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Nong Dang and Friends

Hemato Rama

Common Problems in Hematology 2026

Educational Course For Residency Program in Medicine
Supported by Berlin

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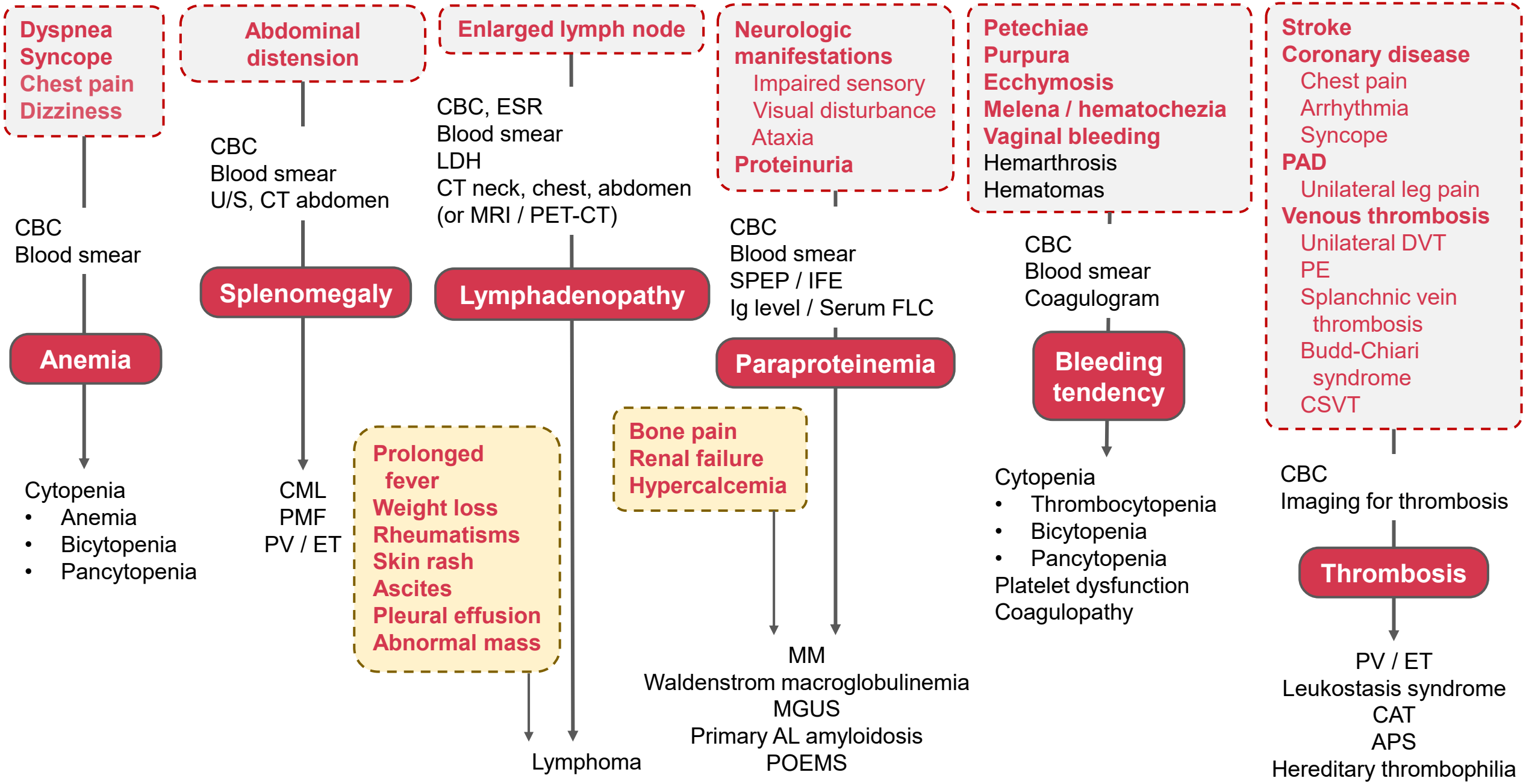
April 25, 2026

Outline

Case-based MCQs

- **Q1** A 52 y.o. patrol business owner
  Worsening fatigue for 4 months.
- **Q2** A 40 y.o. orchard farmer
  Progressive fatigue for 2 months.
- **Q3** A 28 y.o. nursing practitioner
  Off-and-on transient confusion for 3 weeks
- **Q4** An 80 y.o. retired teacher
  Progressing spontaneous ecchymoses for a week
- **Q5** A 30 y.o. pregnant banker
  Antenatal consultation
- **Q6** A 55 y.o. street vendor
  Acute dyspnea for 3 days
- **Q7** A 40 y.o. athlete
  Sudden right hemiparesis with aphasia
- **Q8** A 60 y.o. shoemaker
  Subacute fever with acute GI bleeding
- **Q9** A 35 y.o. TikToker
  Progressive dyspnea for 3 months
- **Q10** A 62 y.o. university lecturer
  Progressive dyspnea for 2 week

Symptomatology for Hematologic Problems




Case 1

Q1

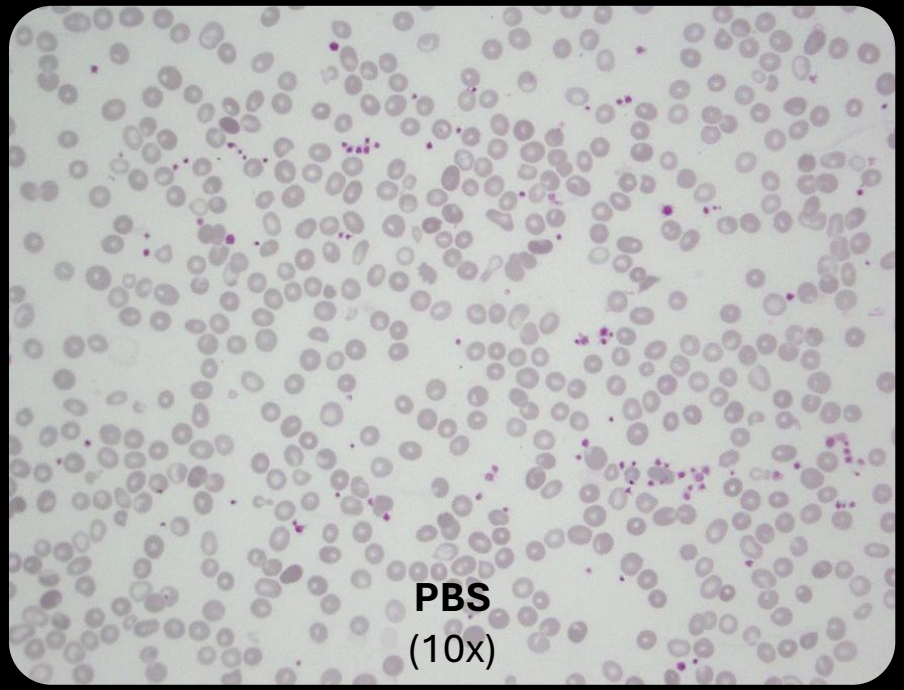
A 52-year-old female patrol business owner presents to the clinic with a 4-month history of worsening fatigue, intermittent "pins and needles" sensations in her feet, and a sore, smooth tongue. She has a history of Hashimoto thyroiditis with currently treated with L-thyroxine replacement. Physical examination reveals conjunctival pallor, a beefy red tongue with loss of papillae, and decreased vibration sense in the lower extremities. There is no jaundice or organomegaly.

Laboratory investigations:

- CBC: Hb 8.5 g/dL, Hct 26%, MCV 105 fL, WBC count 3,800/μL (N 45, L 45, M 5), platelet count 130,000/μL.
- Total bilirubin 1.4 mg/dL and LDH 850 U/L. Ferritin 350 ng/mL.
- Direct Coombs test is negative.

What is the most likely diagnosis?

A. Acquired hypocupremia
B. Atypical hemolytic uremic syndrome (aHUS)
C. Cobalamin deficiency
D. Mixed-type autoimmune hemolytic anemia (AIHA)
E. Paroxysmal nocturnal hemoglobinuria (PNH)



PBS
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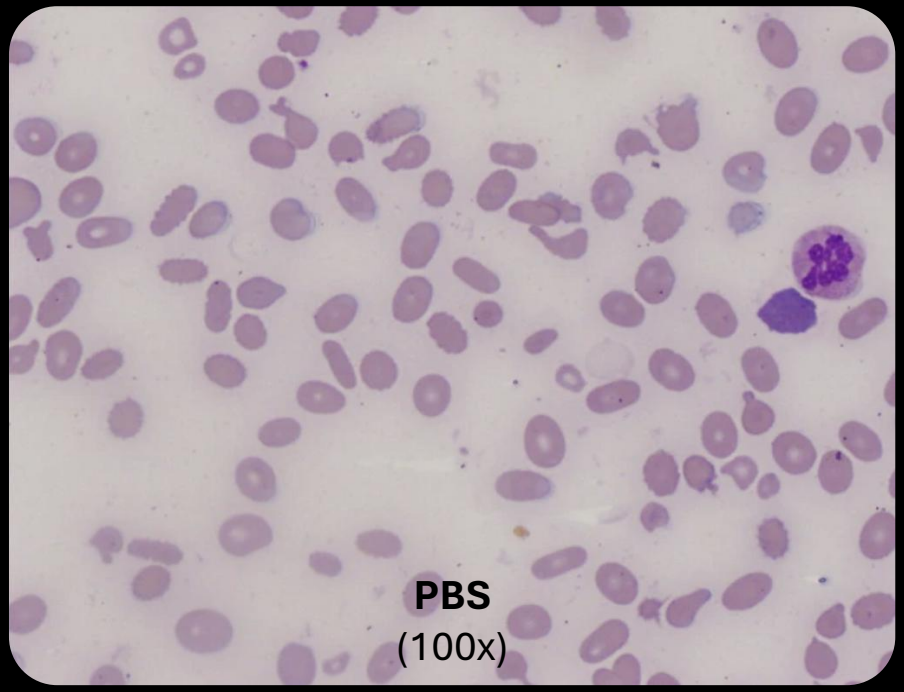

PBS
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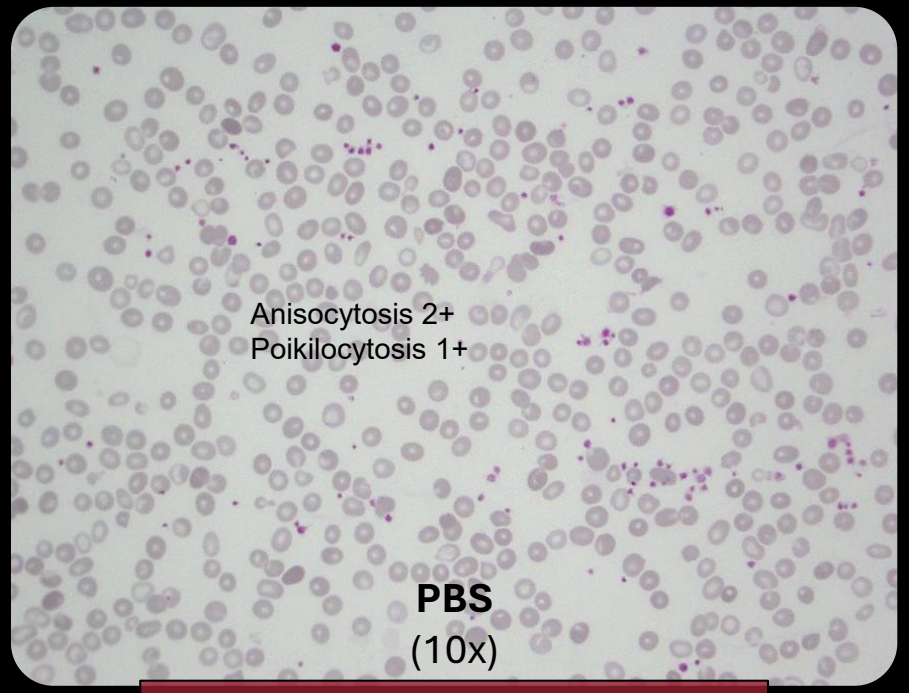
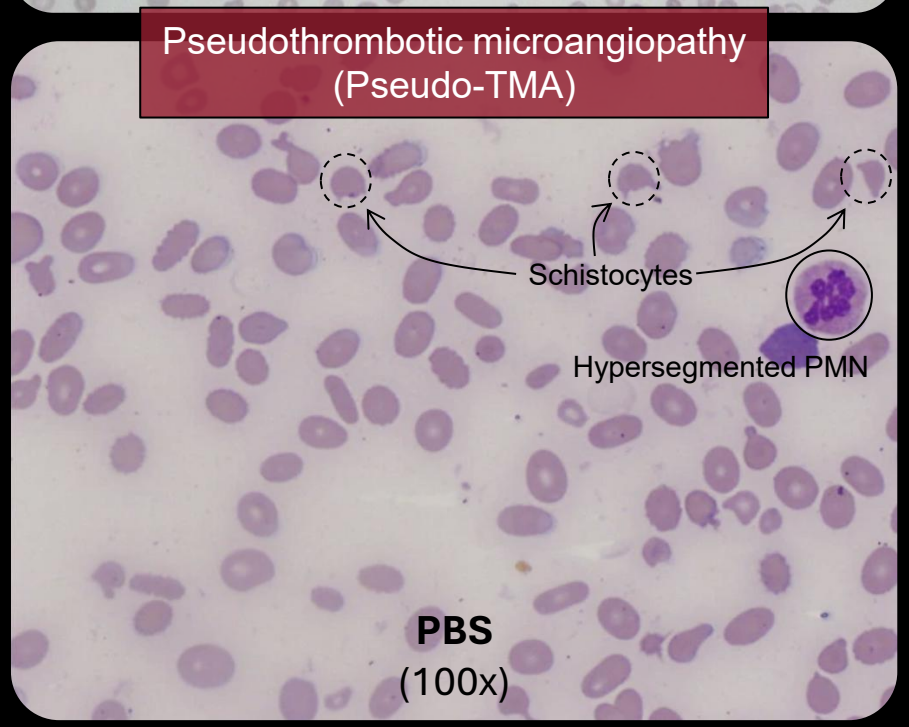




Cobalamin (Vitamin B12) Deficiency

How to Approach Case 1

1

Chronic dyspnea

- Cardiac
- Pulmonary
- Others
  - Anemia
  - Endocrine
  - Psychogenic

RI <2%

2

Hypoproliferative anemia

- Nutrient deficiency
- ↓ EPO activity
- ↓ Space in marrow
- Stem cell defect

Supporting data
MCV >100
Hypersegmented PMN
Pseudo-TMA feature

Megaloblastic anemia

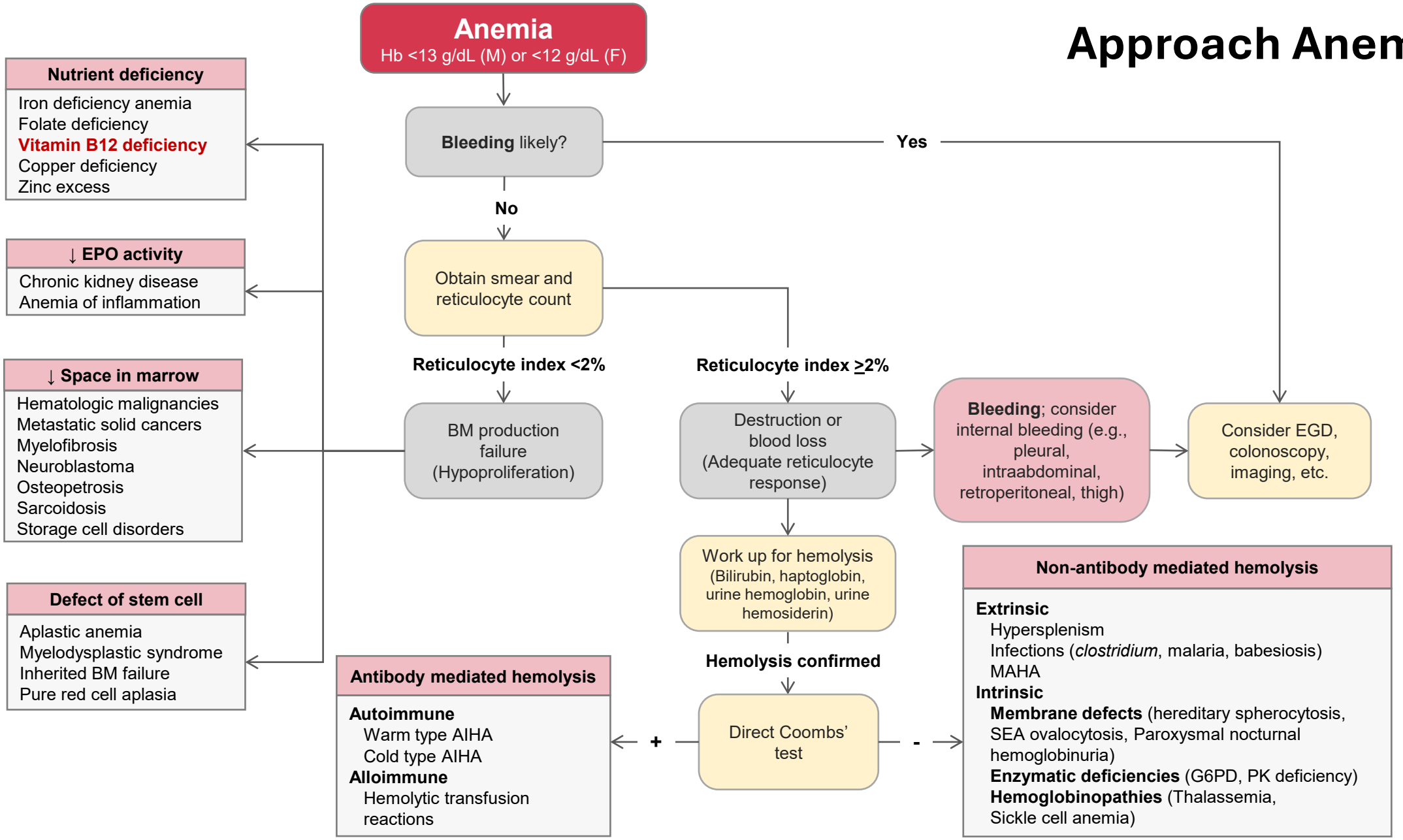
Cobalamin (Vitamin B12) deficiency

Folic deficiency
Copper deficiency
Zinc excess

Pernicious anemia

Supporting data
Hashimoto thyroiditis
Beefy red tongue
Loss of proprioception

Approach Anemia



Approach to Macrocytic Anemia (MCV > 100 fL)

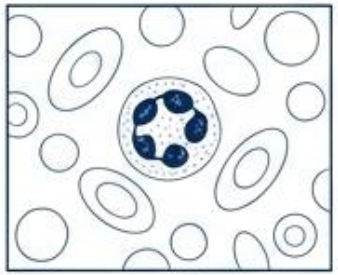
MCV > 100 fL

Reticulocyte Count < 1%
(Underproduction)

Peripheral Smear
Evaluation

Megaloblastic

– Impaired DNA synthesis
– Causes:
  - B12 Deficiency
  - Folate Deficiency
  - Drug-induced
    (Methotrexate, Hydroxyurea)

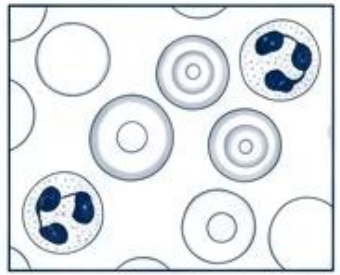


Reticulocyte Count > 2%
(Hyperproliferation)

Workup for Hemolysis or
Acute Hemorrhage

Non-Megaloblastic

– Causes:
  - Liver disease
  - Alcoholism
  - Hypothyroidism
  - MDS



Vitamin B12 Metabolism & Physiology

Panel A: The Gastrointestinal Pathway

Stomach: Dietary B12 cleaved by pepsin/HCl → binds Salivary Haptocorrin **(R-binder)**.

Parietal cells secrete **Intrinsic Factor (IF)**.

↓

Duodenum: Pancreatic proteases degrade haptocorrin → B12 binds to IF.

↓

Terminal Ileum: IF-B12 complex endocytosed via Cubam Receptors (cubilin/amnionless).

