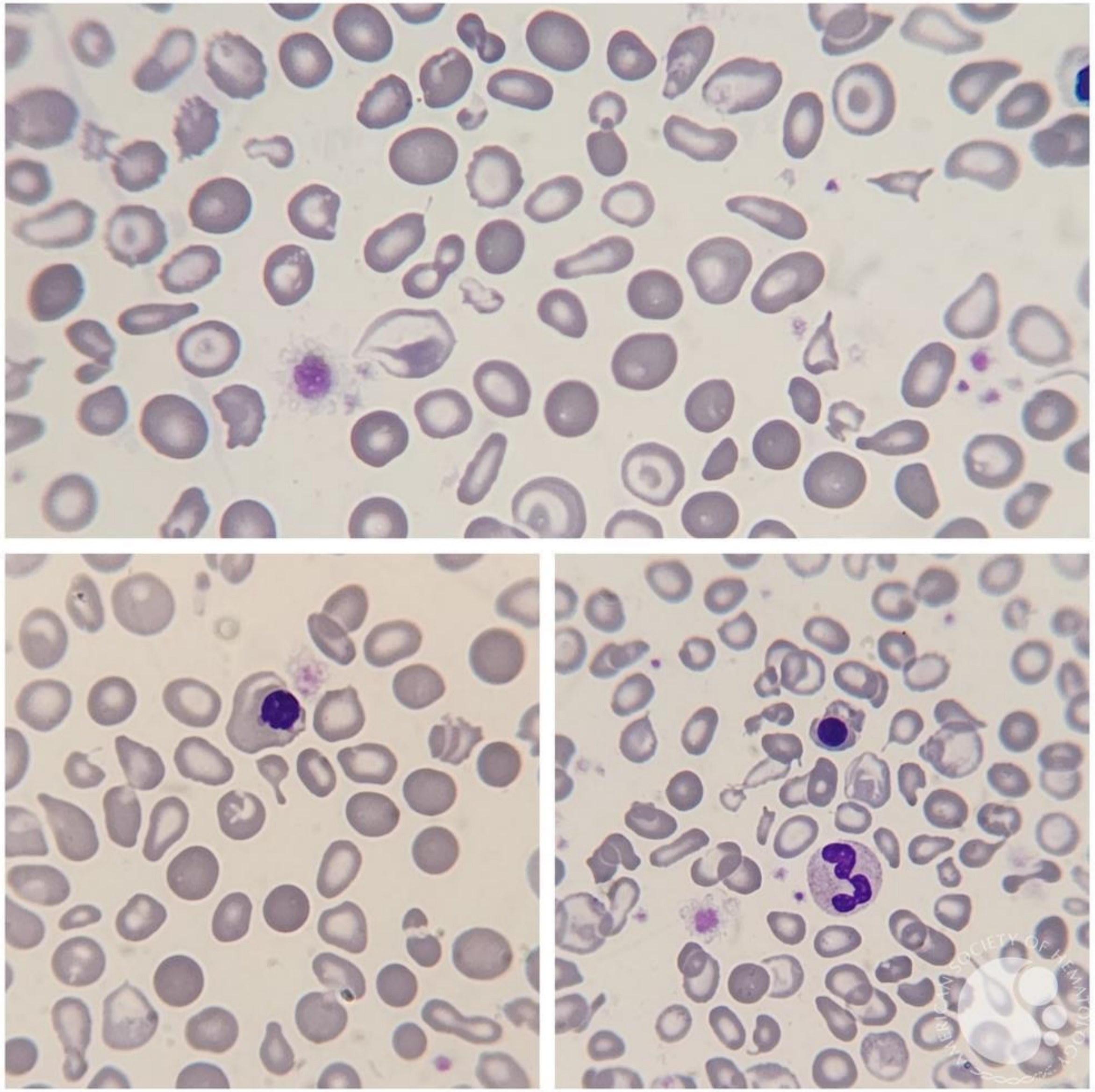
Case 2: Fever, confusion and shortness of breath on exertion

WBC 4.2 - 10.0 x10exp9/L	7.8
RBC 3.80 - 5.10 x10exp12/L	1.58 Low
Hemoglobin 11.2 - 14.9 g/dL	4.5
Hematocrit 36.0 - 48.0 %	15.0 Low
MCV 85.2 - 100.2 fL	94.9
MCH 27.0 - 32.4 pg	28.5
MCHC 29.5 - 34.2 g/dL	30.0
RDW 11.8 - 14.4 %	25.1 High
Platelets 168 - 382 x10exp9/L	5
NRBC % -1.0 - 0.0 %	1.4 High
NRBC (absolute) x10exp9/L	0.1
Seg Neutrophil %	69.0
Seg Neutrophil (absolute) 1.9 - 6.7 x10exp9/L	5.4
Lymphocyte %	21.0
Lymphocyte (absolute) 1.0 - 3.3 x10exp9/L	1.6
Monocyte %	7.0
Monocyte (absolute) 0.3 - 0.9 x10exp9/L	0.5
Eosinophil %	1.0
Eosinophil (absolute) 0.0 - 0.4 x10exp9/L	0.1
Basophil %	0.0
Basophil (absolute) 0.0 - 0.1 x10exp9/L	0.0

Reticulocyte Hgb 30.6 - 36.0 pg	31.0
Immature Reticulocyte Fraction 4.2 - 21.9 %	39.5 (H)
Reticulocyte % 0.9 - 2.7 %	15.3 (H)
Retic Ct Abs 39.0 - 129.9 x10exp9/L	246.0 (H)

	Reference Range & Units
Sodium135 - 145 MEQ/L	130 (L)
Potassium3.6 - 5.1 MEQ/L	3.2 (L)
Chloride98 - 110 MEQ/L	100
CO220 - 29 MEQ/L	22
Anion Gap3 - 13	8
BUN6 - 24 MG/DL	20
BUN Creatinine Ratio	22
Creatinine, Ser0.44 - 1.03 MG/DL	0.89
eGFR>90 mL/min/1.73m 2	88 (L)
Glucose67 - 99 MG/DL	163 (H)
Calcium8.4 - 10.2 MG/DL	7.8 (L)
Magnesium Level1.3 - 1.9 mEq/L	1.5
Phosphorus2.4 - 4.8 MG/DL	2.6
AST (SGOT)12 - 52 IU/L	42
ALT7 - 49 IU/L	18
Alkaline Phosphatase39 - 117 IU/L	74
Protein, Total6.1 - 8.3 G/DL	6.7
Albumin3.4 - 5.1 G/DL	3.5
LDH119 - 265 IU/L	891 (H)
Bilirubin, Total0.1 - 1.2 MG/DL	2.2
Bilirubin, Direct0.0 - 0.4 MG/DL	0.6
Folate, Serum3.5 - 14.7 NG/ML	4.4
Vitamin B-12227 - 1,053 PG/ML	308
Lactate, Whole Blood0.2 - 1.9 MEQ/L	1.8