↓

Bloodstream: Secreted bound to Transcobalamin II (active Holotranscobalamin).

Panel B: The Cellular Enzymatic Map

Reaction 1 (Cytoplasm):

Methylcobalamin acts as cofactor for Methionine Synthase.

Homocysteine + 5-methyl-THF → Methionine + THF

Failure causes '**Folate Trap**' and Hyperhomocysteinemia.

Reaction 2 (Mitochondria):

Adenosylcobalamin acts as cofactor for Methylmalonyl-CoA mutase.

Methylmalonyl-CoA → Succinyl-CoA

Failure causes **Methylmalonic Acid** (MMA) accumulation, impairing lipid metabolism/myelin synthesis.

Etiologies of Vitamin B12 Malabsorption & Deficiency

1. Nutritional / Intake

- Vegan/strict vegetarian diets without supplementation.
- Exclusively breastfed infants of vegan mothers (rapid depletion of minimal liver stores).

2. Gastric Malabsorption

- Pernicious Anemia (Autoimmune Atrophic Gastritis).
- Gastrectomy / Roux-en-Y gastric bypass (loss of IF-producing parietal cells).
- Achlorhydria (age-related or *H. pylori*).

3. Intestinal Malabsorption

- Crohn's disease / Ileal resection (loss of Cubam receptors).
- *Diphyllobothrium latum* (tapeworm competitive consumption).
- Small Intestine Bacterial Overgrowth (SIBO).

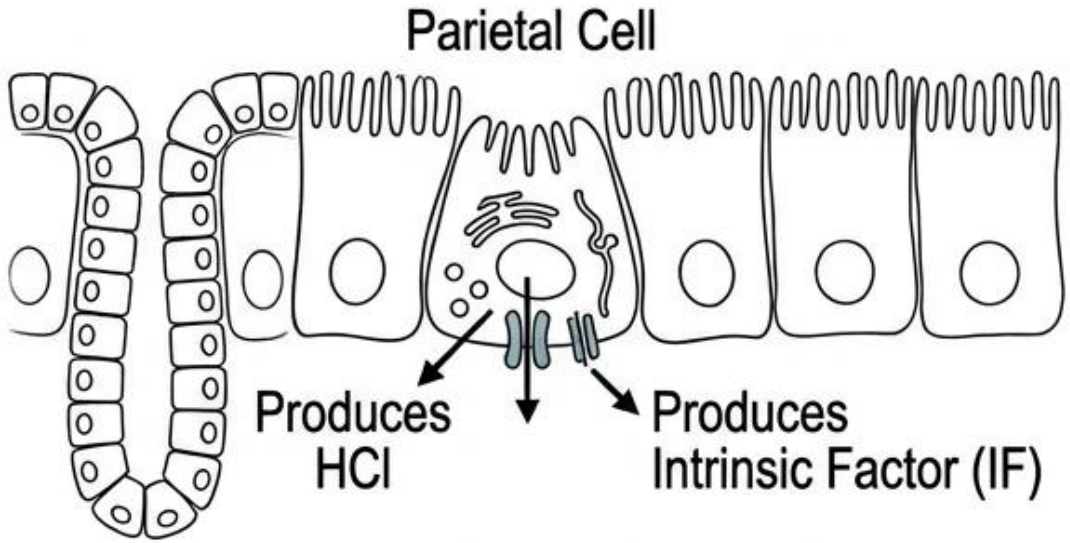
4. Medications & Toxins

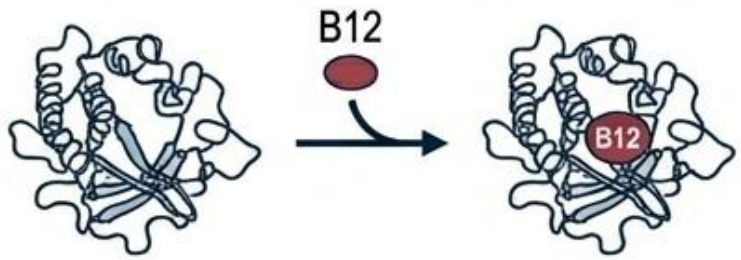
- Metformin & prolonged PPI/H2 blockers (>12 months).
- Nitrous Oxide (N2O): Irreversibly oxidizes the cobalt core from active Co1+ to inactive Co3+.

Pathogenesis of Pernicious Anemia

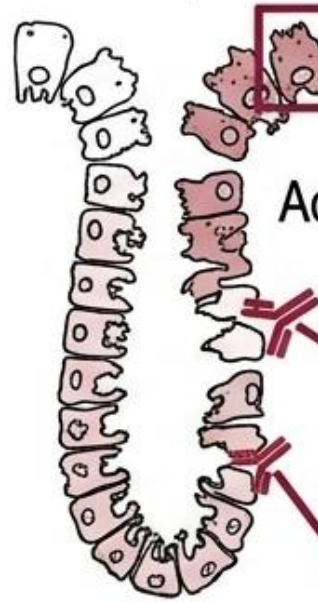
Note: Pernicious Anemia is a late-stage manifestation of autoimmune metaplastic atrophic gastritis, often co-occurring with Type 1 DM, vitiligo, and autoimmune thyroid disease.

Normal Physiology

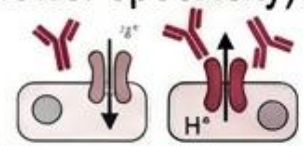




Autoimmune Destruction

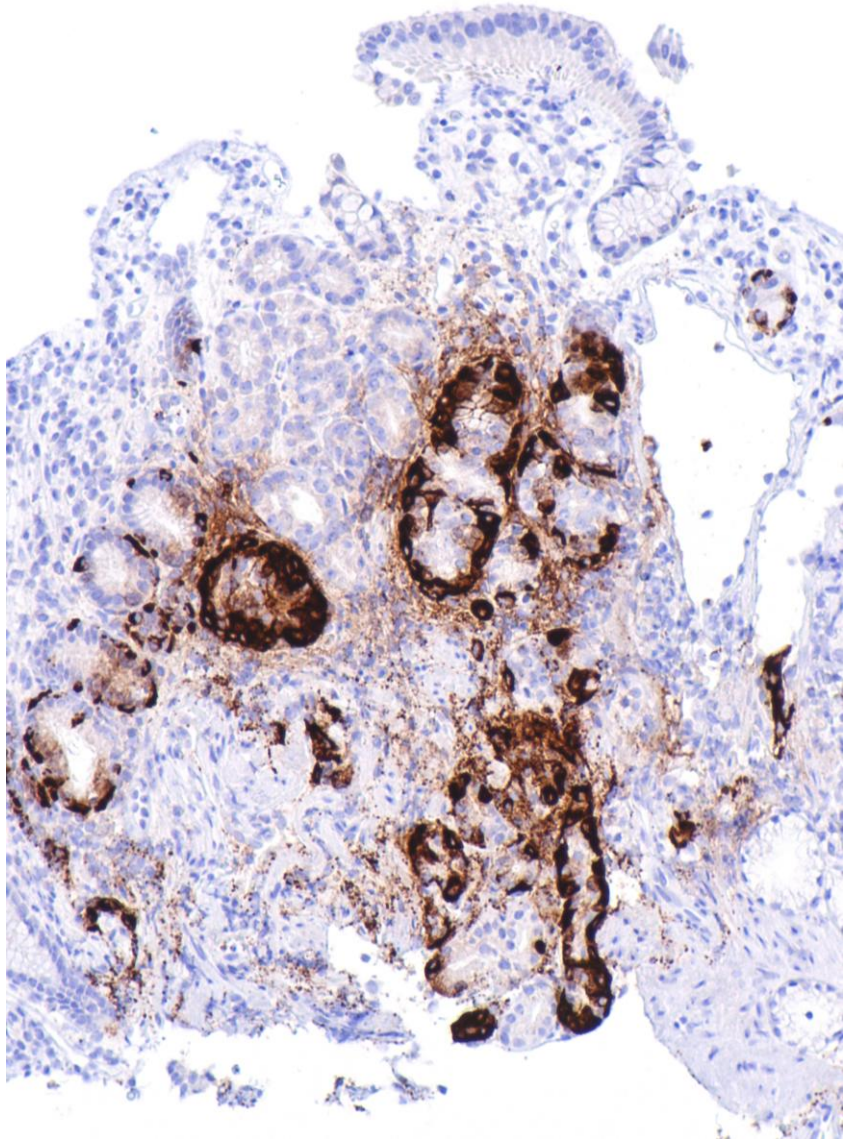


1 **Anti-Parietal Cell Antibodies:** Attack the H^+/K^+ ATPase pump (high sensitivity ~90%, lower specificity).



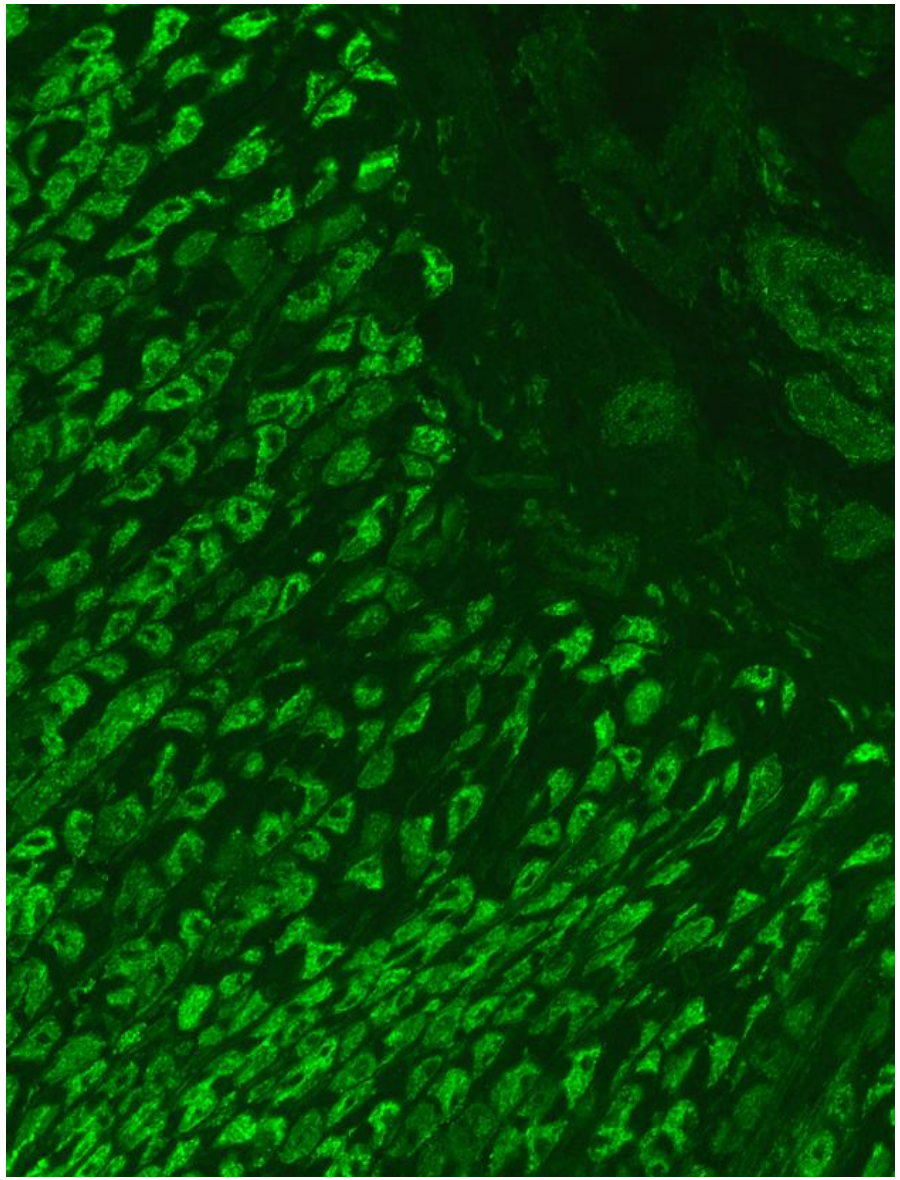
2 **Type I (Blocking) Anti-IF Antibodies:** Bind to the cobalamin-binding site of IF, preventing the initial IF-B12 complex formation.

3 **Type II (Binding) Anti-IF Antibodies:** Bind to a secondary site on IF, preventing the IF-B12 complex from attaching to ileal cubam receptors.



Micrograph showing nodular enterochromaffin-like cell hyperplasia, as demonstrated with chromogranin A immunostaining, in the body of the stomach. Parietal cells are not readily apparent.

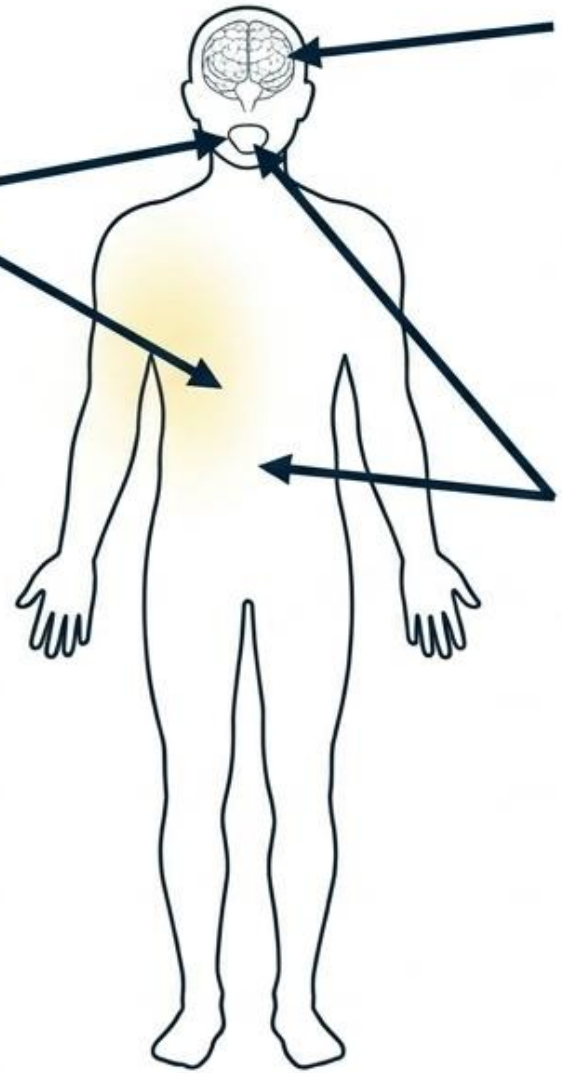
These changes are in keeping with autoimmune metaplastic atrophic gastritis.



Immunofluorescence staining pattern of gastric parietal cell antibodies on a stomach section

Clinical Manifestations: Hematologic, Neurologic, and GI

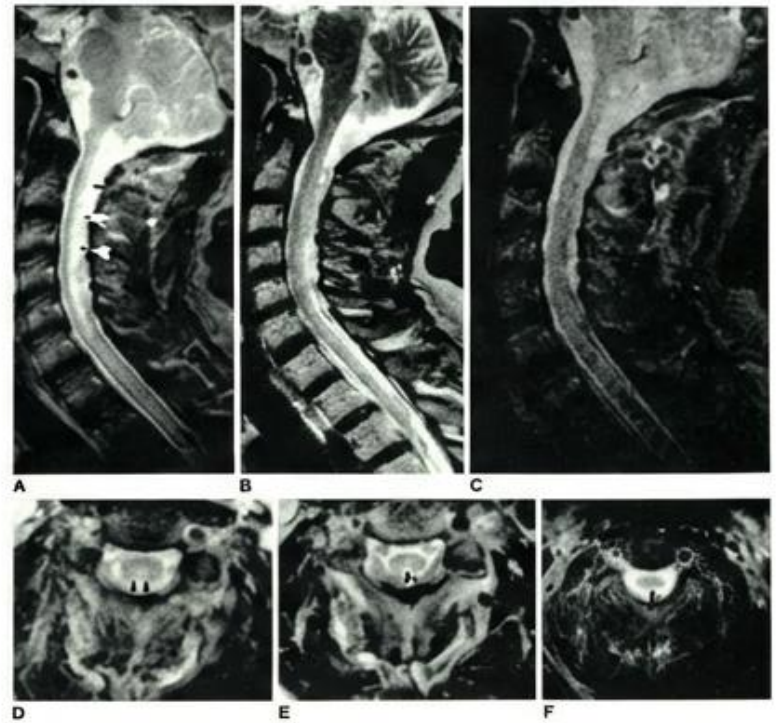
Hematologic:
Insidious onset. Fatigue, pallor, tachycardia, and 'lemon-yellow' skin (pallor mixed with jaundice from intramedullary hemolysis).



Neuro-Psychiatric:
'Megaloblastic Madness' (paranoia, delusions, cognitive decline).

Gastrointestinal:
Hunter glossitis (tender, smooth, red, beefy tongue), dyspepsia, anorexia.

Subacute Combined Degeneration (SCD)

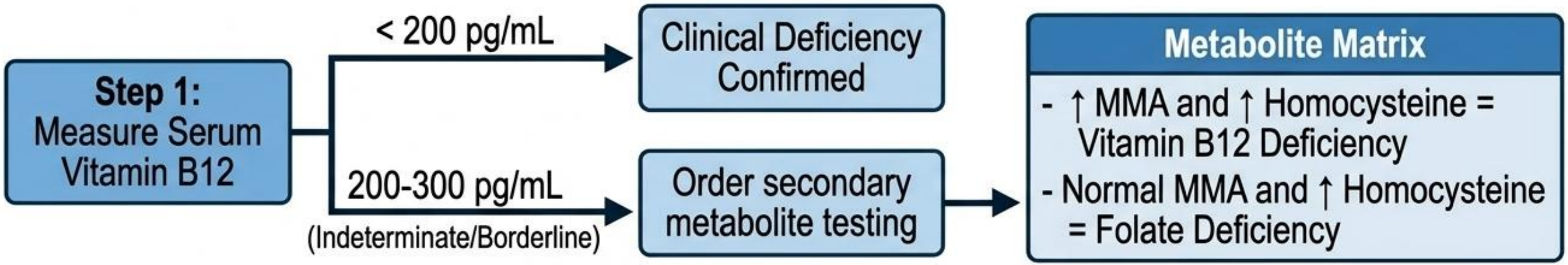


Demyelination of dorsal and lateral columns. Presents as bilateral loss of vibratory/proprioceptive sensation, spasticity, ataxia, and positive Romberg sign.

Crucial Note: Neurologic symptoms can occur in up to 30% of patients without macrocytosis or anemia.

Diagnostic Algorithm & Serological Evaluation

Horizontal Flowchart for B12 Assessment



Comparison Table for Pernicious Anemia Serology

Serological Test	Sensitivity & Specificity	Clinical Utility
Anti-Intrinsic Factor (Anti-IF) Antibodies	Sensitivity: 40-60%. Specificity: ~100%.	Confirmatory rule-in test. BCSH recommends testing in all suspected cases.
Anti-Parietal Cell Antibodies	Sensitivity: ~90%. Specificity: Low.	Not routinely recommended for specific PA diagnosis due to presence in healthy elderly and other autoimmune conditions.

Management Protocols and Long-Term Surveillance

Induction Therapy

Protocol: Intramuscular (IM) Cyanocobalamin/Hydroxocobalamin. 1000 mcg daily or every other day for 1-2 weeks.

Goal: Rapid replenishment of hepatic stores and immediate cessation of neurological progression.

(**Note**: Folate replacement without B12 will correct anemia but allow irreversible neurological damage).

Maintenance Therapy

IM Route: 1000 mcg monthly (Cyanocobalamin) or every 2-3 months (Hydroxocobalamin).

High-Dose Oral Route: 1000-2000 mcg daily.

Mechanism: Relies on 1% to 1.2% passive diffusion pathway independent of Intrinsic Factor. Efficacy proven equivalent to IM in meta-analyses.

Oncological Surveillance

Risk: 11-fold increased risk of gastric carcinoid tumors and elevated risk for gastric adenocarcinoma.

Guideline (AGA/BSG): Baseline endoscopy with topographical biopsies in patients ≥50 years with newly diagnosed PA to confirm corpus-predominant atrophic gastritis and rule out prevalent neoplasia.

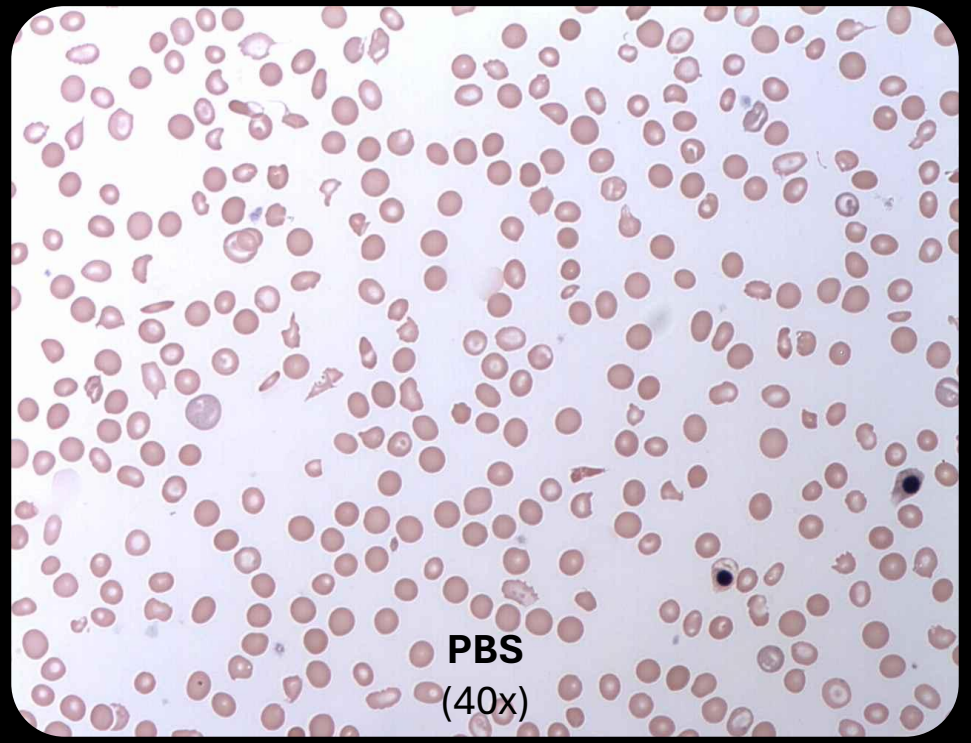

Case 2

Q2

A 40-year-old male orchard farmer presents with progressive fatigue for 2 months. He also reports mild shortness of breath on exertion. He denies bleeding, weight loss, or recent infections. Physical examination shows pallor without organomegaly.

Laboratory investigations:

- CBC: Hb 8.5 g/dL, Hct 26%, MCV 100 fL, WBC count 4,500/µL (N 45, L 45, M 5), platelet count 140,000/µL.
- Total bilirubin 2.0 mg/dL and LDH 450 U/L. Ferritin 14 ng/mL.
- Negative direct Coombs test.
- Urinalysis: positive hemoglobin, RBC 0-1 cells



What is the most appropriate next investigation?

A. Repeated direct Coombs test
B. Lead level
C. Serum ceruloplasmin
D. Flow cytometry for CD55 and CD59
E. Bone marrow aspiration and biopsy

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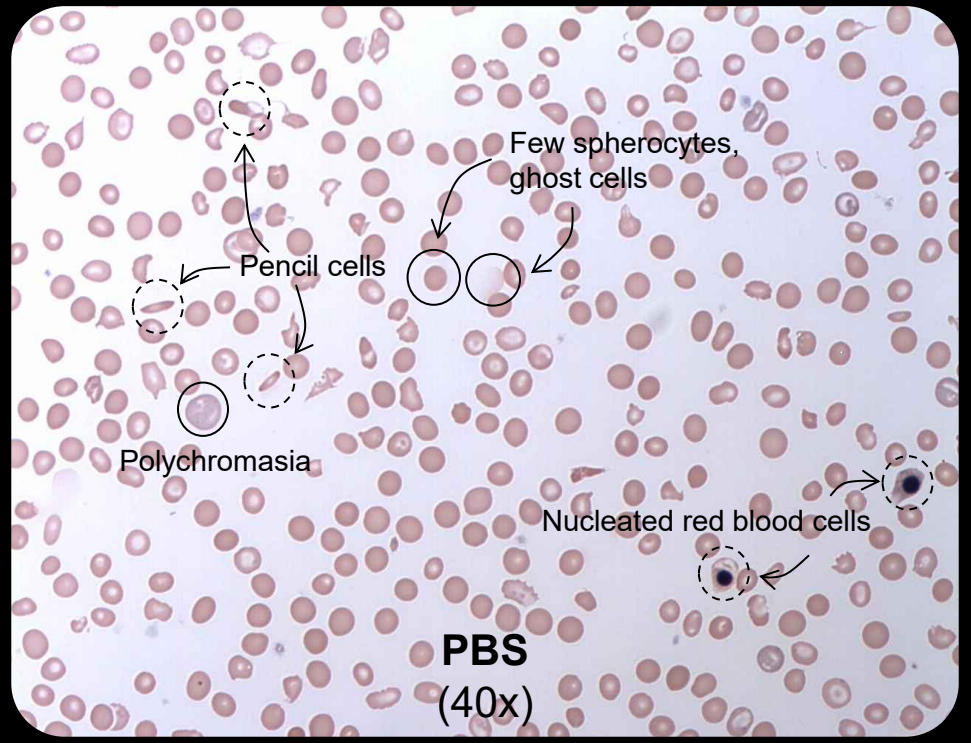
Microcytic 1+, Hypochromic 1+
Anisocytosis 2+
Poikilocytosis 1+



Blood smear interpretation:
1. intravascular hemolysis
2. Iron deficiency anemia

Paroxysmal nocturnal hemoglobinuria

Paroxysmal Nocturnal Hemoglobinuria

How to Approach Case 2

1

Chronic dyspnea

- Cardiac
- Pulmonary
- Others
  - Anemia
  - Endocrine
  - Psychogenic

RI >2%
LDH ↑
Bilirubin ↑

No bleeding history

2

Hemolytic anemia

- Extrinsic
- Intrinsic

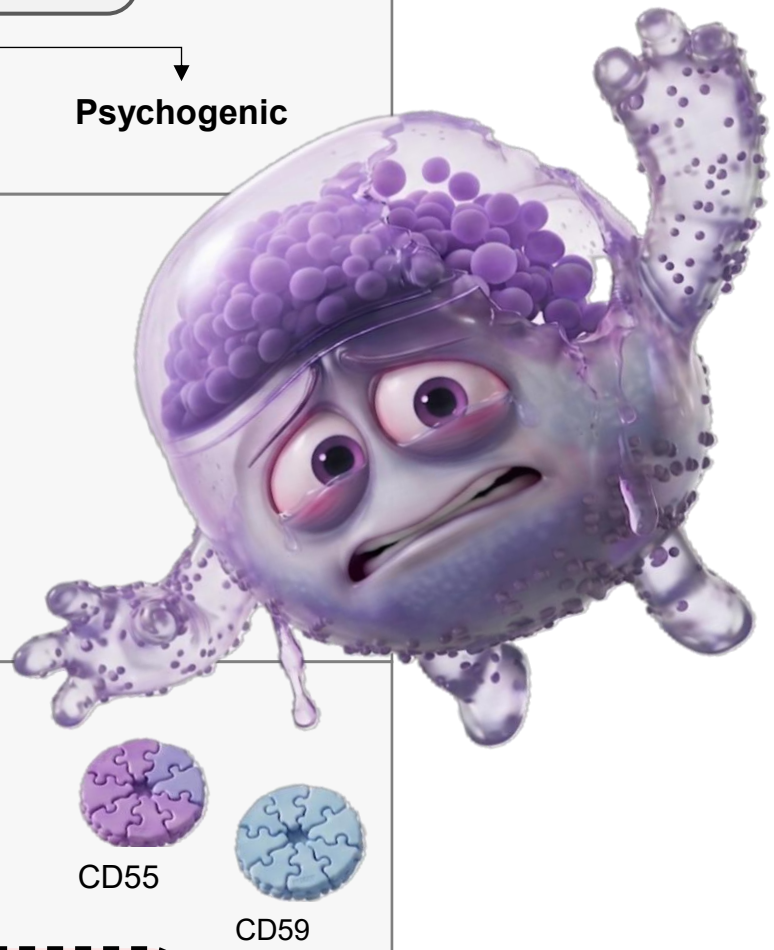
PBS: No MAHA

3

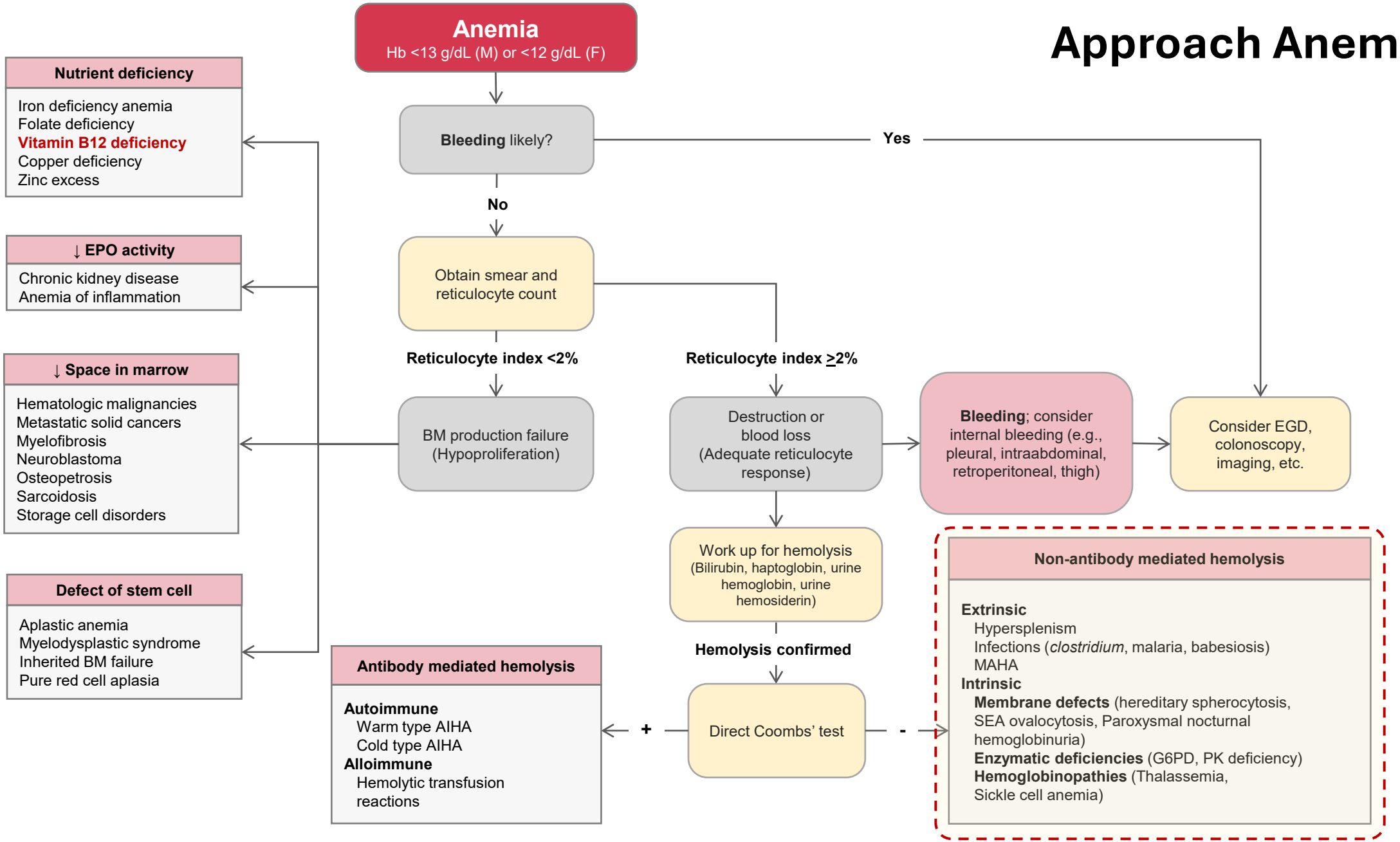
- Membrane defects → Hereditary RBC membranopathies

x Family history
Low ferritin and haptoglobin
FCM for CD55/CD59 +ve

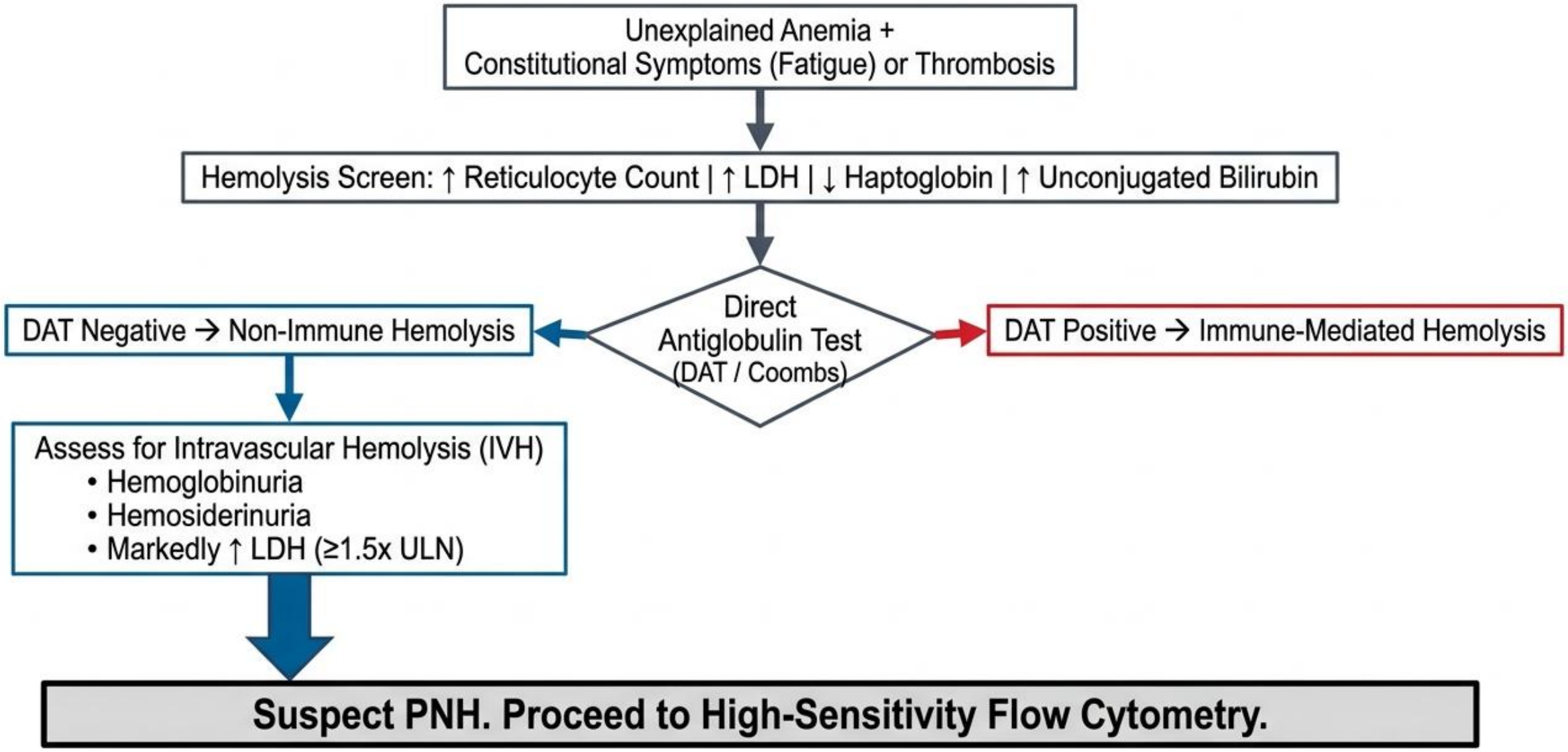
- Acquired clonal disorders → Paroxysmal nocturnal hemoglobinuria (PNH)