	Latest Reference Range & Units
Fibrinogen Level150 - 480 MG/DL	205
D Dimer Level0 - 300 ng/mL	1687
Prothrombin Time10.0 - 13.0 sec	13.0
INR0.8 - 1.2	1.1
PTT24.0 - 37.0 sec	29.0
Direct Antiglobulin Test	NEG
ABORh Type	AB POS
Antibody Screen	NEG



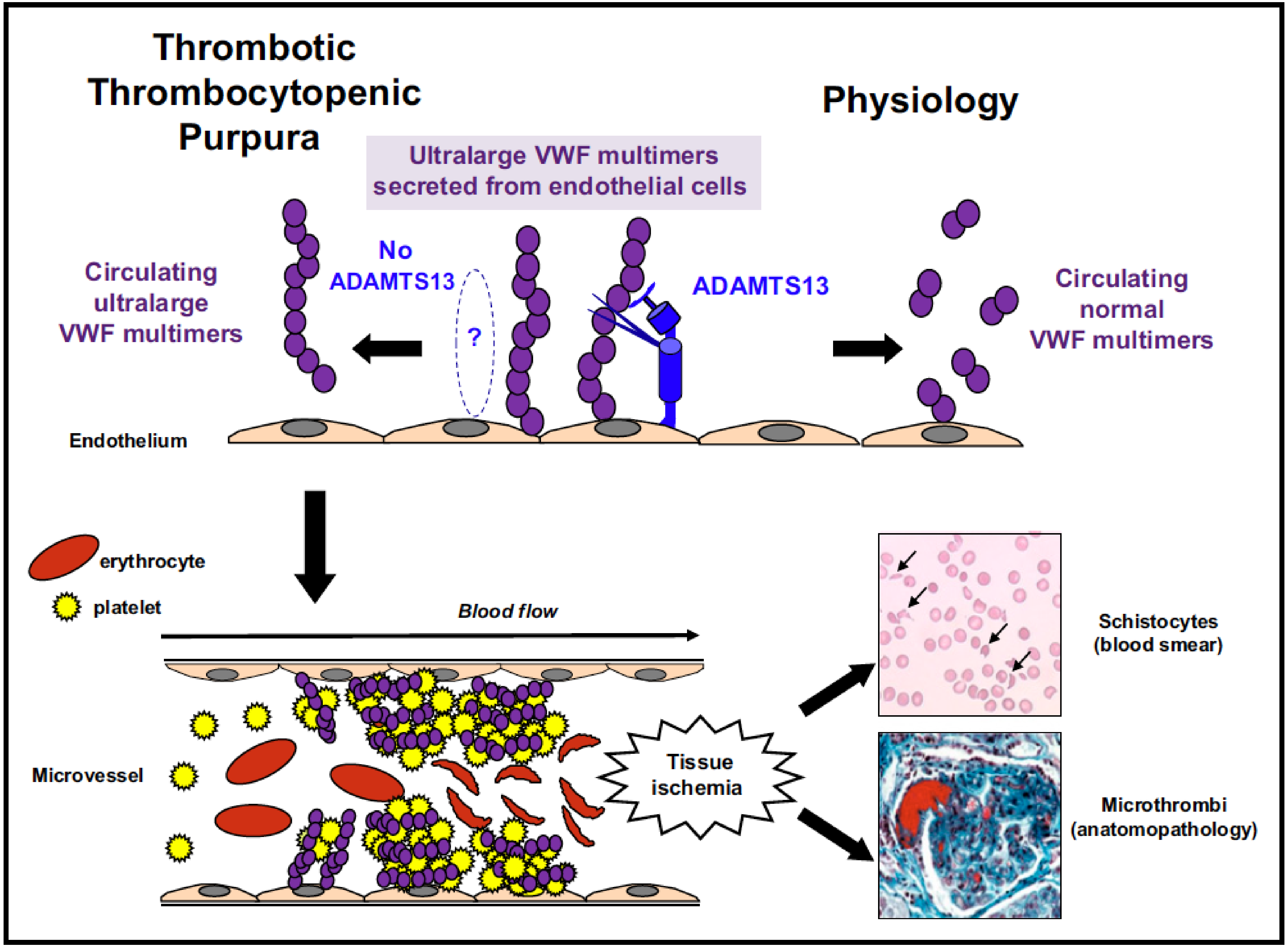
PLASMIC SCORE

1	Platelet count $< 30 \times 10^9/L$	1 Point
2	MCV < 90 fL	1 Point
3	Creatinine < 2 mg/dL	1 Point
4	INR < 1.5	1 Point
5	Evidence of hemolysis based on any below: • Reticulocyte count $> 2.5\%$ • Indirect bilirubin > 2 mg/dL • Undetectable haptoglobin	1 Point
6	No active malignancy	1 Point
7	No history of hematopoietic stem cell or solid organ transplantation	1 Point

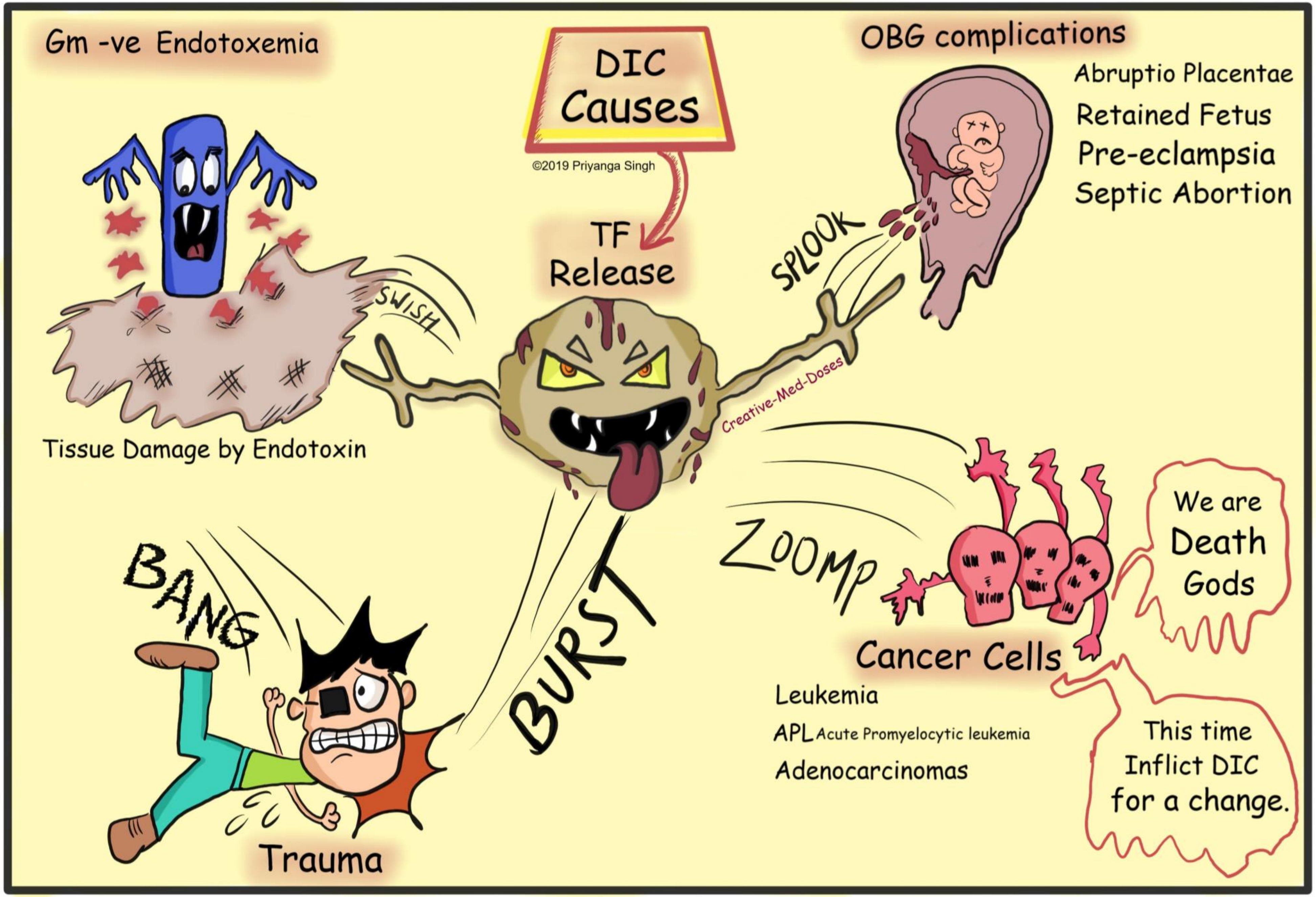
Abbreviations: ADAMTS13, a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13; INR, international normalized ratio; MCV, mean corpuscular volume; PLASMIC, platelets, lysis, active cancer, stem cell or solid organ transplant, MCV, INR, and creatinine.

[a]Risk stratification: high risk, 7 points; intermediate risk, 5-6 points; low risk, 0-4 points.

Bendapudi PK, Hurwitz S, Fry A, et al. Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study. Lancet Haematol. 2017



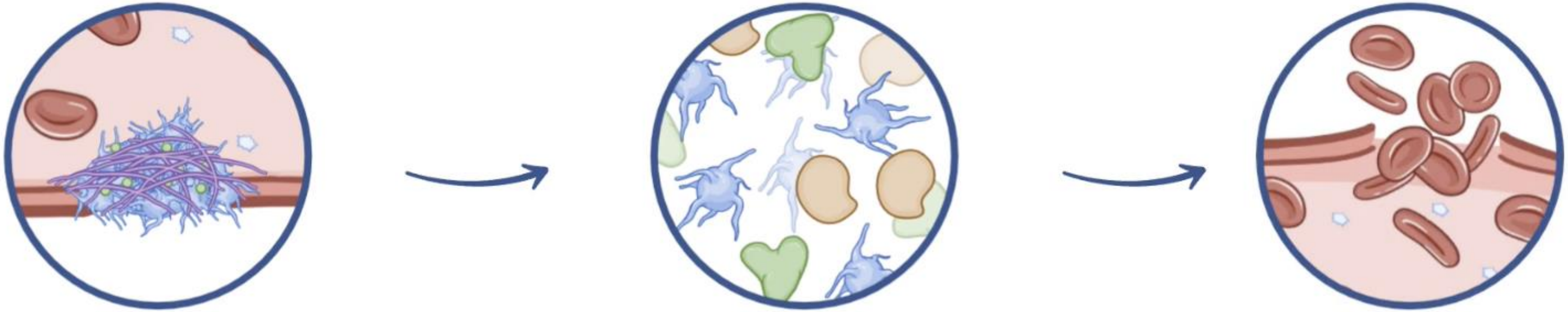
Joly BS, Coppo P, Veyradier A. Thrombotic thrombocytopenic purpura. Blood. 2017



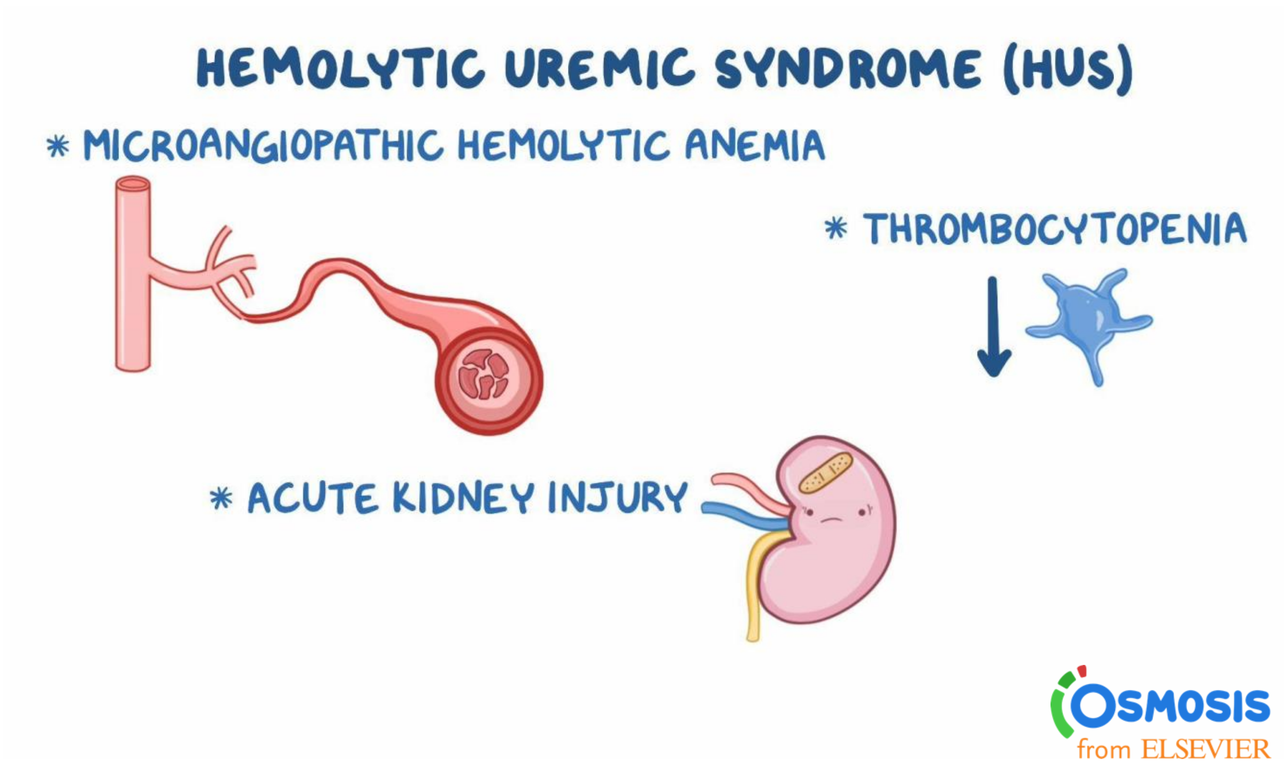
creativemeddoses.com/topics-list/disseminated-intravascular-coagulation/