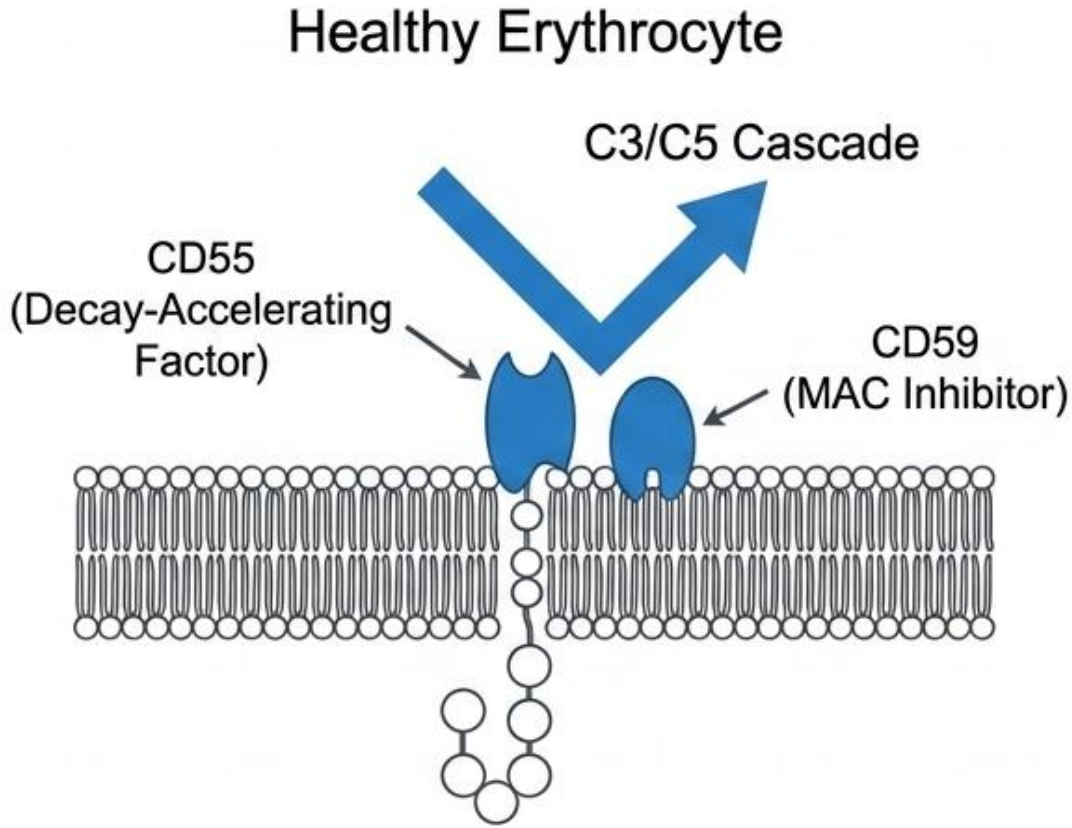
Approach Anemia

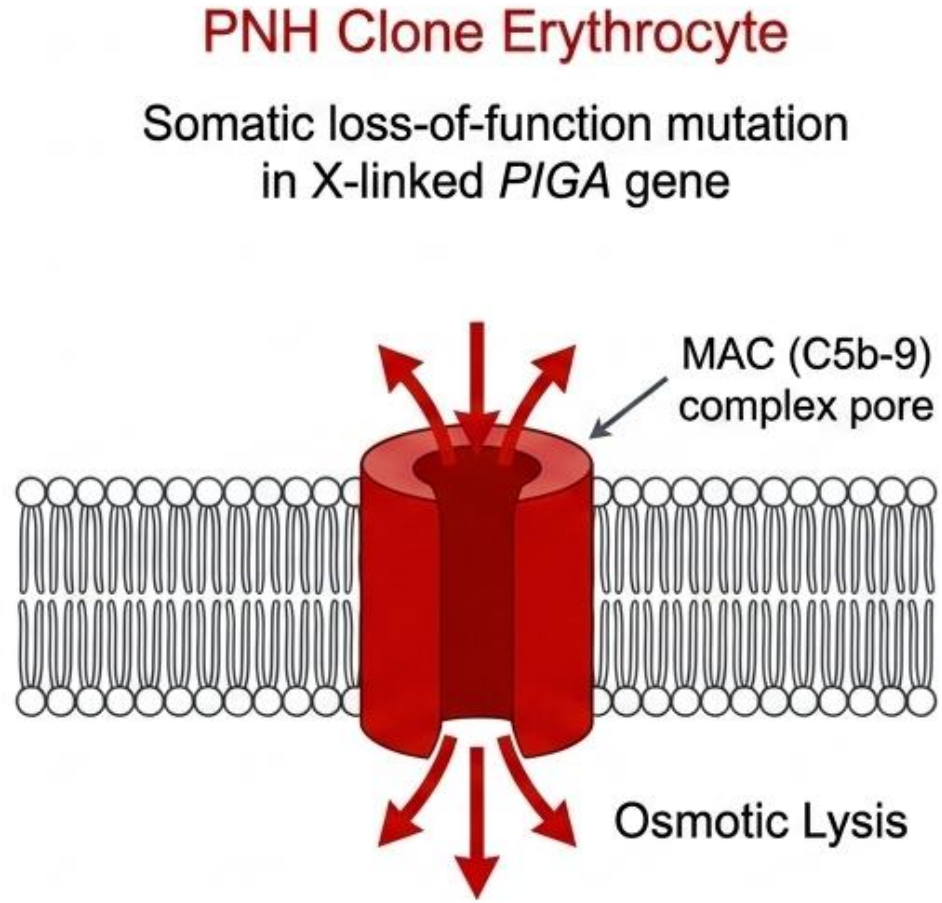


Approach to Chronic Hemolytic Anemia

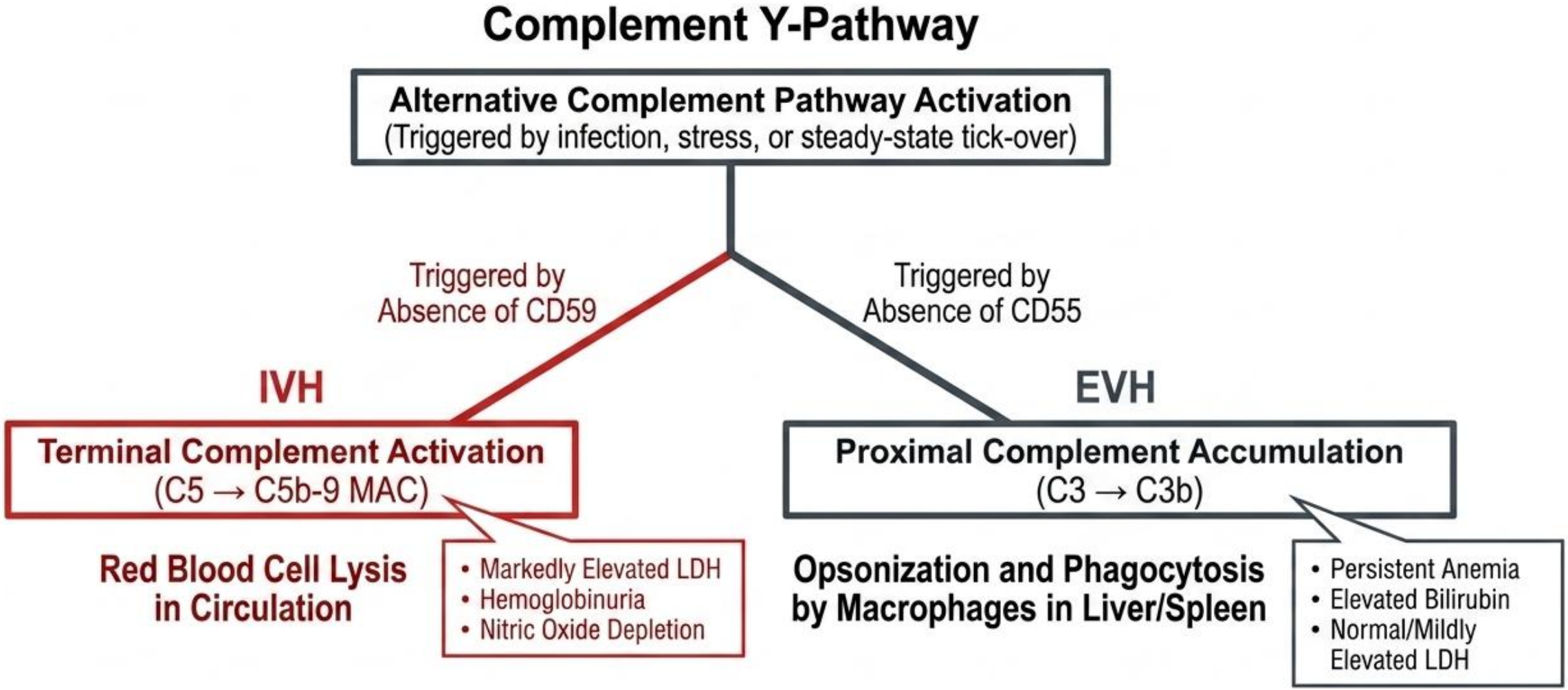


Pathophysiology:
The *PIGA* Mutation and GPI-Anchor Loss





The Dual Mechanisms of Hemolysis



Clinical Manifestations: The PNH Triad

Fatigue

Dysphagia

Esophageal spasms

Erectile dysfunction

(Driven by Nitric Oxide scavenging)

Intravascular Hemolysis

Thrombophilia

Venous/Arterial Clots: Leading cause of mortality (40-67% of deaths).

High predilection for atypical sites: Hepatic (Budd-Chiari), Cerebral Sinus, Splanchnic veins.

Chronic Kidney Disease (CKD) - up to 64% incidence

Pulmonary Hypertension - ~50% incidence

Bone Marrow Failure

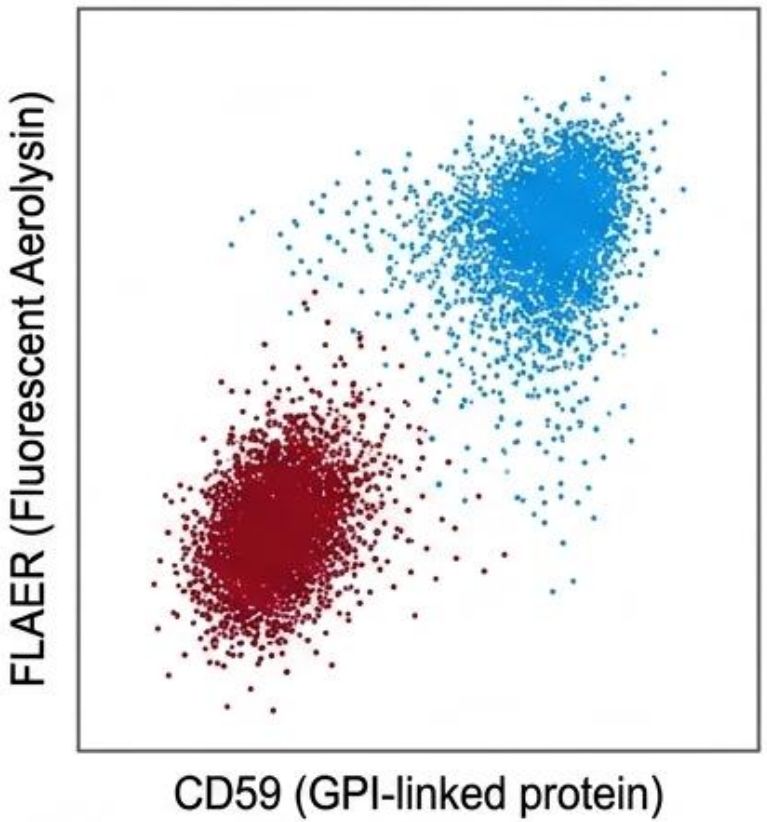
Cytopenias

Overlap with Aplastic Anemia (AA)

Overlap with Aplastic Anemia (AA)

Overlap with Myelodysplastic Syndromes (MDS)

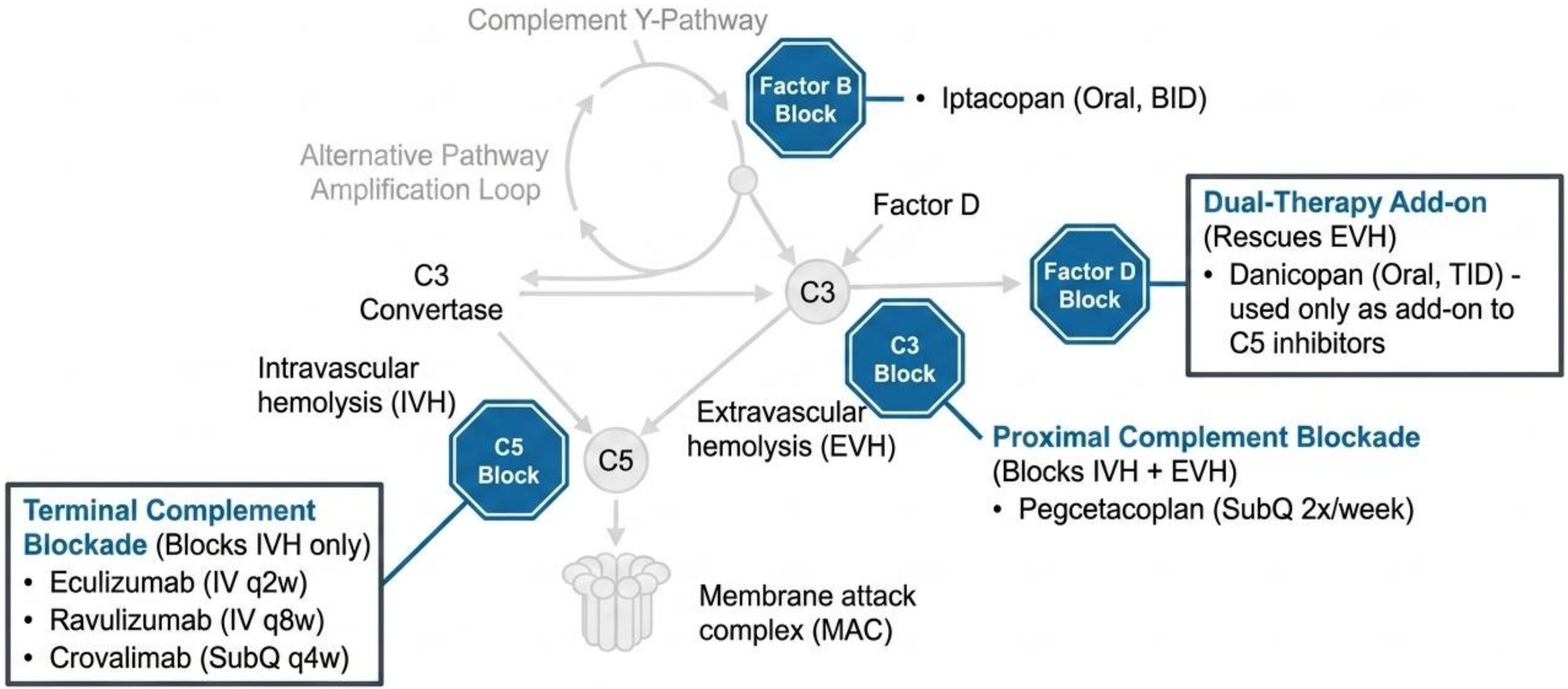
Diagnosis and Clinical Classification



High-sensitivity flow cytometry (FLAER) on granulocytes/monocytes accurately sizes the clone.

Classification	Clone Size	Hemolysis	BMF	Clinical Focus
Classical PNH	Large (>50%)	**Prominent (High LDH)**	Subclinical	**Hemolysis & Thrombosis**
PNH with BMF (AA/MDS)	Small to Moderate (<50%)	Mild/Absent	Prominent cytopenias	Treating underlying marrow failure
Subclinical PNH	Minute (<1%)	Absent	Associated with AA	Routine monitoring only

Management: The Complement Inhibitor Era



Management: Special Scenarios and HSCT

Breakthrough Hemolysis

Triggered by severe complement amplification (infection, surgery, trauma).

1. Confirm medication adherence.
2. Rule out/treat underlying infection.
3. Consider inhibitor dose intensification or switching to/adding a proximal inhibitor.

Pregnancy

Extremely high thrombotic risk. Requires multidisciplinary coordination.

- Prophylactic anticoagulation (LMWH) is mandatory.
- C5 inhibitors (Eculizumab/Ravulizumab) are considered safe and standard of care to prevent catastrophic maternal/fetal outcomes.

Allogeneic Stem Cell Transplant (Allo-HSCT)

The only curative option, but carries high morbidity/mortality.

Indication: No longer frontline for classical PNH. Reserved exclusively for PNH in the context of **severe refractory Bone Marrow Failure (Aplastic Anemia)** or **evolution** to **MDS/AML**.

Case 3

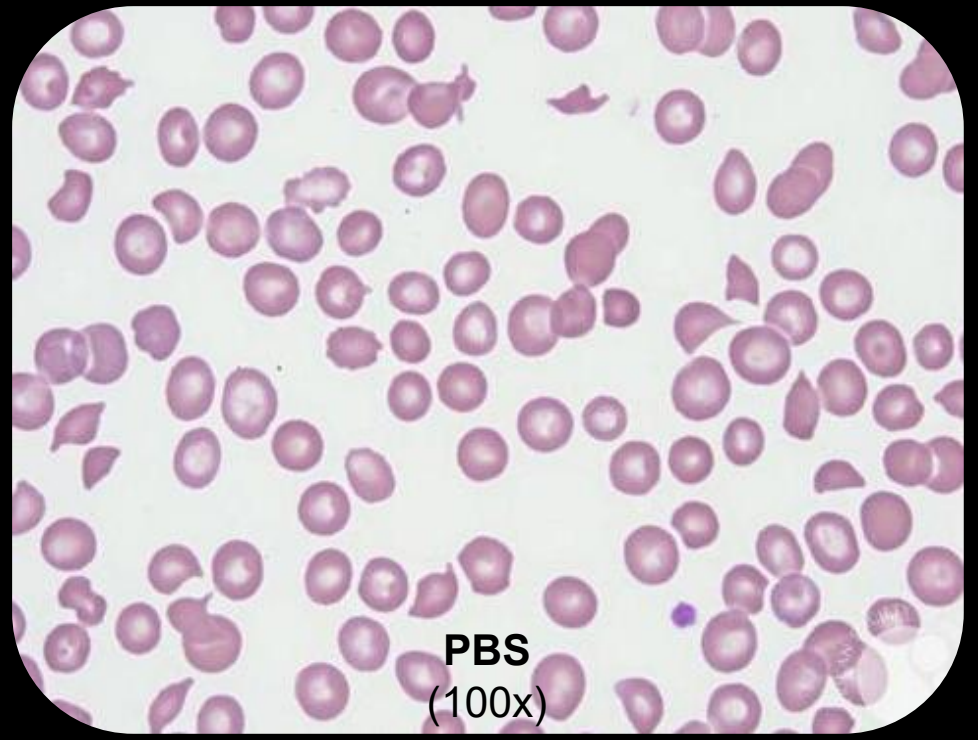
Q3

A 28-year-old nurse presents to the emergency department with a 3-day history of easy bruising, and an episode of transient confusion and slurred speech earlier in the morning that has since resolved.

On physical examination, she is afebrile and normotensive. Scattered superficial ecchymoses are noted over her bilateral lower extremities, and there is mild scleral icterus. Neurological examination is currently non-focal and unremarkable.

Laboratory investigations:

- CBC: Hb 7.2 g/dL, Hct 21%, MCV 72 fL, WBC count 8,500/μL (N 65, L 30, M 5), platelet count 8,500/μL.
- Total bilirubin 4.1 mg/dL, direct bilirubin 0.7 mg/dL, and LDH 1,450 U/L. Direct antiglobulin test is negative.
- PT, aPTT, and Fibrinogen are within normal limits.



Which of the following initial therapies is the most appropriate?

A. Therapeutic plasma exchange and high-dose corticosteroids
B. Caplacizumab
C. Eculizumab
D. Recombinant ADAMTS13 (apadamtase alfa)
E. Both A and B

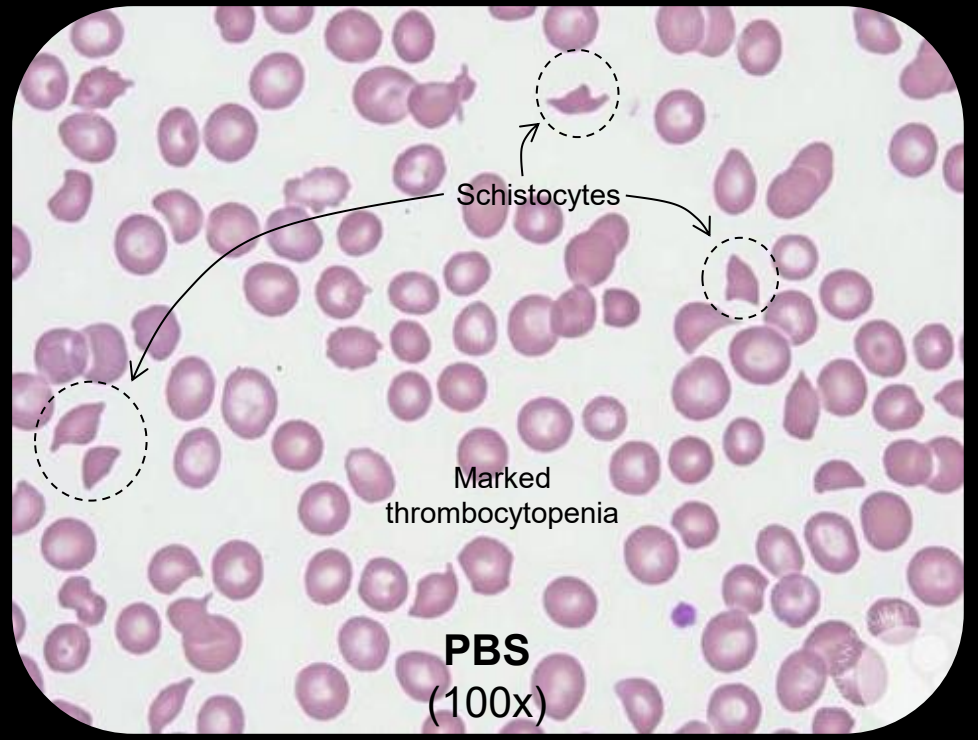
Q3

A 28-year-old nurse presents to the emergency department with a 3-day history of easy bruising, and an episode of transient confusion and slurred speech earlier in the morning that has since resolved.

On physical examination, she is afebrile and normotensive. Scattered superficial ecchymoses are noted over her bilateral lower extremities, and there is mild scleral icterus. Neurological examination is currently non-focal and unremarkable.

Laboratory investigations:

- CBC: Hb 7.2 g/dL, Hct 21%, MCV 72 fL, WBC count 8,500/μL (N 65, L 30, M 5), platelet count 8,500/μL.
- Total bilirubin 4.1 mg/dL, direct bilirubin 0.7 mg/dL, and LDH 1,450 U/L. Direct antiglobulin test is negative.
- PT, aPTT, and Fibrinogen are within normal limits.



Which of the following initial therapies is the most appropriate?

A. Therapeutic plasma exchange and high-dose corticosteroids
B. Caplacizumab
C. Eculizumab
D. Recombinant ADAMTS13 (apadamtase alfa)
E. Both A and B

Thrombotic Thrombocytopenic Purpura

Thrombotic Thrombocytopenic Purpura (TTP)

The Historical Pentad

- MAHA
- Thrombocytopenia
- Fever
- Renal Impairment
- Neurological Deficits

Present in < 5% of cases

The Modern Diagnostic Threshold

Unexplained MAHA

\+

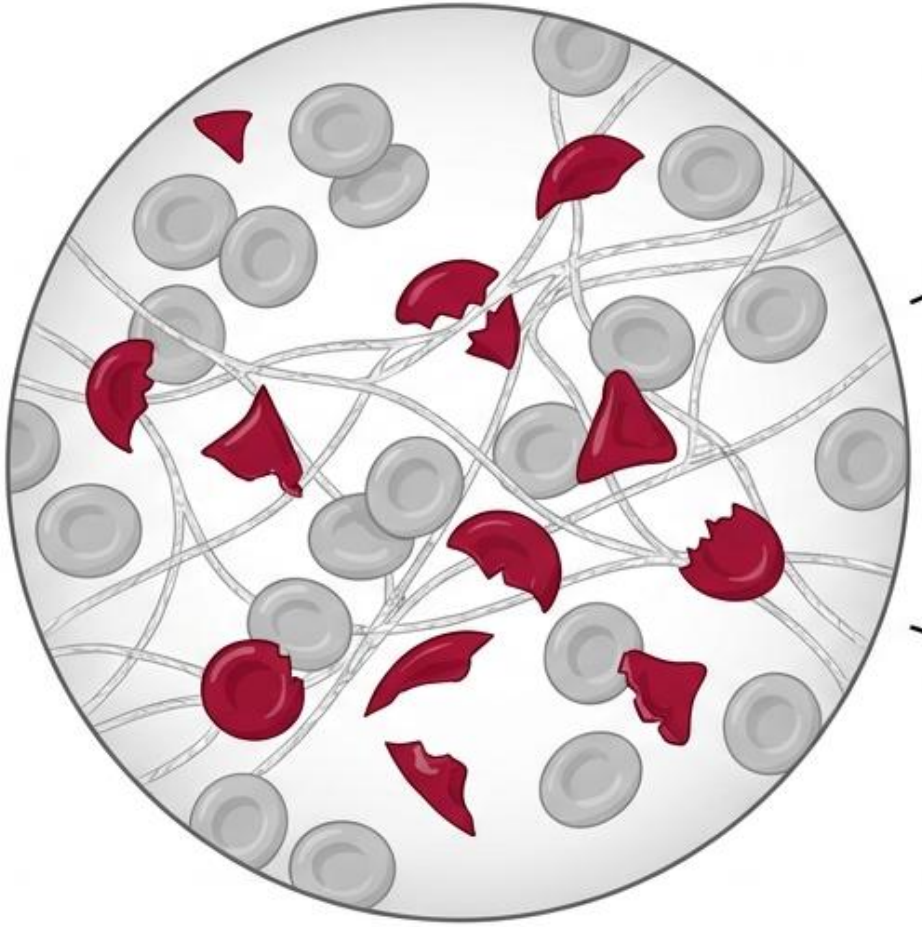
Thrombocytopenia

= **Suspect TTP/TMA**

TTP is a medical emergency characterized by profound microvascular thrombosis driven by severe deficiency of the von Willebrand factor-cleaving protease, ADAMTS13 (<10% activity). Without urgent intervention, **mortality exceeds 90%**; with timely plasma exchange and targeted **quadruple therapy**, survival reaches 85-90%.

The Microangiopathic Presentation: MAHA & Consumptive Thrombocytopenia

Lab Profile Matrix



Peripheral Smear: Shearing & Consumption

1. Hemolysis Markers

- ↑ Lactate Dehydrogenase (LDH)
  (Tissue & RBC destruction)
- ↓ Haptoglobin
  (Rapid binding of free hemoglobin)
- ↑ Indirect Bilirubin

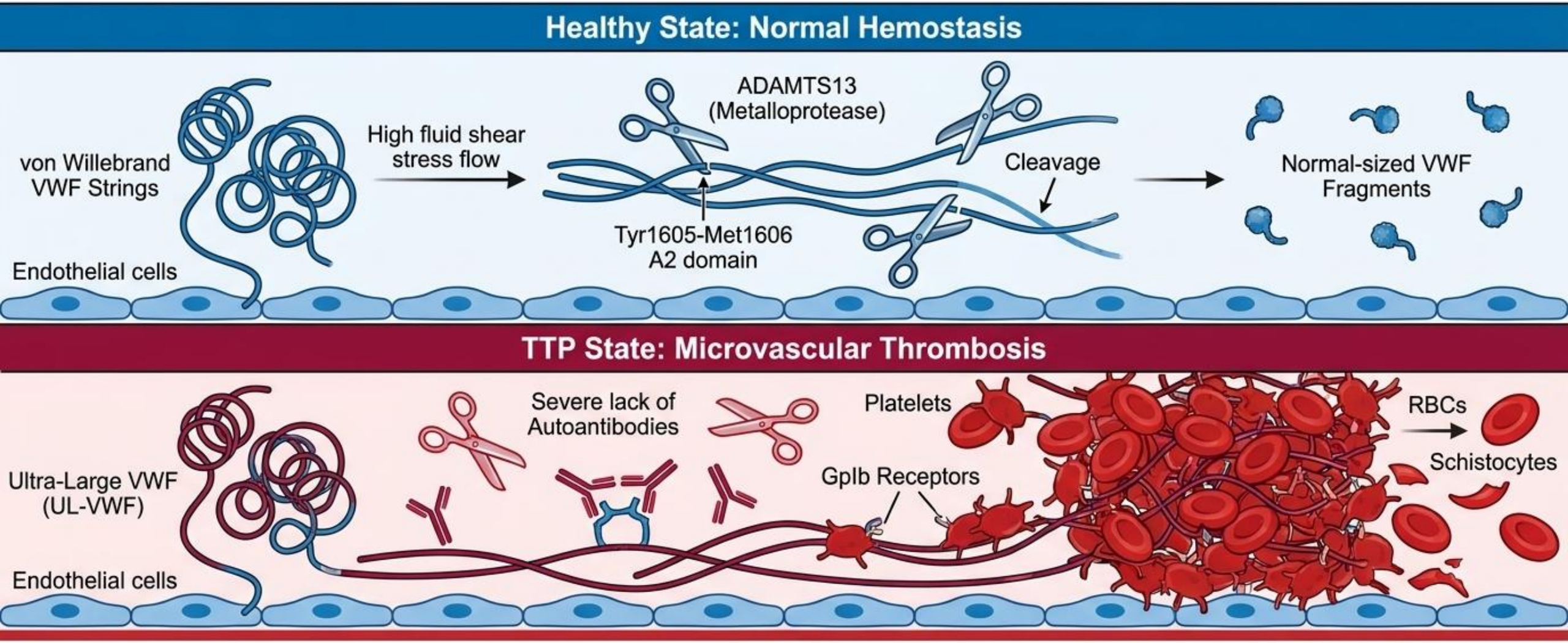
2. Compensatory Response

- ↑ Reticulocyte Count
  (Bone marrow response)

3. Platelet Consumption

- Platelets typically $< 30 \times 10^9/L$
  (Trapped in systemic microthrombi)
- Normal coagulation profile
  (PT/aPTT usually normal, differentiating from DIC)

Molecular Pathophysiology: The VWF—ADAMTS13 Axis



Acquired (iTTP): ~95% of cases.
Autoantibody-mediated inhibition or clearance of ADAMTS13 (often targeting spacer/cys-rich regions).

Congenital (cTTP / Upshaw-Schulman): ~5% of cases
Biallelic pathogenic mutations in the ADAMTS13 gene resulting in absent or dysfunctional protease.

Clinical Risk Stratification: The PLASMIC Score Matrix

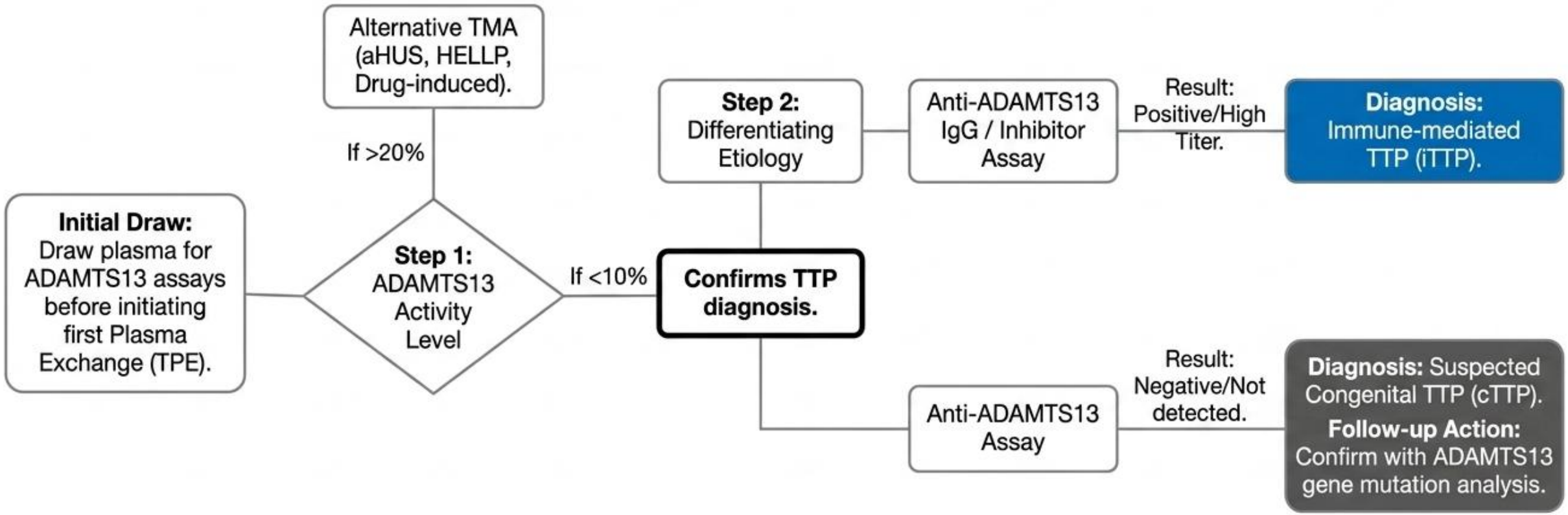
The Criteria Checklist

- **P**latelet count < 30 × 10^9/L (+1) ✓
- **L**emolysis present (Retics, LDH, Schistocytes, ↓Haptoglobin) (+1) ✓
- **A**bsence of active cancer (+1) ✓
- **S**tem-cell or solid organ transplant history absent (+1) ✓
- **M**CV < 90 fL (+1) ✓
- **I**NR < 1.5 (+1) ✓
- **C**reatinine < 2.0 mg/dL (176.8 µmol/L) (+1) ✓

Action Matrix

	Low Risk (0-4): Seek alternative TMA diagnoses (e.g., aHUS, DIC).
	Intermediate Risk (5): Send ADAMTS13 testing; initiate TPE if no other cause identified; expert consultation.
	High Risk (6-7): PPV 72%, Sensitivity 90%. **Action:** Draw ADAMTS13 and **immediately initiate TPE. Do not wait for lab confirmation.**

Diagnostic Confirmation: ADAMTS13 Assay Architecture



Assays utilize FRET (FRETS-VWF73) or rapid chemiluminescence (e.g., AcuStar) to measure cleavage activity. High-titer inhibitory antibodies generally target the spacer domain and heavily predict relapse risk.

Acute Management: The "Quadruple Therapy" Protocol (ISTH 2020)

1. Therapeutic Plasma Exchange (TPE)

- **Target**: Systemic Plasma
- **Action:** Physically removes anti-ADAMTS13 autoantibodies and UL-VWF multimers; replenishes functional ADAMTS13.

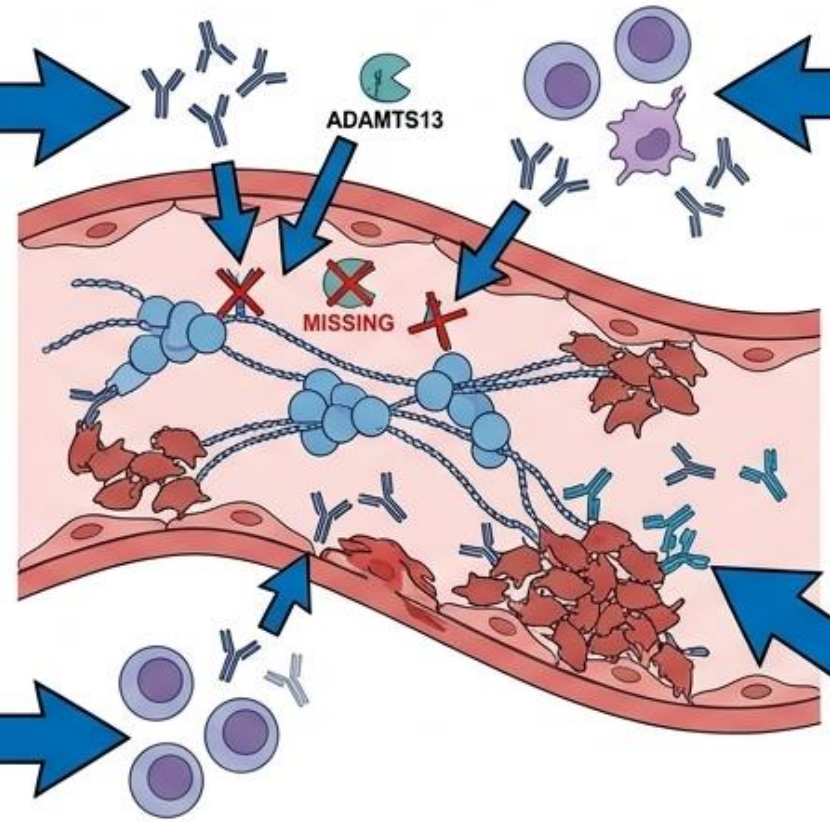
(Strong Recommendation)

3. Rituximab

- **Target**: B-Lymphocytes (CD20+)
- **Action**: Eradicates the specific B-cell clones producing the anti-ADAMTS13 autoantibodies.

(Conditional/Standard in severe cases)

TTP pathological blood vessel
publication (Zheng XL, et al.)



2. Corticosteroids

- **Target**: Immune System
- **Action**: Broadly suppresses active inflammation and autoantibody production.

(Strong Recommendation)

4. Caplacizumab

- **Target**: VWF A1 Domain
- **Action**: An anti-VWF nanobody that blocks VWF-platelet GpIb interaction, immediately halting microthrombus formation.

(Conditional/Targeted)

Management in Special Populations: Refractory iTTP & Pregnancy

Rituximab-Refractory iTTP

- **Definition**: Failure of platelet response or clinical deterioration despite 5 days of TPE + Steroids + Rituximab.
- **Escalation Strategy**: Bortezomib (proteasome inhibitor) targets long-lived, CD20-negative plasma cells. Effective in ~59% of rituximab-refractory cases.
- **Alternative Options**: Cyclosporine, Splenectomy (rare).

Pregnancy-Associated TTP

- **Diagnostic Pitfall**: High clinical overlap with HELLP syndrome. Key discriminator: LDH/AST ratio ≥ 22.12 strongly favors TTP over HELLP.
- **Management Nuances**:
  - **iTTP in pregnancy**: Daily TPE + Corticosteroids. (Caplacizumab and Rituximab carry placental risks and require careful multidisciplinary review).
  - **cTTP in pregnancy**: Often presents for the first time in pregnancy. Managed via prophylactic solvent/detergent-treated plasma infusions to maintain ADAMTS13 levels.

Long-Term Prognosis & Chronic Monitoring

1. Defining Remission

- **Clinical Response**: Platelets > 150×10^9/L and normalized LDH.
- **Clinical Remission**: Sustained response for ≥30 days post-TPE/caplacizumab cessation.

2. Relapse Monitoring (The Preemptive Strategy)

- Serial monitoring of ADAMTS13 activity is mandatory during remission.
- **Red Flag**: A drop in ADAMTS13 activity < 20% during remission is a highly sensitive predictor of clinical relapse.
- **Intervention**: Preemptive administration of Rituximab is indicated to restore ADAMTS13 activity and prevent acute clinical relapse.

3. Chronic Sequelae

- **Survival** has drastically improved, but patients suffer from a high burden of chronic morbidities due to prior diffuse microvascular ischemia.
- **Key Morbidities**: Neurocognitive decline (memory/concentration deficits), early-onset hypertension, major cardiovascular events, and clinical depression.


Case 4

Q4

An 80-year-old retired teacher with no prior history of bleeding disorders presents to the emergency department with spontaneous extensive ecchymoses on his arms (as shown in the figure) and legs and hematuria. He denies any recent trauma, new medications, or anticoagulant use. His past medical history includes hypertension and osteoarthritis. On examination, he is hemodynamically stable but has large bruises and a mildly swollen right thigh.

Laboratory investigations:

- CBC: Hb 9.1 g/dL, Hct 28%, MCV 70 fL, WBC count 14,000/µL (N 65, L 25, M 8), platelet count 220,000/µL.
- PT and aPTT show 13 sec. (normal), and 72 sec. (prolonged).
- Mixing study for aPTT remains prolonged. Fibrinogen 200 mg/dL.

Which condition does the patient suffer from?

A. Acquired factor VIII inhibitor
B. Acquired factor X deficiency
C. Acute disseminated intravascular coagulation (DIC)
D. Chronic DIC
E. Lupus anticoagulant positivity

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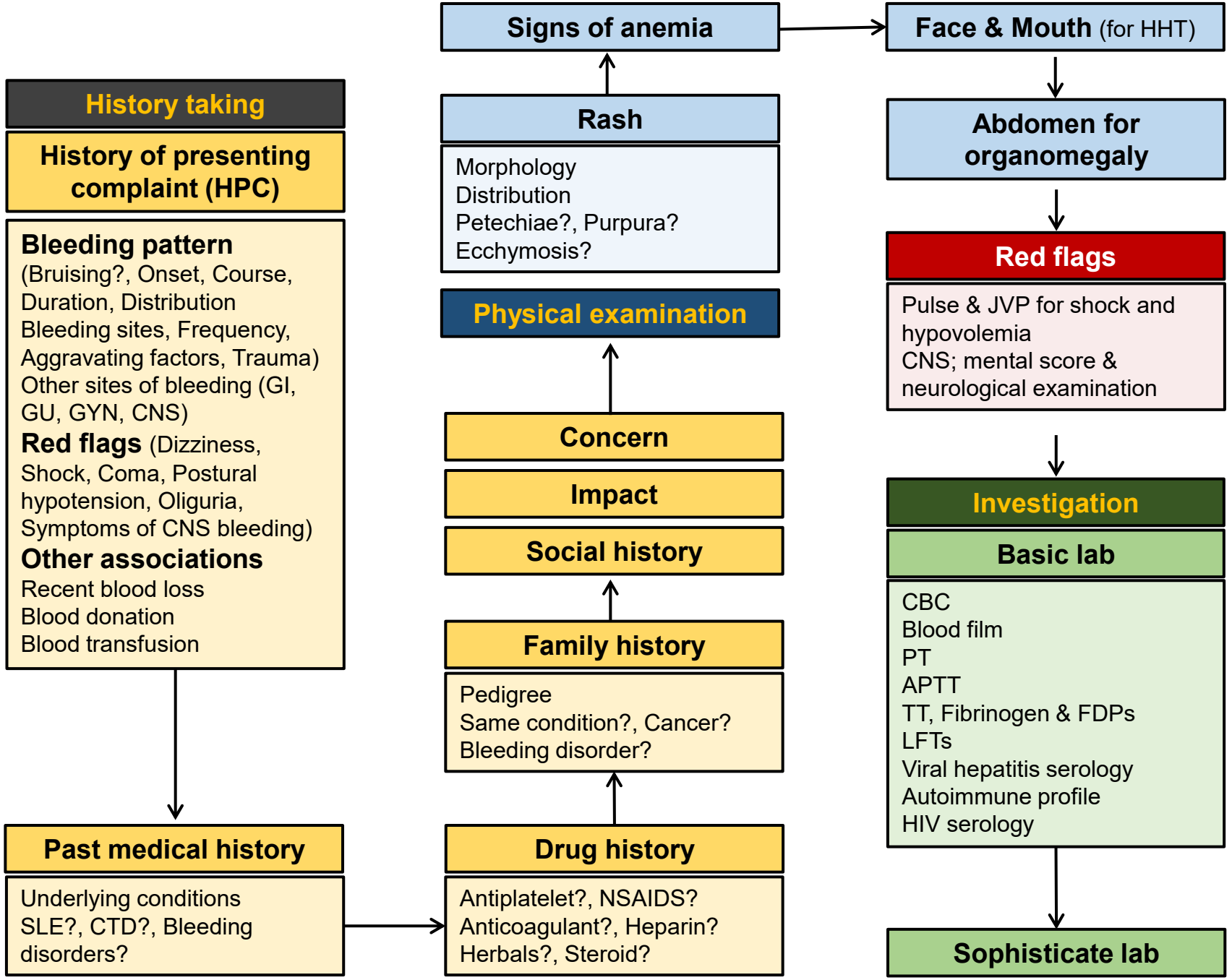
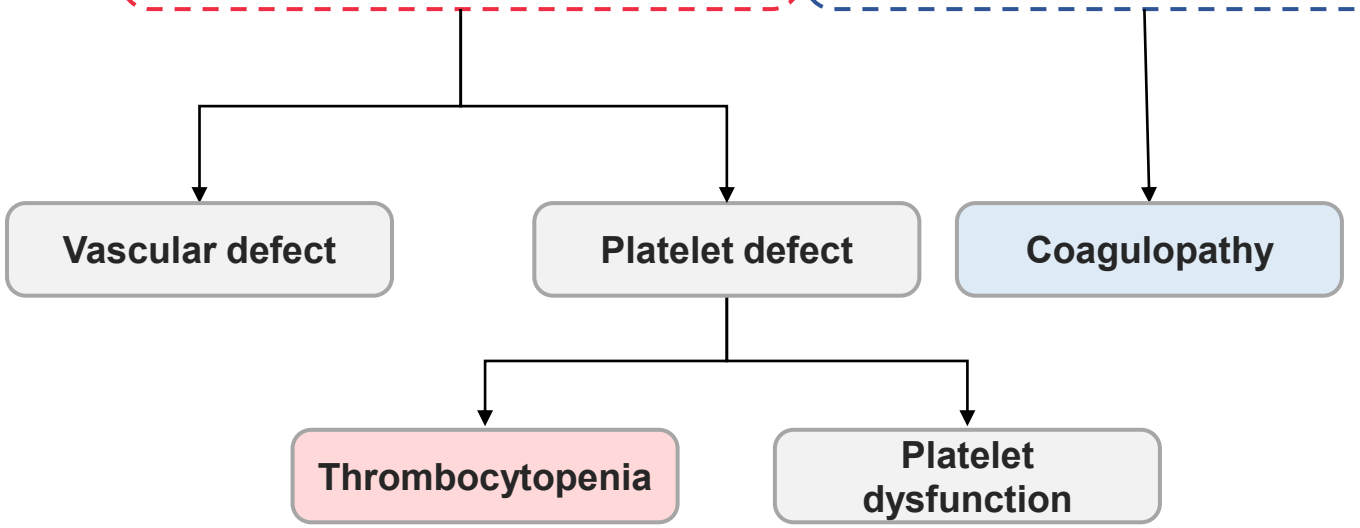
Acquired Factor VIII Inhibitor