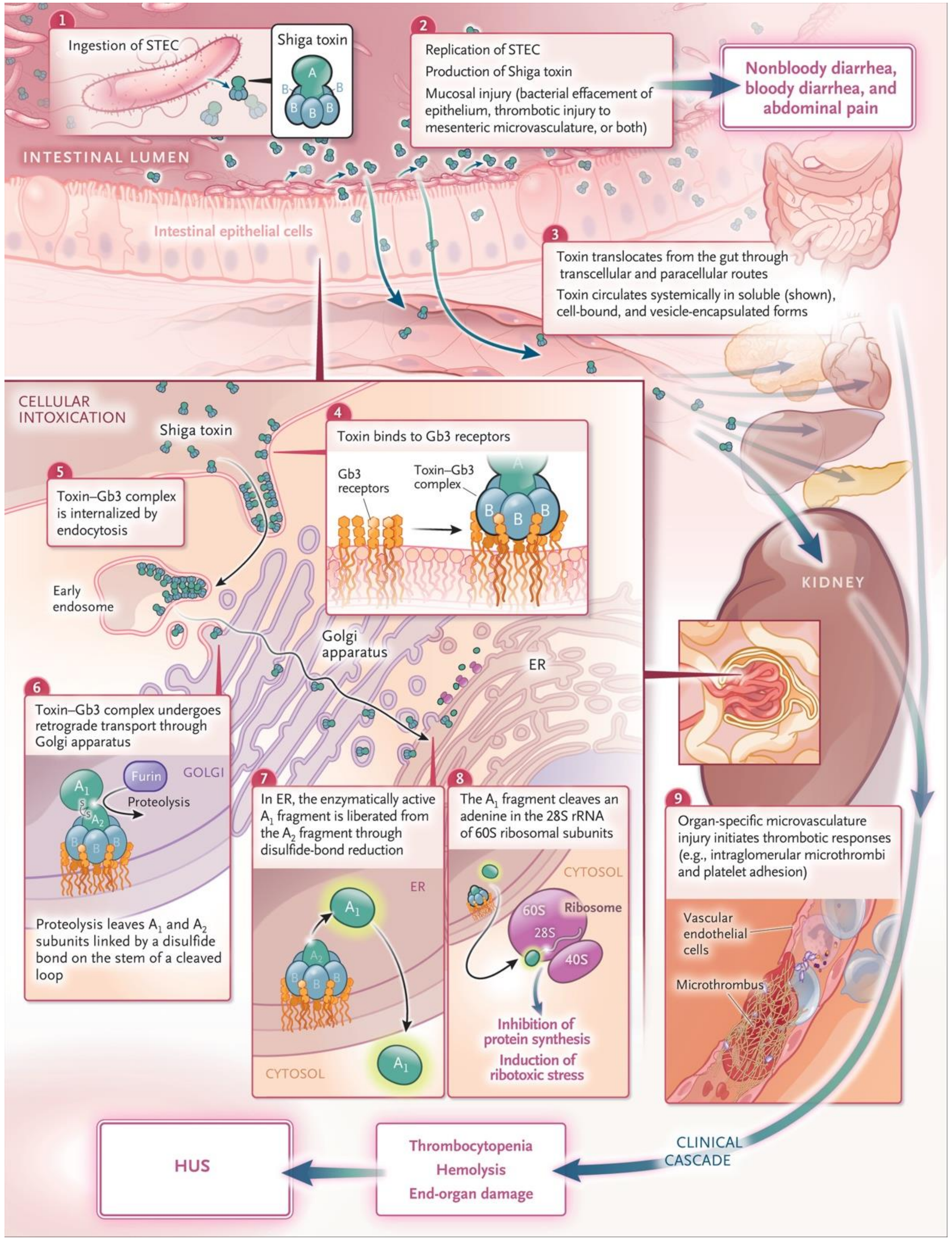
DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