Approach Bleeding

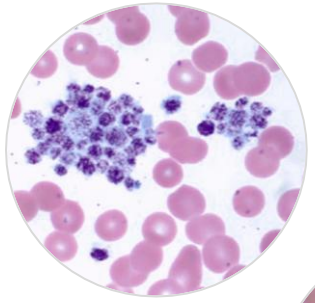


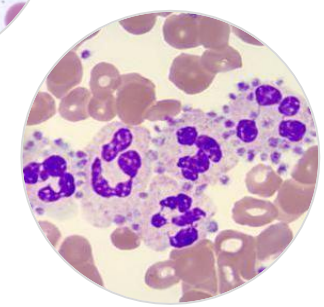
Primary vs Secondary Hemostasis

Features	Primary hemostasis	Secondary hemostasis
Onset of bleeding after trauma	Spontaneous / immediately trauma	Delayed after
Sites of bleeding • Skin • Mucous membrane • Other sites	**Superficial surfaces** Petechiae, ecchymoses Nasal, oral, GI, GU Rare	**Deep tissues** Hematomas Rare Joint, muscle, retroperitoneal
Bleeding responding to pressure	Yes	No



Approach Thrombocytopenia





Thrombocytopenia

Exclude **pseudo-thrombocytopenia**
(Platelet clumping, satellitism)

Underproduction

- Aplastic anemia
- Amegakaryocytic thrombocytopenia
- Acute leukemia
- Infection
- Drug induced / Ethanol induced
- Myelopthisis
- Megaloblastic anemia

etc.

Peripheral destruction

Immune

- Primary immune thrombocytopenia (ITP)
- Secondary ITP (SLE, HIV, HCV, H. pylori, Lymphoma, CLL, Drug, Graves's disease)

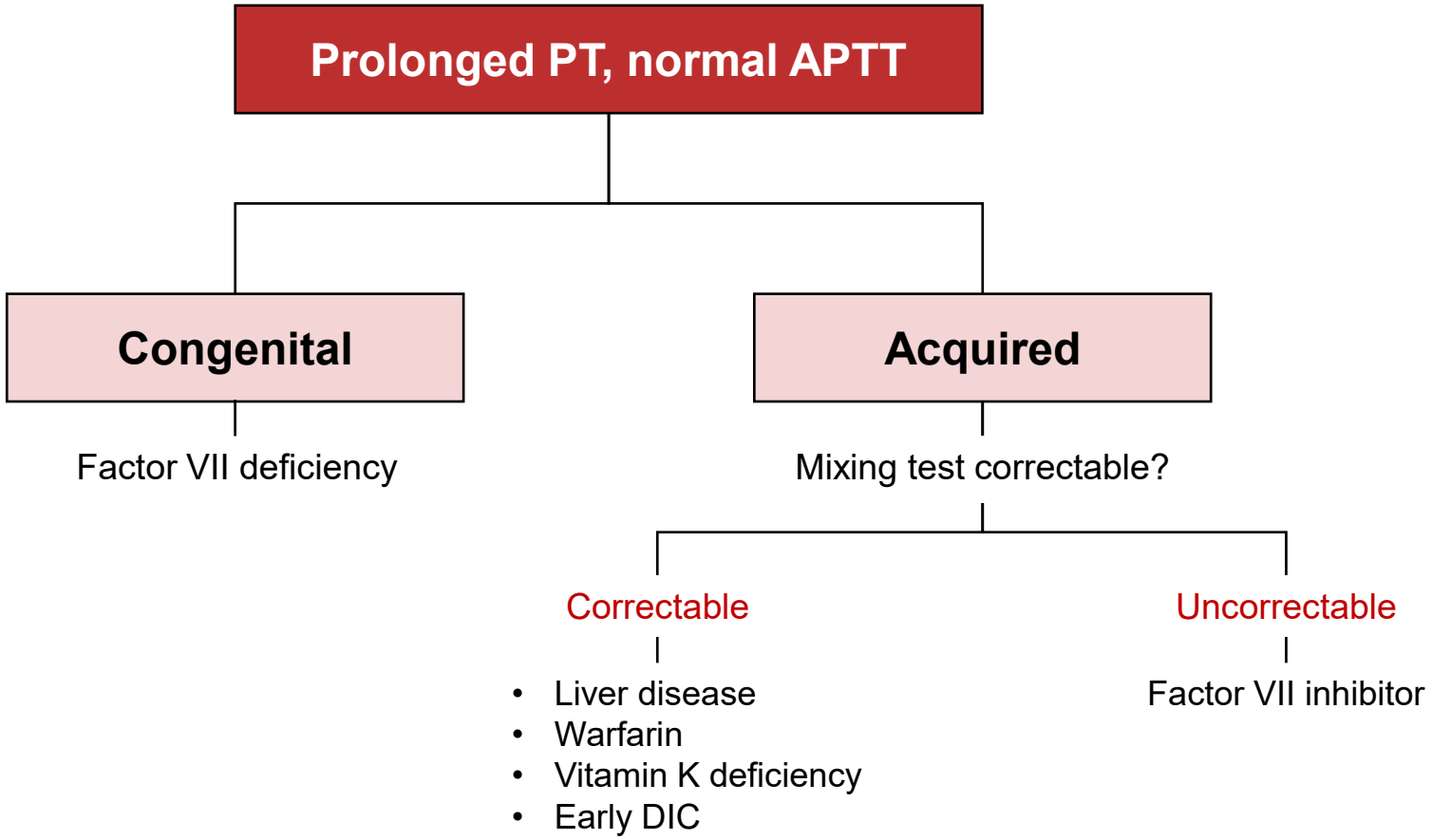
Non-immune

- MAHA (TTP, HUS, DIC)

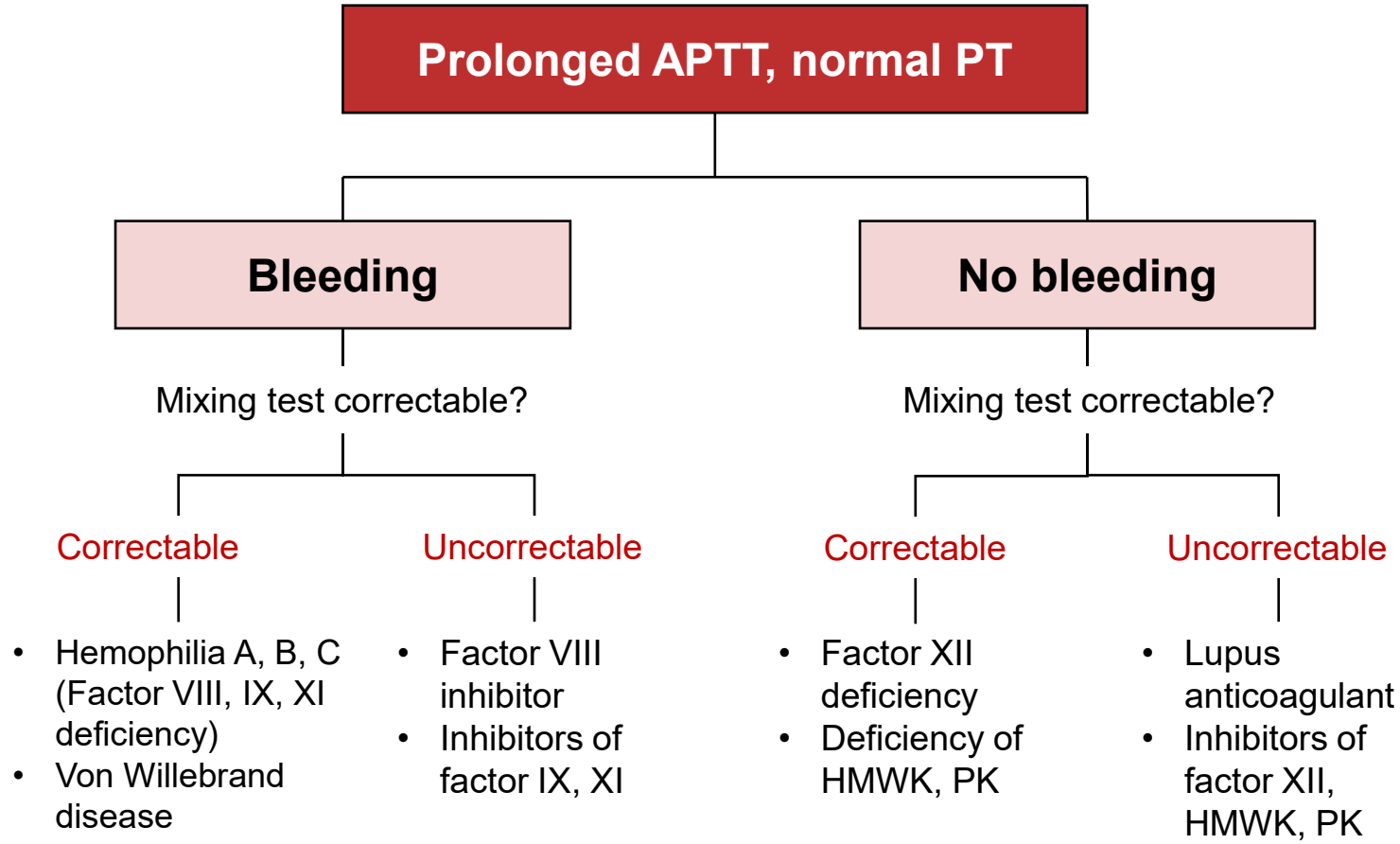
Dilutional thrombocytopenia or Sequestration

SLE	Systemic lupus erythromatosus
HCV	Hepatitis C virus
CLL	Chronic lymphocytic leukemia
TTP	Thrombotic thrombocytopenic purpura
HUS	Hemolytic uremic syndrome
DIC	Disseminated intravascular coagulation

Approach Coagulopathy: Isolated PT Prolongation



Approach Coagulopathy: Isolated APTT Prolongation



****Mixing study does not correct or prolongs with 1 to 4-hour incubation**

- Bleeding disorder: check factors VIII
  - Acquired factor VIII inhibitor
- No bleeding disorder: check diluted Russell's viper venom test
  - Lupus anticoagulant

Approach to Isolated aPTT Prolongation

Clinical Presentation

Unexpected severe bleeding (cutaneous/internal) **OR** asymptomatic pre-operative finding

+

Isolated prolonged aPTT (Normal PT, Normal TT).

Perform Mixing Study

Mix patient plasma 1:1 with normal plasma.

Evaluate aPTT immediately AND after 2-hour incubation at 37°C.

Immediate Correction

Indicates Factor Deficiency (e.g., FVIII, FIX, FXI, FXII).

Action: Proceed to specific factor assays.

No Correction (Immediate or Delayed)

- **If immediate:** Suspect Lupus Anticoagulant (LA) or high-titer inhibitor.
- **If prolonged only after 2 hours:** Characteristic of time- and temperature-dependent FVIII Autoantibody (AHA).

Pathophysiology and Risk Factors

Pathophysiology of AHA

- **Autoantibodies:** Polyclonal IgG (predominantly IgG1 and IgG4) target specific functional domains (A2, C2) of endogenous Factor VIII.
- **Type II Kinetics:** Unlike alloantibodies in congenital hemophilia (Type 1, linear), AHA autoantibodies exhibit non-linear, Type 2 kinetics.
- **Mechanism:** Antibodies accelerate FVIII clearance and sterically hinder its activation by thrombin or interaction with VWF.
- **Clinical Implication:** Incomplete inactivation occurs. Residual FVIII levels are unpredictable and do not strictly correlate with bleeding severity.

Risk Factors & Etiology Matrix

Category	Prevalence	Details
Idiopathic	~50%	No underlying disease identified; primarily affects the elderly (>60 years).
Autoimmune	~15%	Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis, Sjögren's syndrome.
Malignancy	~10-15%	Solid tumors (prostate, lung, colon) and lymphoproliferative disorders.
Pregnancy	~2-7%	Postpartum period (typically 1 to 4 months post-delivery).
Other	<10%	Infections (including recent COVID-19 cases), dermatologic diseases, adverse drug reactions.

Diagnosis of Acquired Factor VIII Inhibitor

Core Diagnostic Triad: Definitive Diagnosis = Isolated prolonged aPTT + Low FVIII:C Activity + Detectable FVIII Inhibitor

Laboratory Workup

Specific Factor Assays
Markedly reduced Factor VIII coagulant activity (FVIII:C). Note: Other intrinsic factors (IX, XI, XII) may appear artificially low in vitro due to substrate depletion.

Inhibitor Quantification
Nijmegen-modified Bethesda Assay. Measures neutralizing capacity in Bethesda Units (BU). Due to Type 2 kinetics, report the dilution titer closest to 50% inhibition.

Differential Caveats

Lupus Anticoagulant (LA) Interference
LA can mimic or coexist with AHA. Differentiate using LA-insensitive aPTT reagents, chromogenic FVIII FVIII assays, or anti-FVIII ELISA.

CLINICAL PEARL: Bleeding phenotype and severity do not reliably correlate with the absolute inhibitor titer (BU) or residual FVIII activity. Treat the patient, not the number.

Management: Hemostatic Therapy (Bleeding Control)

Principle: Initiate anti-hemorrhagic treatment for severe or active bleeding immediately, regardless of inhibitor titer or residual FVIII level.

Classification	Drug	Dose/Notes
First-Line Bypassing Agents		
	Recombinant activated FVII (rFVIIa)	90–120 mcg/kg bolus every 2–3 hours until hemostasis is achieved.
	Activated Prothrombin Complex Concentrate (aPCC / FEIBA)	50–100 IU/kg every 8–12 hours. Maximum daily dose: 200 IU/kg/day.
Alternative & Novel Therapies		
	Recombinant Porcine FVIII (rpFVIII / Obizur)	Initial dose 200 IU/kg. Effective due to low cross-reactivity with human FVIII autoantibodies.
	Emicizumab	Bispecific antibody mimicking FVIIIa. Emerging as an effective option for hemorrhage prophylaxis in AHA.
Not Recommended for Severe Bleeding		
	Human FVIII Concentrates & DDAVP	Generally ineffective for severe bleeds due to rapid neutralization by the autoantibody and non-linear kinetics.

Management: Autoantibody Eradication (IST)

Goal: Initiate Immunosuppressive Therapy (IST) immediately upon diagnosis to eliminate the autoantibody, eradicate the producing clone, and restore normal hemostasis.

First-Line Therapy (Initiate Immediately)

Corticosteroid Monotherapy: Prednisone 1 mg/kg/day for 4–6 weeks.

Combination Therapy: Prednisone + Cyclophosphamide (1.5–2 mg/kg/day) for a maximum of 6 weeks.

Second-Line Therapy (Refractory or Contraindicated)

Rituximab: Anti-CD20 monoclonal antibody (375 mg/m²/week for 4 weeks). Often used if first-line fails or as first-line if chemotherapeutics are contraindicated.

Clinical Cautions

- **Infection Risk:** Sepsis related to IST is a leading cause of mortality, particularly in the frail/elderly. Balance rapid eradication with infectious risk.
- **Pregnancy:** Cyclophosphamide and alkylating agents are strictly contraindicated in postpartum AHA due to the risk of infertility.

Monitoring

Monitor aPTT and FVIII:C monthly during the first 6 months post-remission to detect relapse.

Case 5

Q5

A 30-year-old female banker presents to the high-risk obstetrics clinic for her first prenatal visit at 8 weeks gestation. Her past medical history is significant for three consecutive, unexplained spontaneous pregnancy losses, all occurring before 10 weeks of gestation. She denies any personal history of venous thromboembolism, stroke, or other arterial thrombotic events.

Following her third miscarriage, laboratory testing revealed a strongly positive lupus anticoagulant and high titers of anticardiolipin IgG antibodies. These tests were repeated 14 weeks later and remained strongly positive.

What is her diagnosis and which is the most appropriate pharmacological regimen in this patient?

	Diagnosis	Management
A.	Primary antiphospholipid syndrome	Prophylactic-dose low-molecular-weight heparin and low-dose aspirin
B.	Primary antiphospholipid syndrome	Therapeutic-dose low-molecular-weight heparin and low-dose aspirin
C.	Secondary antiphospholipid syndrome	Prophylactic-dose low-molecular-weight heparin and low-dose aspirin
D.	Secondary antiphospholipid syndrome	Therapeutic-dose low-molecular-weight heparin and low-dose aspirin
E.	Secondary antiphospholipid syndrome	Low dose aspirin

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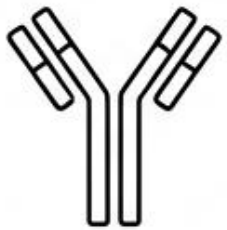
C.	Secondary antiphospholipid syndrome	Prophylactic-dose low-molecular-weight heparin and low-dose aspirin
D.	Secondary antiphospholipid syndrome	Therapeutic-dose low-molecular-weight heparin and low-dose aspirin
E.	Secondary antiphospholipid syndrome	Low dose aspirin

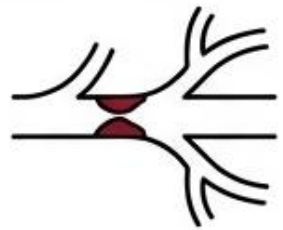
Obstetric antiphospholipid syndrome (Obstetric APS)

Obstetric Antiphospholipid Syndrome

The APS Spectrum: A Thrombo-Inflammatory Disease



Autoantibody Driven
Persistent presence of Lupus Anticoagulant (LA), anti-cardiolipin (aCL), and anti-β2-glycoprotein I (aβ2GPI).



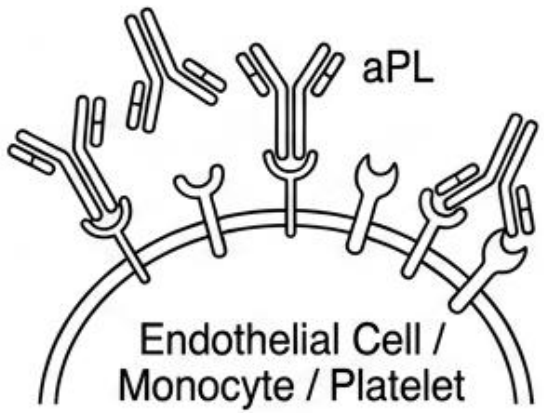
Vascular Thrombosis
Venous, arterial, or microvascular occlusions in any tissue.