RARE but LIFE-THREATENING CONDITION

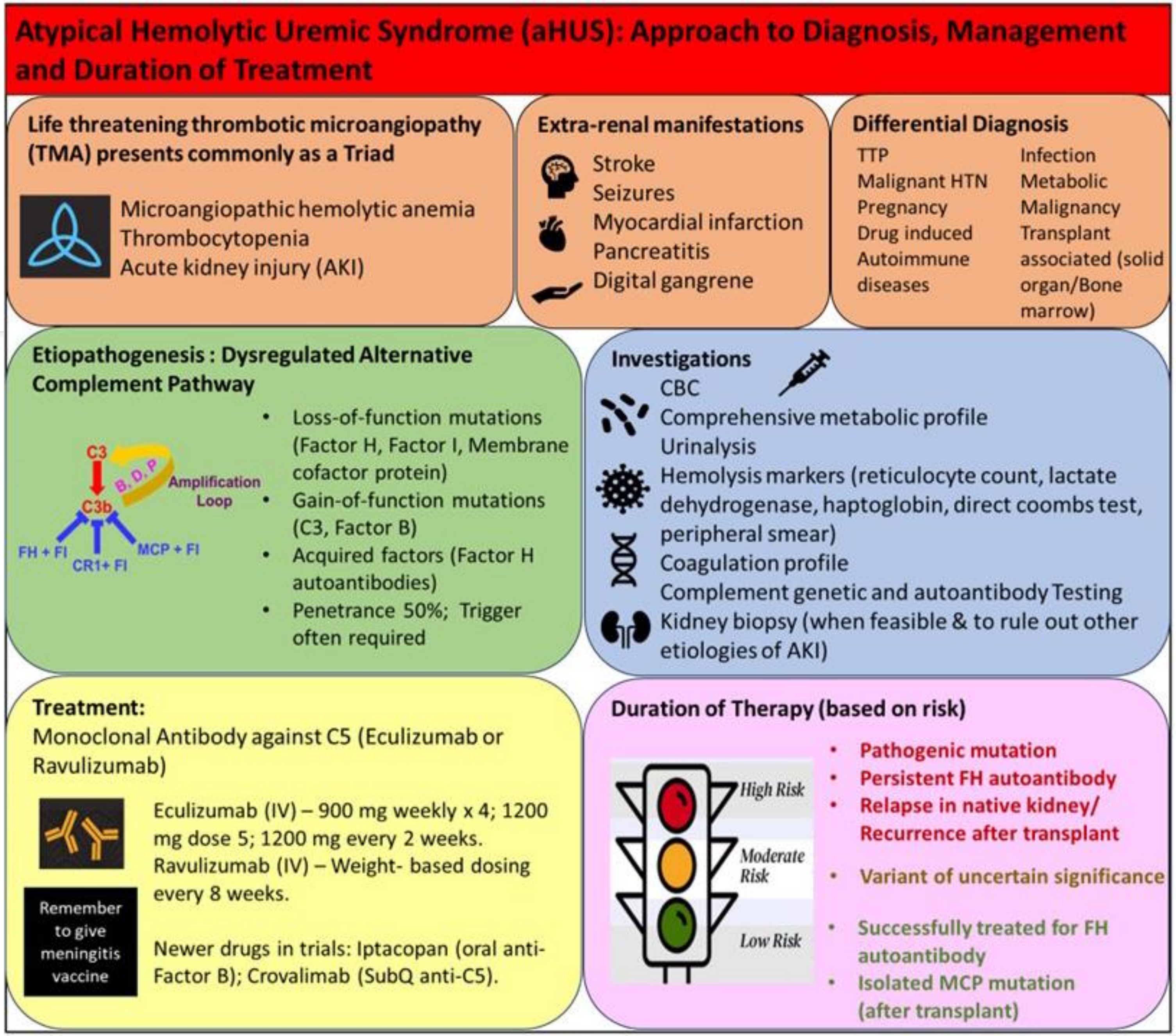


* ACCELERATED CLOTTING within BLOOD VESSELS
* ↑↑ CONSUMPTION of PLATELETS & CLOTTING FACTORS
* UNCONTROLLABLE BLEEDING



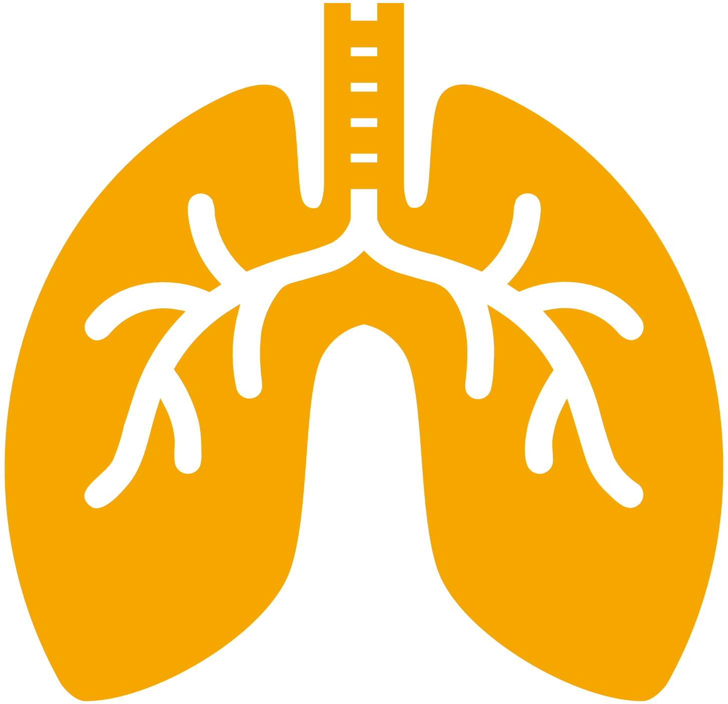


Freedman SB, van de Kar NCAJ, Tarr PI. Shiga Toxin-Producing *Escherichia coli* and the Hemolytic-Uremic Syndrome. N Engl J Med. 2023



Anuja Java; Atypical hemolytic uremic syndrome: diagnosis, management, and discontinuation of therapy. *Hematology Am Soc Hematol Educ Program* 2024

Case 3: Palpitations and shortness of breath on exertion



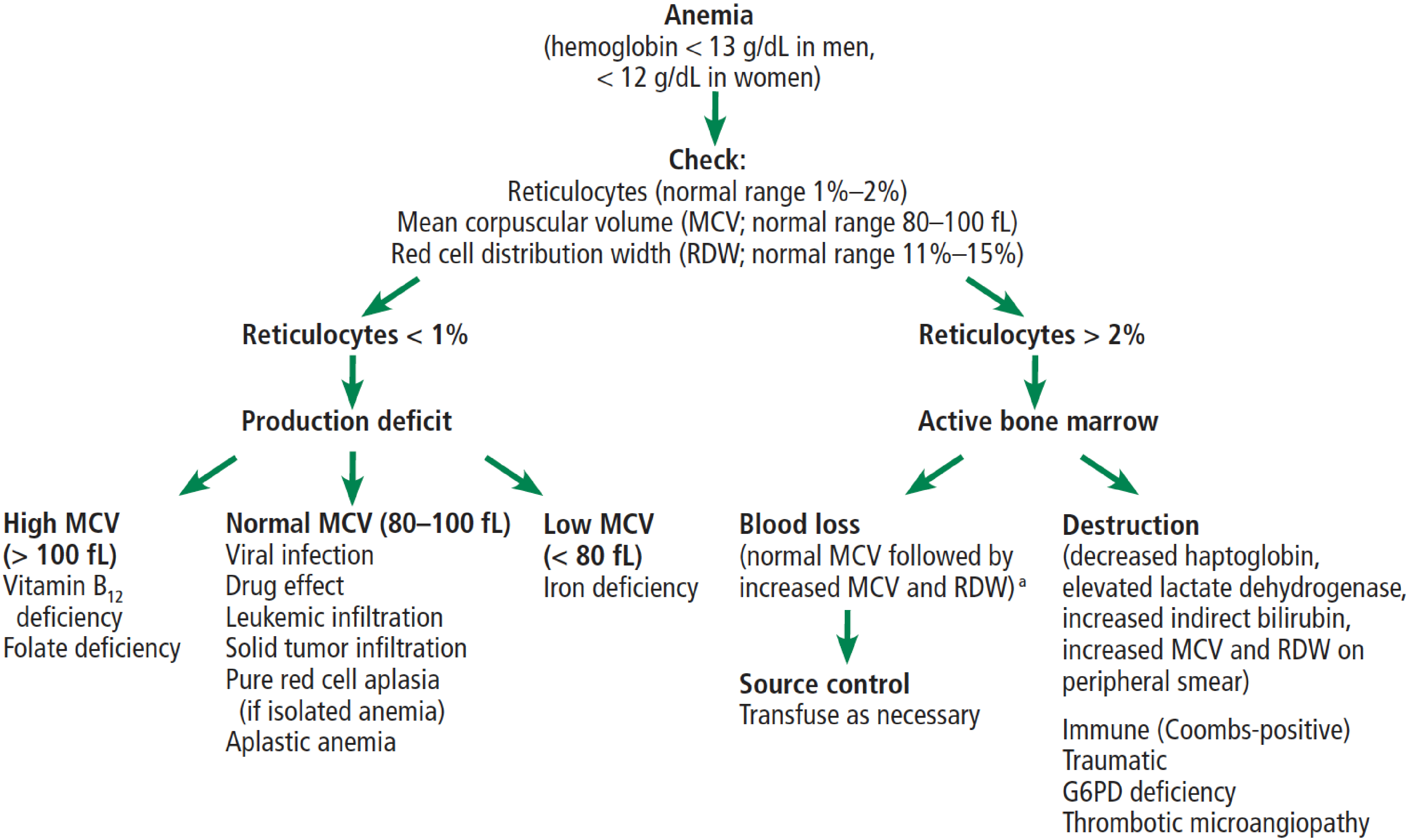
	Reference Range & Units
WBC3.5 - 11.0 x10exp9/L	**12.4 (H)**
RBC3.70 - 5.00 x10exp12/L	2.24
Hemoglobin11.0 - 15.0 G/DL	**6.8 (L)**
Hematocrit32.0 - 45.0 %	**19.3 (L)**
MCV80.0 - 98.0 fL	**102.6**
MCH26.0 - 34.0 PG	29.2
MCHC32.0 - 36.0 G/DL	33.2
RDW11.5 - 14.5 %	13.3
Platelets150 - 400 x10exp9/L	256
Seg Neutrophils %%	32.0
Lymphocytes %%	59.0
Monocytes %%	7.0
Eosinophils %%	1.0
Basophils %%	0.0
Segs Absolute1.5 - 7.5 x10exp9/L	4.0
Lymphocytes Absolute1.0 - 4.0 x10exp9/L	**7.3 (H)**
Monocytes Absolute0.2 - 0.8 K/uL	**0.9 (H)**
Eosinophils Absolute0.0 - 0.5 K/uL	0.1
Basophils Absolute0.0 - 0.2 x10exp9/L	0.0

Reticulocyte Hgb 30.6 - 36.0 pg	31.0
Reticulocyte % 0.9 - 2.7 %	**6.3 (H)**
Retic Ct Abs 39.0 - 129.9 x10exp9/L	**141.0 (H)**

Haptoglobin 63 – 273 MG/DL	**<8 (L)**

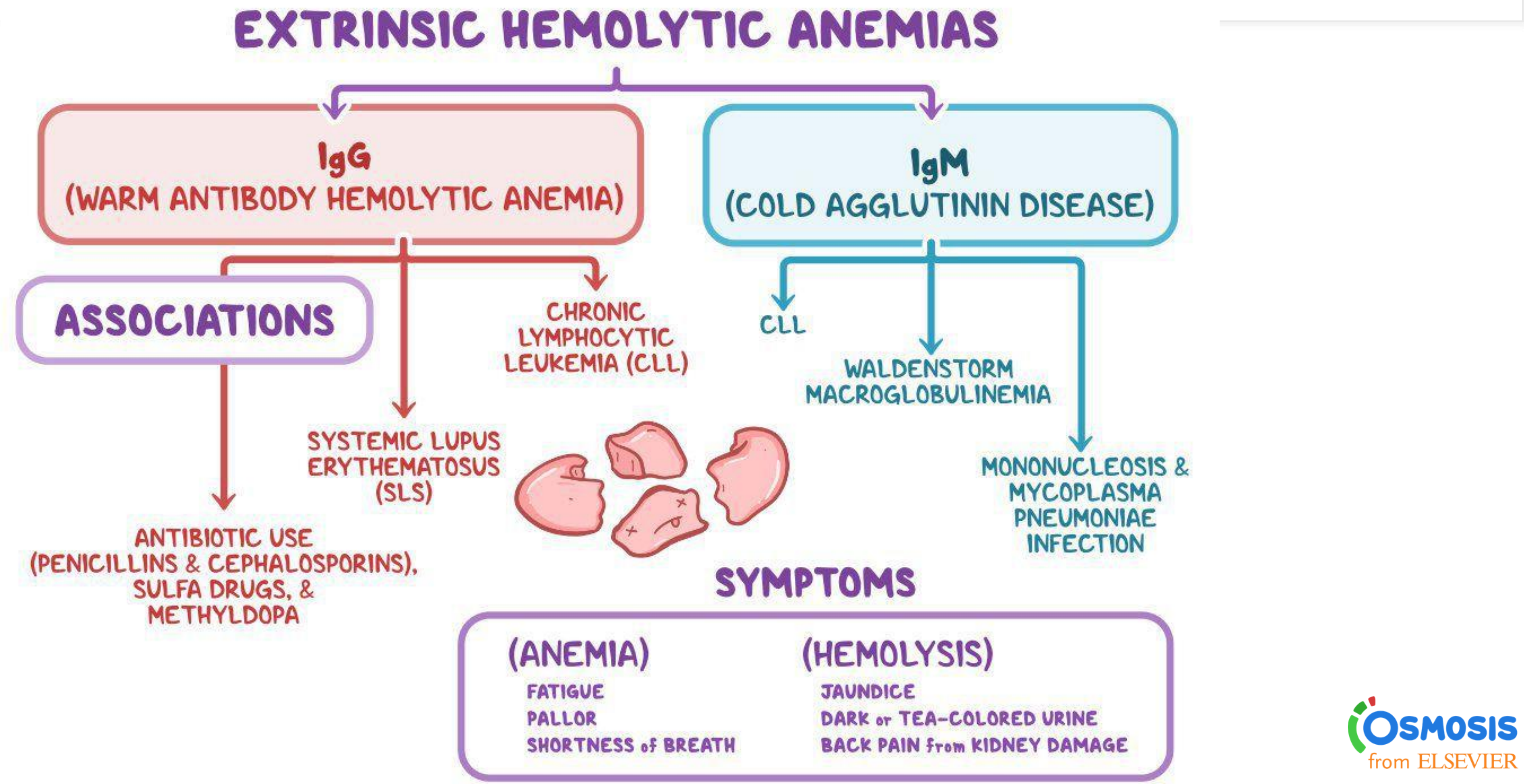
	Reference Range & Units
Sodium135 - 145 MEQ/L	**134 (L)**
Potassium3.6 - 5.1 MEQ/L	4.0
Chloride98 - 110 MEQ/L	102
CO222 - 32 MEQ/L	**21 (L)**
Anion Gap3 - 13	11
BUN6 - 24 MG/DL	**26 (H)**
Creatinine, Ser0.44 - 1.03 MG/DL	0.83
eGFRAbnormal <60 ML/MIN/1.73M	>60
Glucose67 - 99 MG/DL	**187 (H)**
Calcium8.5 - 10.5 MG/DL	8.5
Magnesium Level1.3 - 1.9 MEQ/L	1.7
AST (SGOT)10 - 42 IU/L	**153 (H)**
ALT6 - 45 IU/L	**108 (H)**
Alkaline Phosphatase34 - 104 IU/L	98
Protein, Total6.0 - 8.0 G/DL	6.8
Albumin3.5 - 5.0 G/DL	3.9
LDH100 - 220 IU/L	**696 (H)**
Bilirubin, Total0.2 - 1.3 MG/DL	**4.0 (H)**
Bilirubin, Direct0.0 - 0.3 MG/DL	**0.8 (H)**