Pregnancy Morbidity
Recurrent loss, placental insufficiency, and severe preeclampsia.

Key Takeaway: APS is not an isolated prothrombotic state; it is a systemic immune-mediated inflammatory syndrome.

Pathophysiology I: The "Two-Hit" Vascular Model

Hit 1: Sensitization



aPL bind to target antigens (primarily β2GPI) on endothelial cells, monocytes, and platelets. Creates a baseline procoagulant state.

Hit 2: Trigger

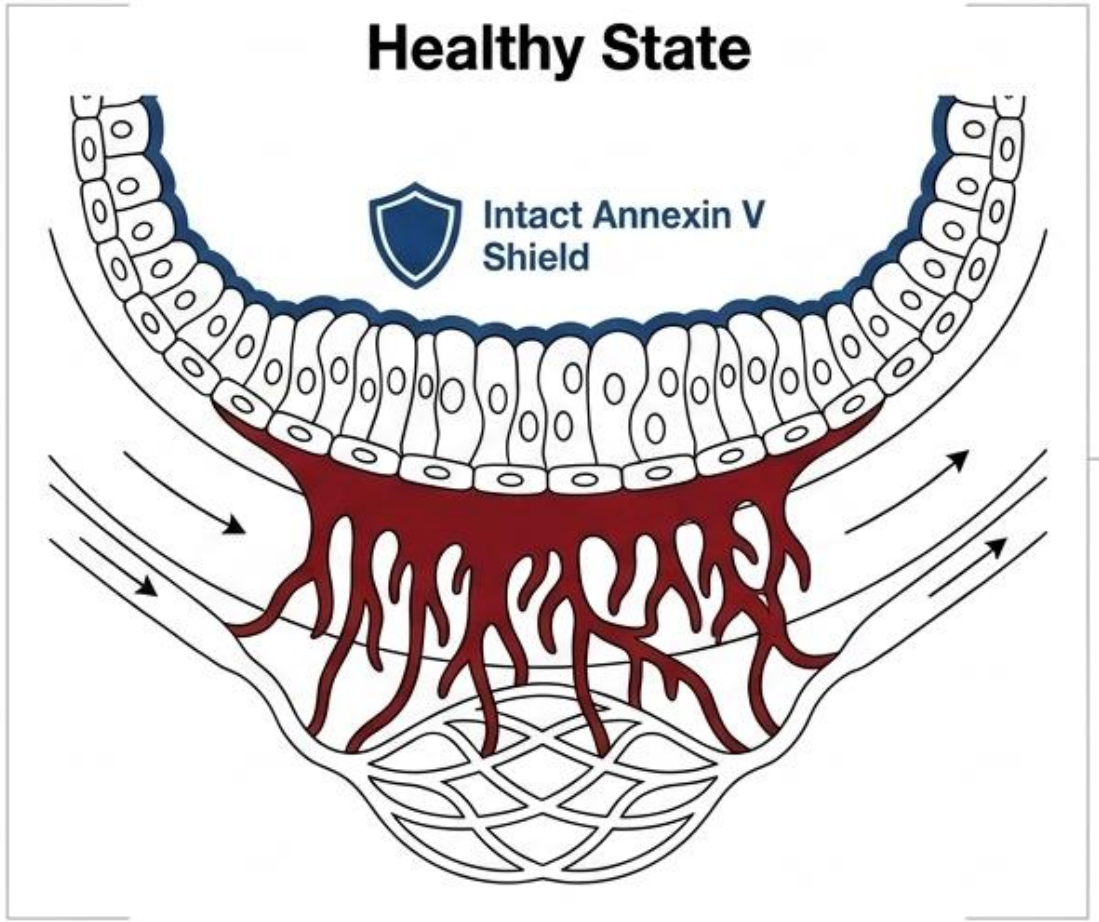
A secondary stimulus (infection, surgery, pregnancy, trauma) hits the sensitized system.

Amplification of Inflammatory & Coagulation Pathways

- Complement cascade activation
- Tissue Factor (TF) upregulation
- Protein C suppression

Macrovascular fibrin clots

Pathophysiology II: Obstetric APS (Beyond Thrombosis)



Annexin V Shield Disruption

aPL displace the protective Annexin V anticoagulant shield on syncytiotrophoblasts, exposing procoagulant phosphatidylserine.

Complement & Inflammation

aPL trigger C5a activation → neutrophil recruitment (NETosis) → release of anti-angiogenic factors (sFlt-1) sequestering VEGF/PlGF.

Impaired Placentation

Direct inhibition of extravillous trophoblast (EVT) invasion prevents normal remodeling of uterine spiral arteries → hypoxia and placental insufficiency.

Clinical Phenotypes: Primary vs. Secondary APS

Primary APS

- Occurs in isolation without underlying systemic autoimmune disease.
- Represents ~60% of all APS cases.

Secondary APS

- Associated with systemic autoimmune diseases, predominantly Systemic Lupus Erythematosus (SLE).
- Represents ~30-40% of cases.

Clinical Implications of Secondary APS (APS + SLE)

Significantly higher morbidity and mortality compared to SLE alone:

20-fold increase in maternal mortality

3-7 fold higher thrombosis risk

Up to **50%** risk of preeclampsia

Obstetric APS (OAPS): Clinical Hallmarks by Gestational Age

<10 Weeks (Early Pregnancy)

Recurrent early miscarriage.

Most frequent manifestation (up to 40% of OAPS pregnancies). Driven by early placentation failure.

>10 Weeks (Late Pregnancy)

Fetal demise of morphologically normal fetuses.

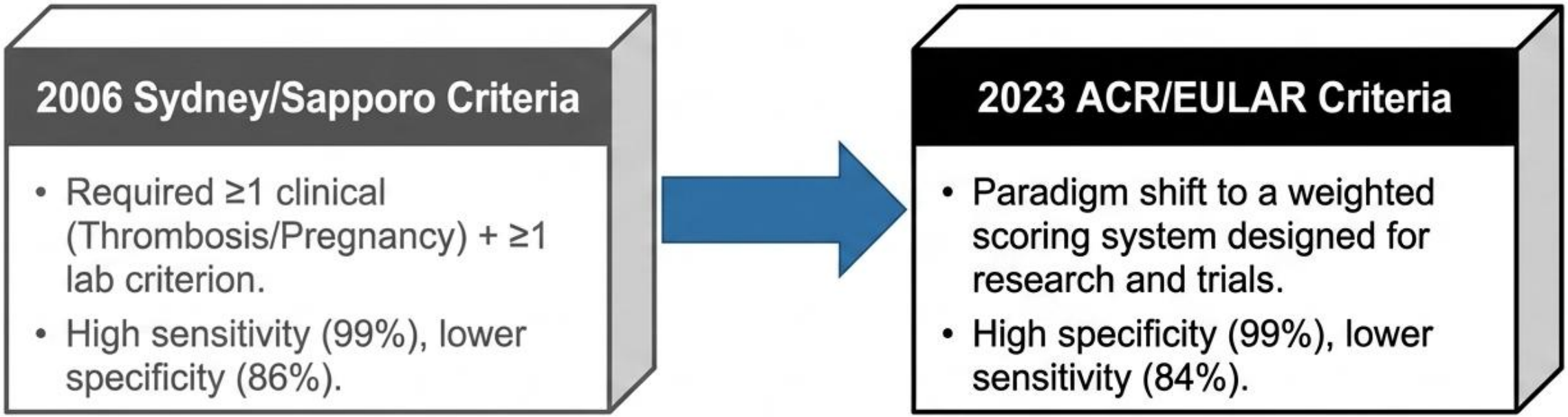
2nd/3rd Trimester (Placental Insufficiency)

Fetal Growth Restriction (FGR), oligohydramnios, and abnormal Doppler flows (umbilical/uterine arteries).

<34 Weeks (Preeclampsia)

Severe, early-onset preeclampsia driven by sFt-1 release and spiral artery dysregulation, frequently requiring iatrogenic preterm delivery.

Diagnostic Evolution: Sapporo (2006) to ACR/EULAR (2023)



New Classification Rule

- **Entry Criterion**: ≥1 positive aPL test within 3 years of an APS-associated clinical criterion.
- **Classification Rule**: Must accumulate ≥3 points from Clinical domains AND ≥3 points from Laboratory domains.

CLINICAL DOMAINS SCORING MATRIX
(>= 3 Points Required for Classification)

Domains 1-3: Vascular Thrombosis
– Macrovascular Venous Thromboembolism (VTE)
– Macrovascular Arterial Thrombosis
– Microvascular Thrombosis

Domain 4: Obstetric (High Yield)
– >= 3 consecutive pre-fetal (<10w) or early fetal (10w- 15w6d) deaths: 1 pt
– Fetal death (16w–33w6d) without Preeclampsia (PE) or Placental Insufficiency (PI): 1 pt
– PE with severe features (<34w) OR PI with severe features (<34w): 3 pts
– PE AND PI with severe features (<34w): 4 pts

Domain 5: Cardiac
– Cardiac valve thickening or vegetation: 2 pts

Domain 6: Hematologic
– Thrombocytopenia (lowest platelet count 20 x 10^9/L to 130 x 10^9/L): 2 pts

Clinical Pearl: Note the low weight (1 pt) of early miscarriages compared to the high weight (3-4 pts) of severe early-onset preeclampsia/placental insufficiency, reflecting a stronger causal link to aPL-mediated placental pathology.

LABORATORY DOMAINS SCORING MATRIX

(>= 3 Points Required for Classification)

The Persistence Rule**: Except for the single LA criterion, aPL **positivity must be confirmed** on **2 or more occasions at least 12 weeks apart.

Domain 7 (Functional Assays)

Lupus Anticoagulant (LA)

- Single positive LA (within 3 years of clinical event): 1 pt
- **Persistent positive LA: 5 pts (Strongest predictor of adverse outcomes)**

Domain 8 (Solid-Phase ELISAs)

aCL and/or aB2GPI Antibodies

- Moderate-high positive IgM: 1 pt
- **Moderate positive IgG: 4 pts**
- **High positive IgG (Both aCL AND aB2GPI): 7 pts**

Clinical Pearl: 'Triple Positivity' (LA + aCL + aB2GPI) and isolated IgG isotypes carry significantly higher thrombotic and obstetric risk than isolated IgM or low-titer presentations, directly reflecting their assigned point weight.

The 2023 ACR/EULAR Classification Domains

Clinical Domains (Need ≥3 points)		Laboratory Domains (Need ≥3 points, tested ≥2 times, 12 weeks apart)	
Macrovascular Venous (Up to 5 pts)	**5 pts)**	**Lupus Anticoagulant:**	
Macrovascular Arterial (Up to 7 pts)	**7 pts)**	**Lupus Anticoagulant:**	
Microvascular (Up to 5 pts)	**5 pts)**	Persistent positive (5 pts)	**(5 pts)**
Obstetric:		**Solid Phase (aCL/aβ2GPI):**	
≥3 pre-fetal deaths (1 pt)	**(1 pt)**	Moderate positive IgG (4 pts)	**(4 pts)**
Fetal death w/o PE/PI (1 pt)	**(1 pt)**	High positive IgG (7 pts)	**(7 pts)**
Severe PE/PI <34w (3 pts)	**(3 pts)**	Moderate/High IgM (1 pt)	**(1 pt)**
Severe PE AND PI <34w (4 pts)	**(4 pts)**		
Cardiac/Hematologic:			
Valve thickening (2 pts)	**(2 pts)**		
Thrombocytopenia (2 pts)	**(2 pts)**		

Management Principles: The aPL Risk Profile

High-Risk Profile

Presence of Lupus Anticoagulant (LA), "Triple Positivity" (LA + aCL + aβ2GPI), or persistently high aPL titers.

Carries a high risk of recurrence and obstetric failure.

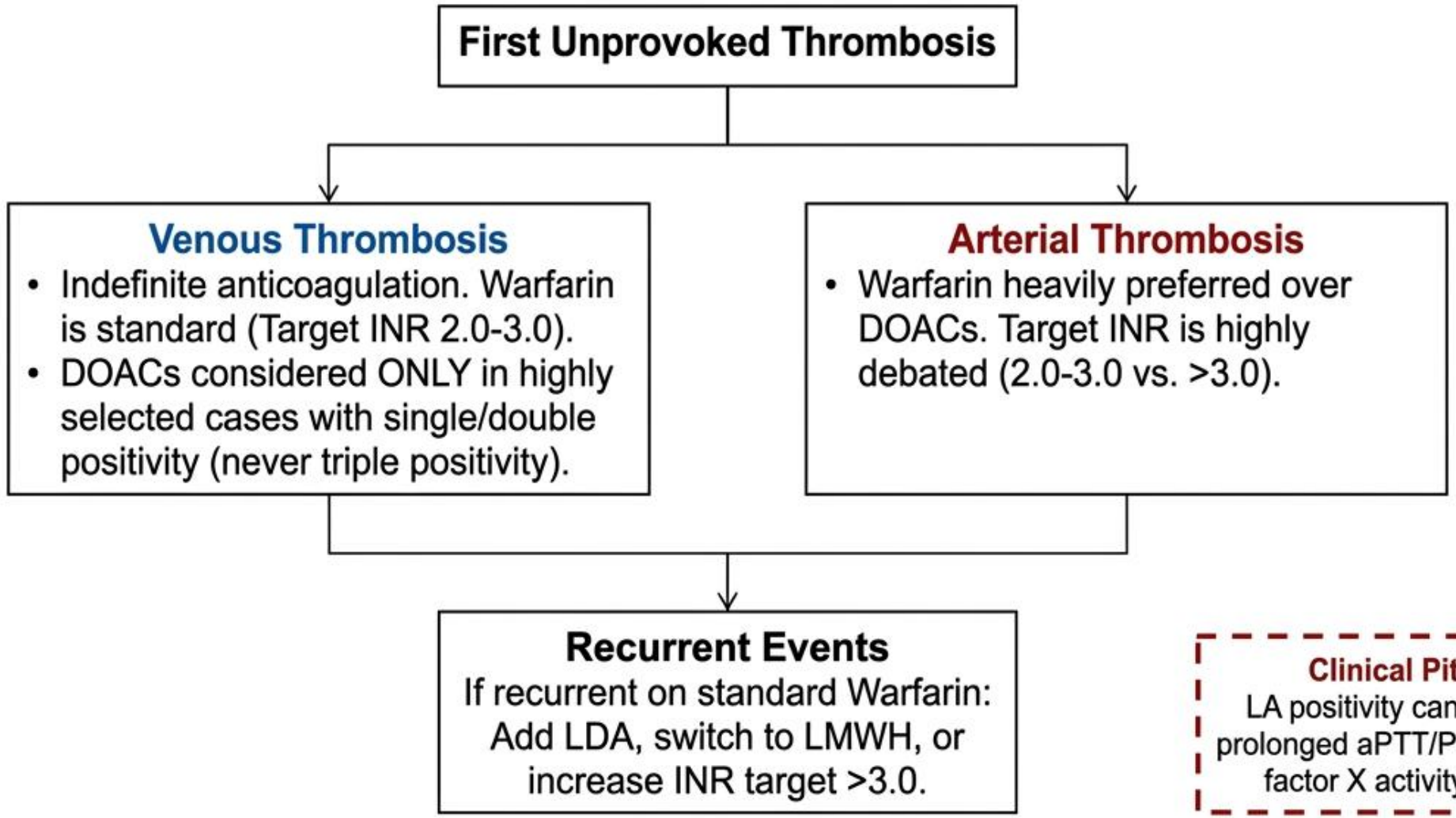
Low-Risk Profile

Isolated or intermittent positivity, or low/medium titers of aCL/aβ2GPI alone.

Primary Prophylaxis Rule (No prior events)

- Asymptomatic carriers are generally not treated.
- Low-Dose Aspirin (LDA, 75-100mg) is recommended for high-risk profiles, SLE patients, or those with concurrent CV risk factors.

Management of Vascular APS (TAPS)



Clinical Pitfall Alert
LA positivity can cause falsely prolonged aPTT/PT/INR. Consider factor X activity monitoring.

Management of Obstetric APS (OAPS): Standard of Care

Pre-conception

Initiate Low-Dose Aspirin (LDA 75-150 mg/day) optimally before conception to facilitate early placentation.

Antepartum (Pregnancy Confirmed)

Initiate prophylactic-dose Low Molecular Weight Heparin (LMWH). Continue LDA.

Peri-operative (Delivery)

Stop LMWH 12-24 hours prior to induction/neuraxial anesthesia. LDA can be stopped 7 days prior.

Postpartum

High thrombotic risk period. Continue LDA + prophylactic LMWH for 6-12 weeks postpartum regardless of delivery route.

Management in Pregnancy: Vascular vs. Obstetric Phenotypes

	Obstetric APS (No prior thrombosis)	Vascular APS (Prior thrombosis)
Antepartum	LDA + Prophylactic LMWH.	Switch Warfarin to Therapeutic LMWH + LDA. Must switch ASAP (<6 weeks gestation) to avoid warfarin embryopathy.
Postpartum	LDA + Prophylactic LMWH for 6 weeks.	Restart Warfarin (Target INR 2.0-3.0) 4-12 hours post-delivery + bridge. Lifelong anticoagulation resumes.

Case 6

Q6

A 55-year-old female street vendor presents with acute dyspnea on exertion for 3 days and pleuritic chest pain. She reports significant weight loss and a history of recurrent dyspepsia. On examination, her SpO_2 is 92% and heart rate is 110/min.

Arterial blood gas reveals PaO_2 60 mmHg, $PaCO_2$ 18 mmHg, and respiratory alkalosis. Troponin I is negative. CBC shows Hb 9.8 g/dL, MCV 72 fL, platelets 500,000/µL, and WBC count of 11,000/µL with neutrophilic predominance. Coagulation studies and creatinine are normal.

What is the most appropriate next investigation?