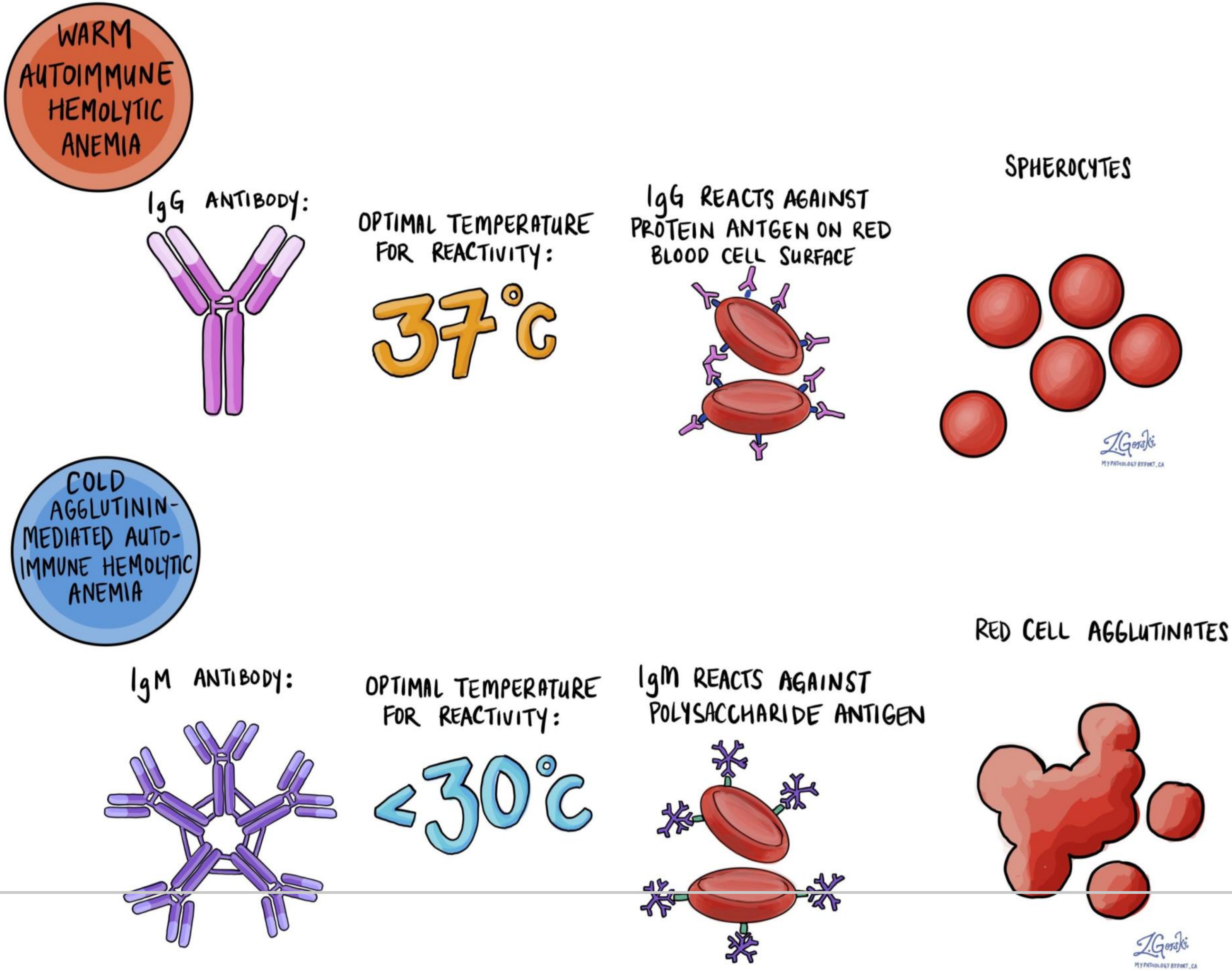
Direct Antiglobulin Test	POS 3+
ABORh	TypeA POS
Antibody Screen	POS
DAT Anti-C3	POS, 1+
DAT Anti-IgG	POS, 3+

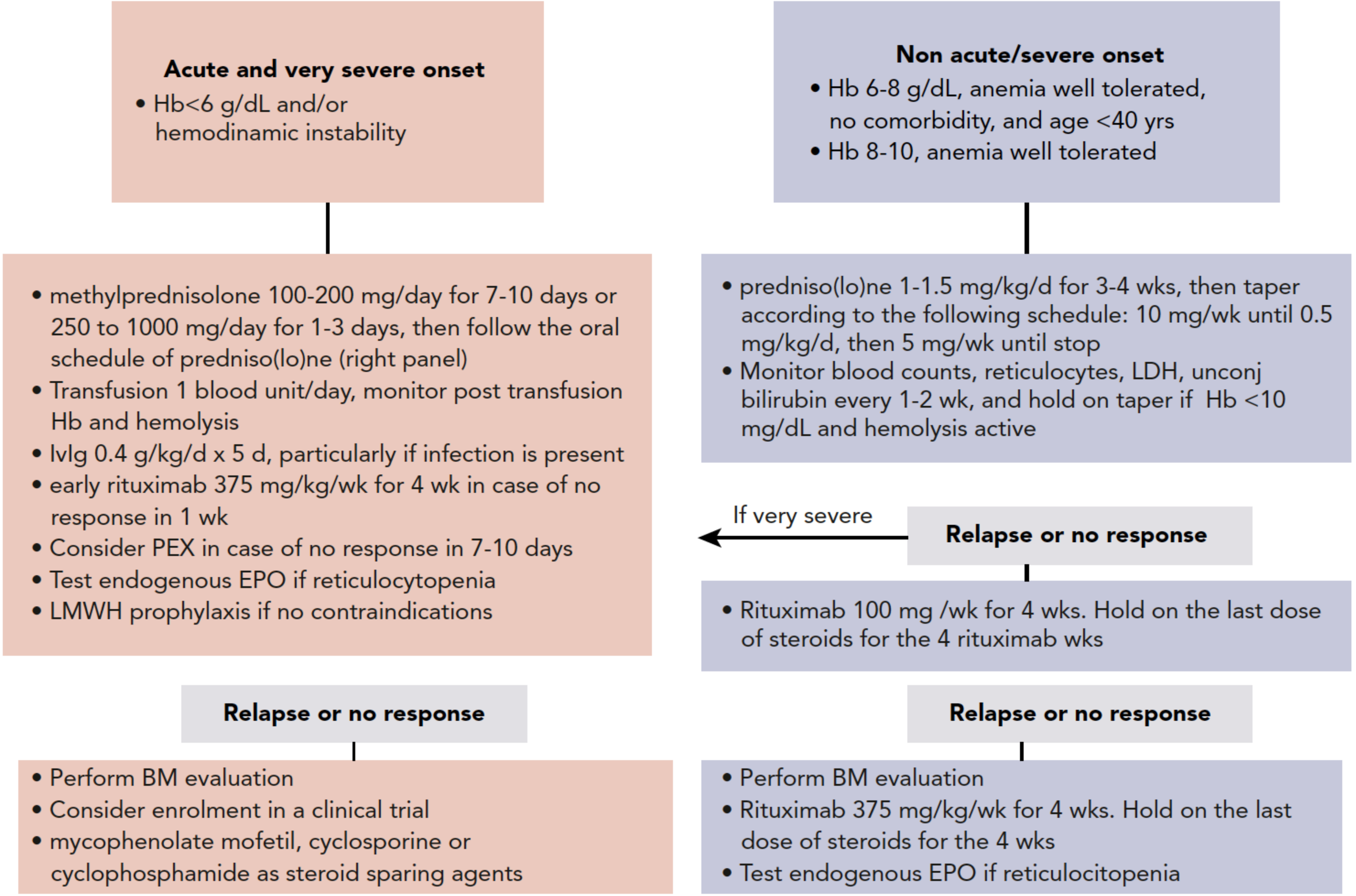


Ghanem S, Gonsky J. Recurrent anemia in a patient with chronic lymphocytic leukemia. Cleve Clin J Med. 2022

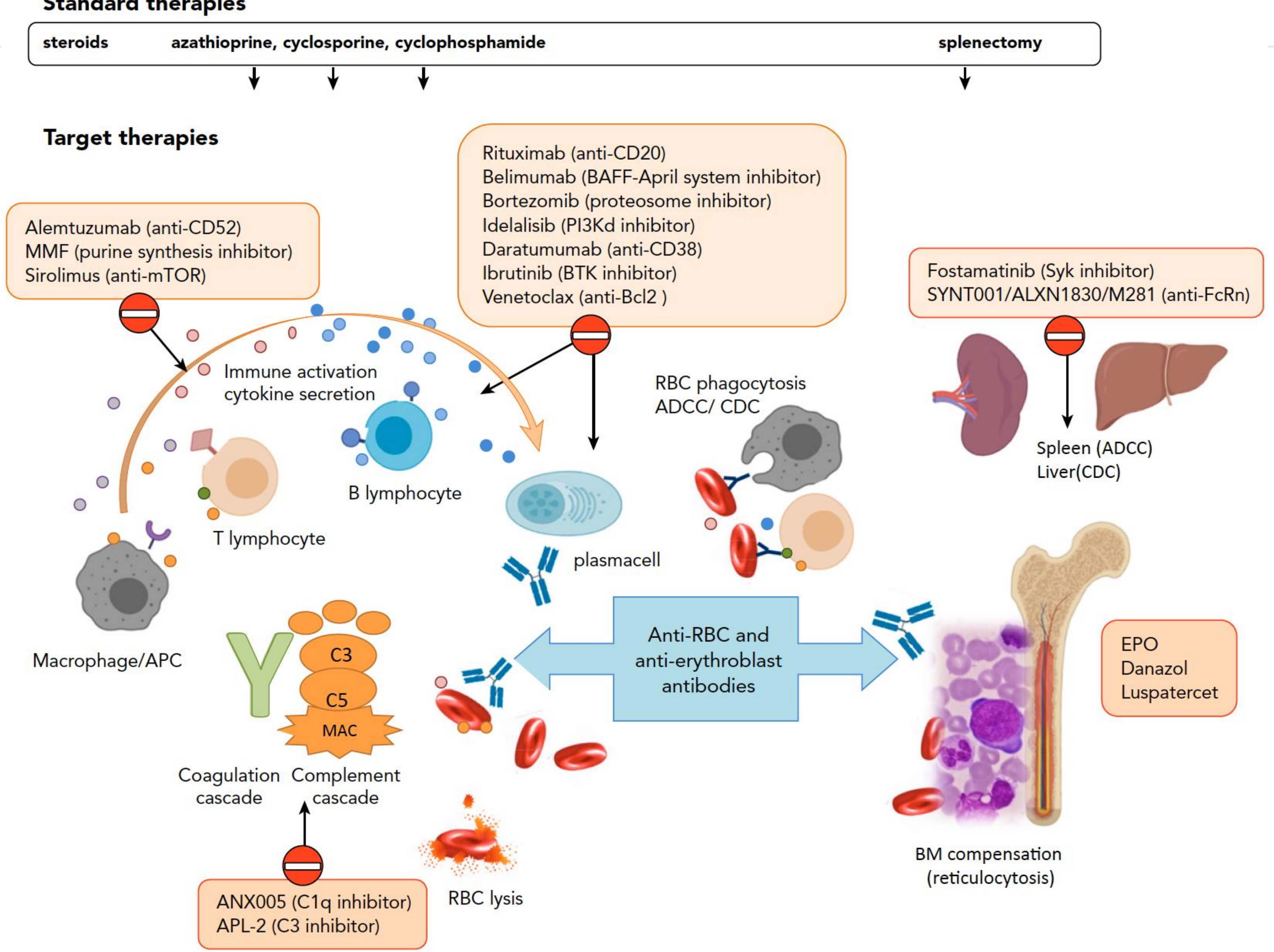
AUTOIMMUNE HEMOLYTIC ANEMIA




WARM AUTOIMMUNE HEMOLYTIC ANEMIA
IgG ANTIBODY:
OPTIMAL TEMPERATURE FOR REACTIVITY:
37°C
IgG REACTS AGAINST PROTEIN ANTGEN ON RED BLOOD CELL SURFACE
SPHEROCYTES
COLD AGGLUTININ-MEDIATED AUTO-IMMUNE HEMOLYTIC ANEMIA
IgM ANTIBODY:
OPTIMAL TEMPERATURE FOR REACTIVITY:
<30°C
IgM REACTS AGAINST POLYSACCHARIDE ANTIGEN
RED CELL AGGLUTINATES



Barcellini W, Fattizzo B. How I treat warm autoimmune hemolytic anemia. Blood. 2021



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