A. Upper gastrointestinal endoscopy
B. D-dimer test
C. CT pulmonary angiography
D. Ventilation-Perfusion (V/Q) scan
E. Transesophageal echocardiogram

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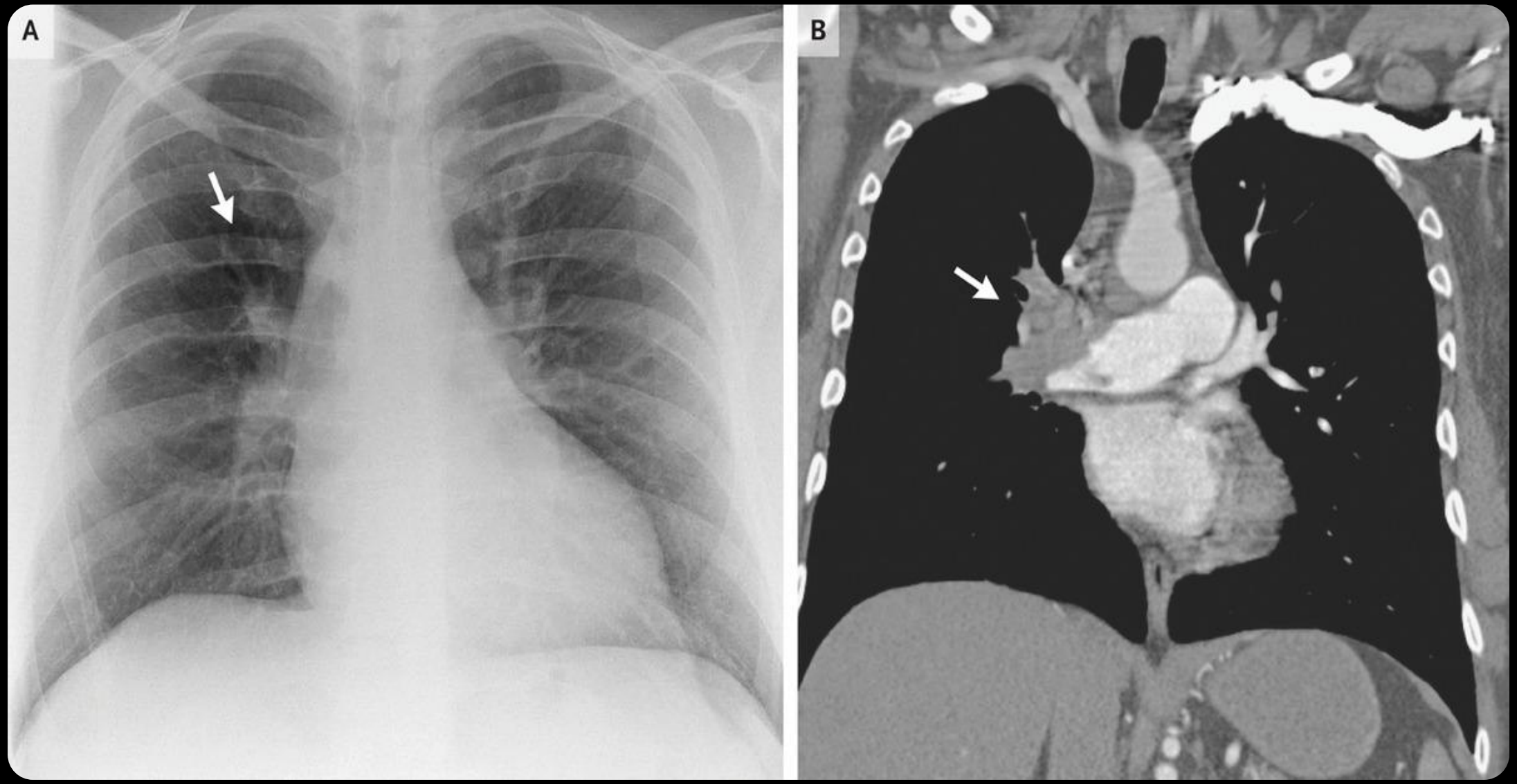
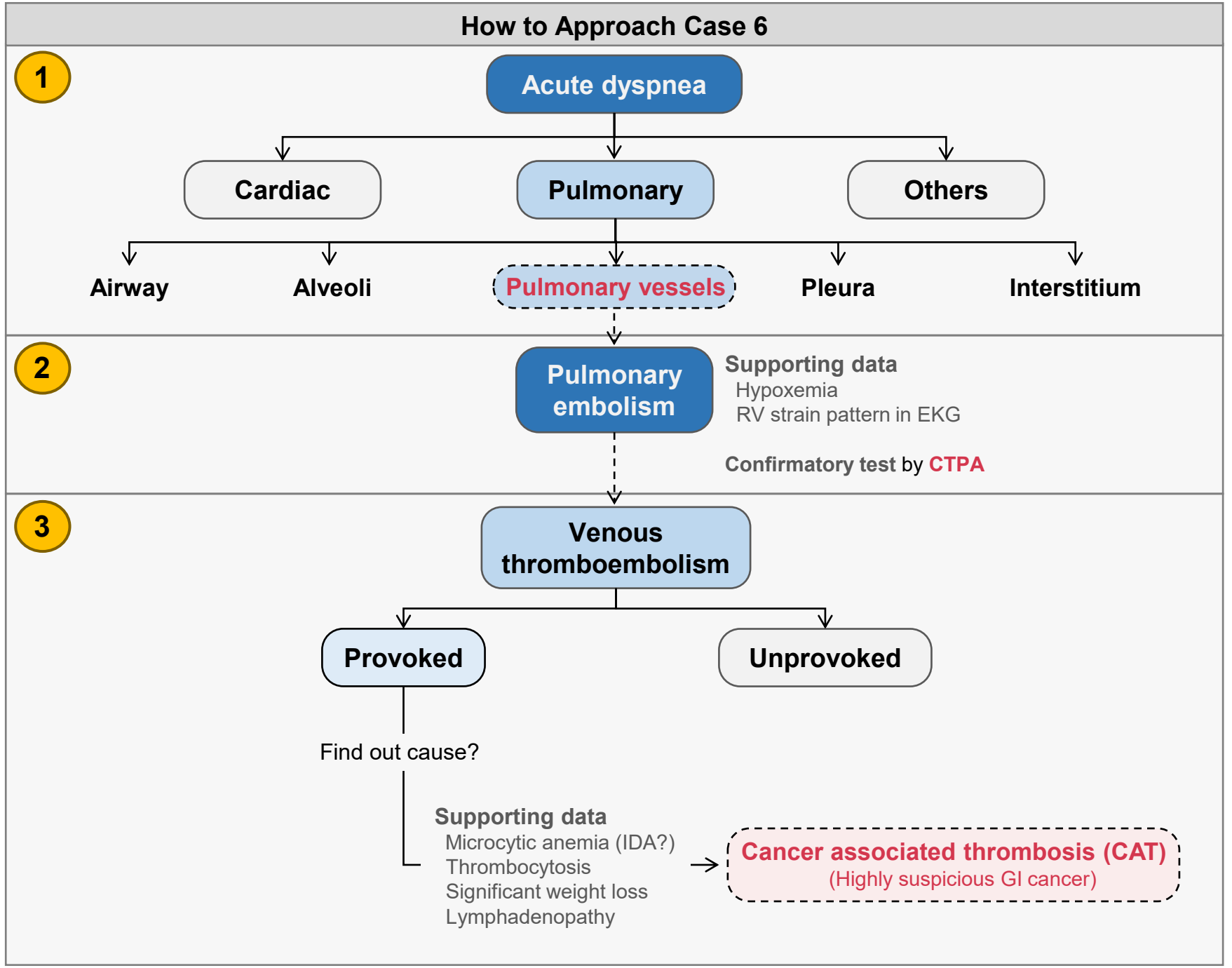
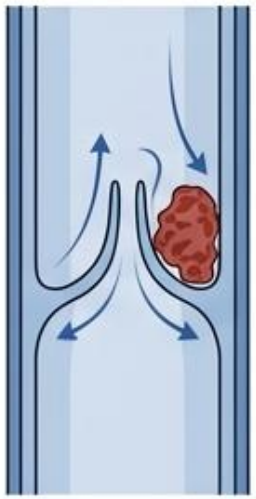


A: CXR shows ‘Westermark sign’ in the right lung.

B: CT pulmonary angiography illustrates multiple filling defects within the right pulmonary trunk.

Cancer Associated Thrombosis


How to Approach Case 6
1
Acute dyspnea
Cardiac
Pulmonary
Others
Airway
Alveoli
Pulmonary vessels
Pleura
Interstitium
2
Pulmonary embolism
Supporting data
Hypoxemia
RV strain pattern in EKG
Confirmatory test by CTPA
3
Venous thromboembolism
Provoked
Unprovoked
Find out cause?
Supporting data
Microcytic anemia (IDA?)
Thrombocytosis
Significant weight loss
Lymphadenopathy
Cancer associated thrombosis (CAT)
(Highly suspicious GI cancer)



DVT

Initiates in distal venous valves; localized inflammation drives pain/swelling (Post-thrombotic syndrome risk).

Stasis

Mechanism: Altered flow in venous valve pockets.

Clinical Links: Immobility (>3 days), Heart Failure, Plaster casts.

Endothelial Injury

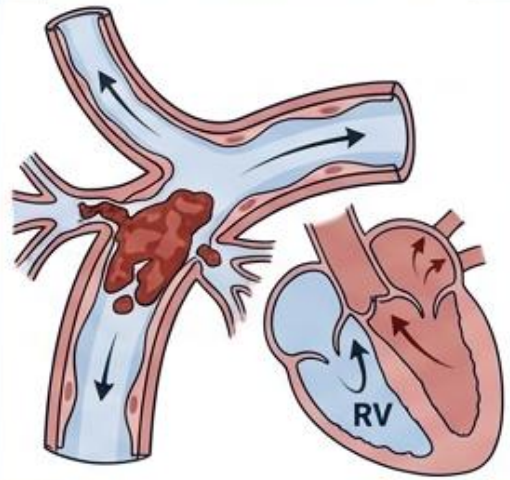
Mechanism: Vascular damage triggering tissue factor.

Clinical Links: Major surgery, Trauma, Venous catheters.

Hypercoagulability

Mechanism: Imbalance of pro/anti-coagulant factors.

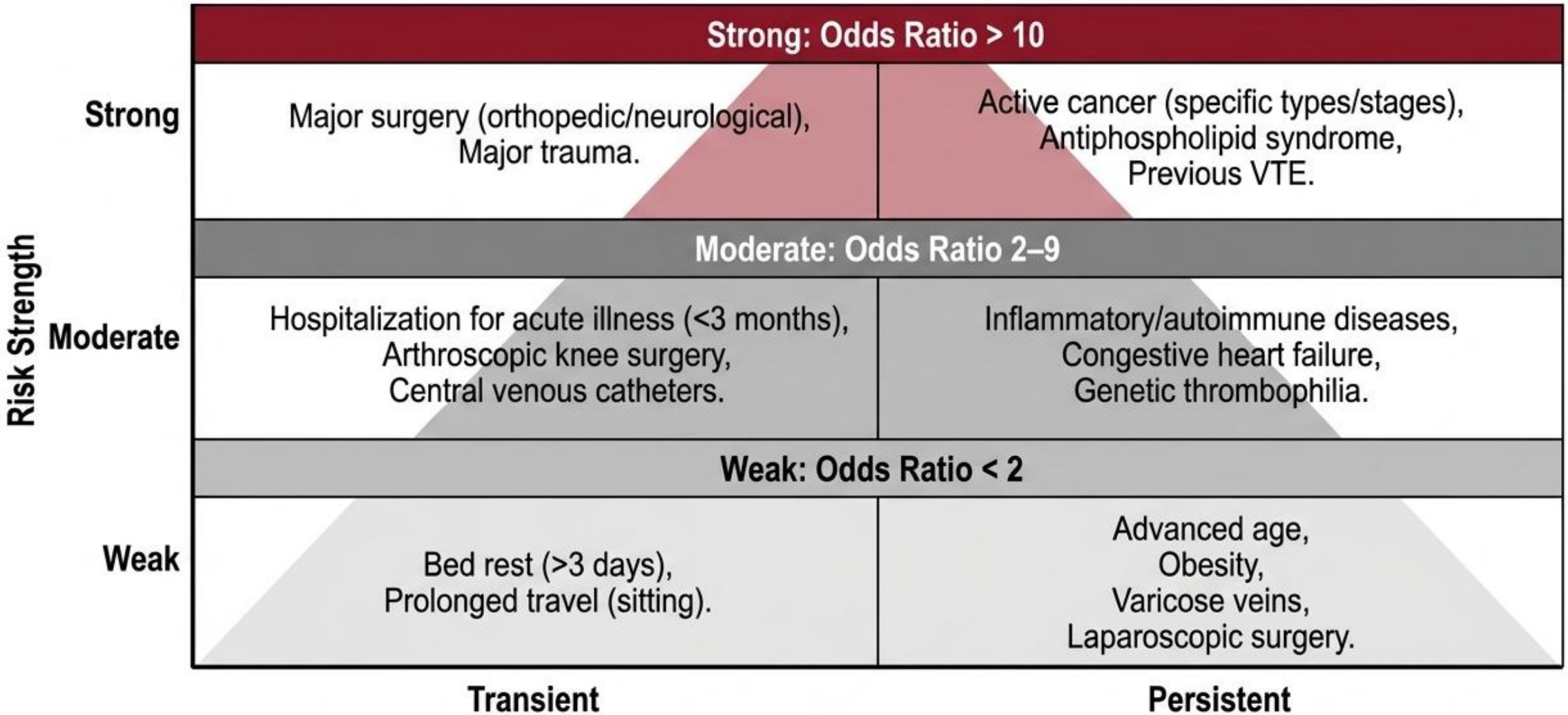
Clinical Links: Active Malignancy, Pregnancy, Genetic Thrombophilias.



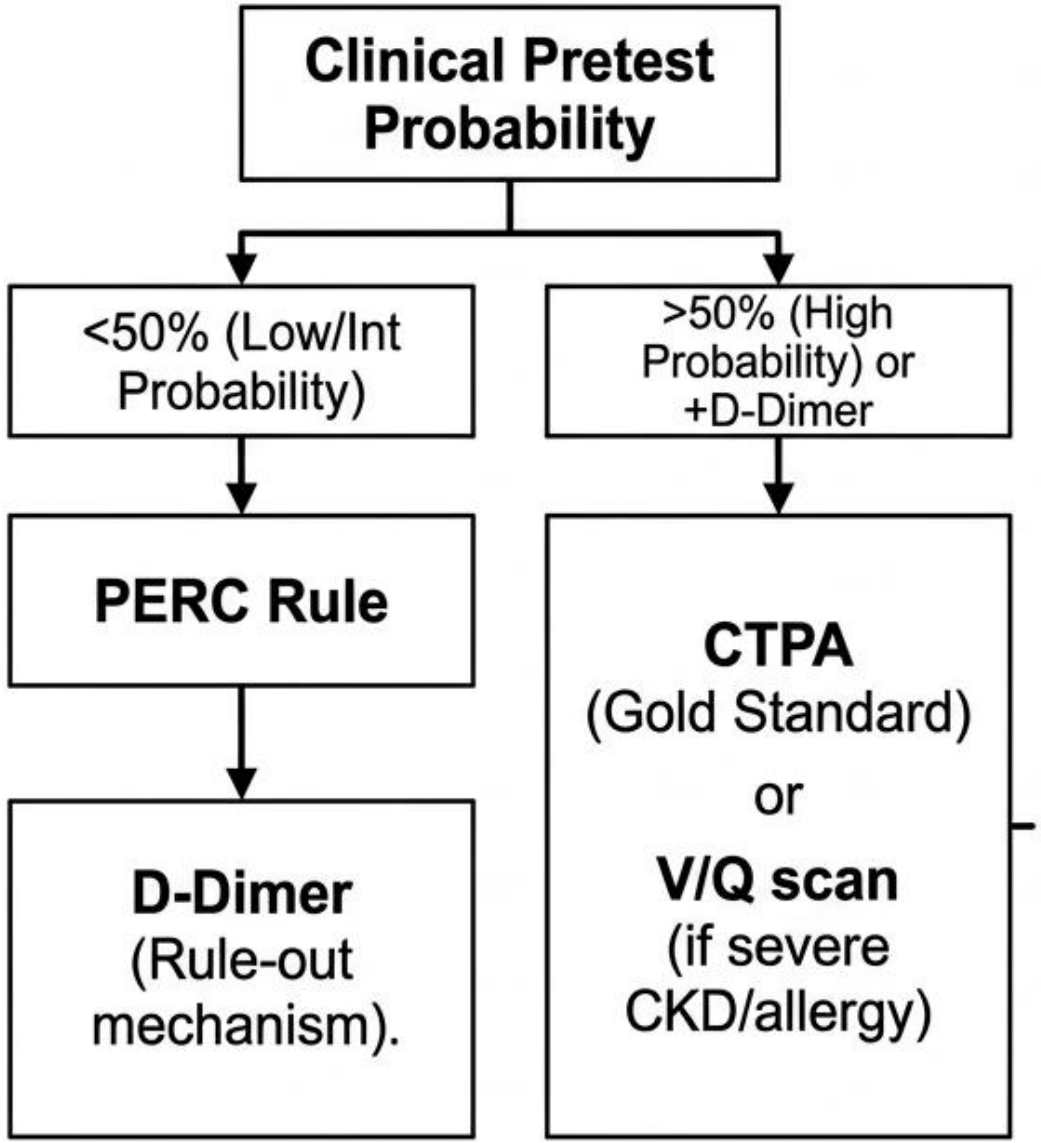
PE

Embolization to pulmonary vasculature causes V/Q mismatch, increased pulmonary artery pressure, and acute Right Ventricular (RV) strain leading to potential shock.

VTE Risk Factors and Stratification



Diagnostic Pathway



AHA/ACC Severity Categories & Actions

Low Risk: Standard DOAC initiation. Outpatient management possible.

Intermediate-Low / Intermediate-High: Anticoagulation + close monitoring for RV dysfunction/hemodynamic decompensation.

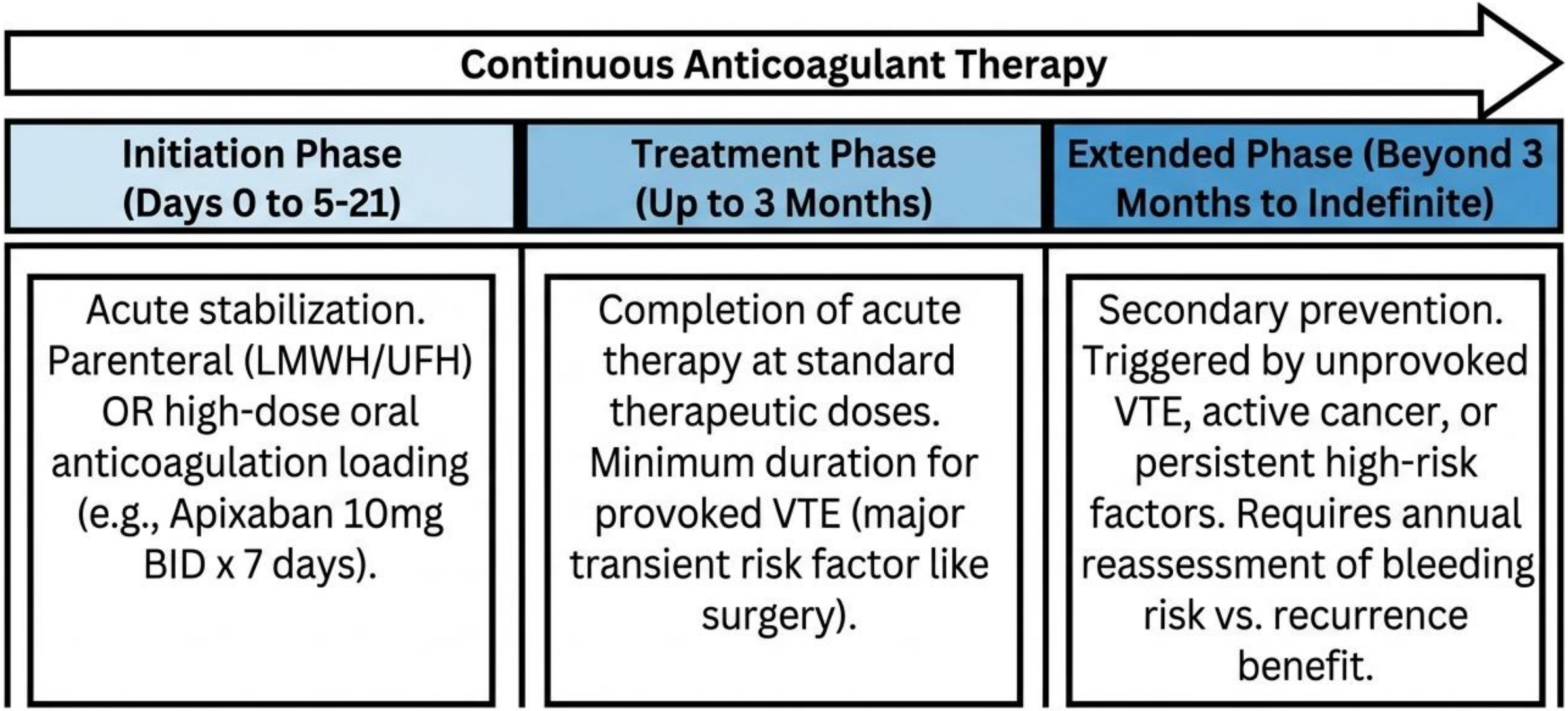
High Risk (Categories D-E): Massive PE with shock. Escalate to Systemic Thrombolysis, Catheter-based extraction, or ECMO via PERT (Pulmonary Embolism Response Team).

Reference: 2026 AHA/ACC Guideline

Anticoagulant Profiler

	Direct Oral Anticoagulants (DOACs)	Low-Molecular-Weight Heparin (LMWH)	Warfarin (VKA)
Examples	Apixaban, Rivaroxaban, Edoxaban, Dabigatran	Enoxaparin, Dalteparin	Vitamin K Antagonist
Mechanism of Action	Direct Factor Xa (or IIa) inhibition.	Enhances Antithrombin, targeting Xa > IIa.	Inhibits Vitamin K epoxide reductase (Factors II, VII, IX, X).
Clinical Pros	No routine monitoring, rapid onset, fewer drug interactions, generally preferred 1st-line.	Preferred in Pregnancy and active GI/GU Cancer.	Safe in mechanical valves, validated in severe CKD/ESRD.
Clinical Cons	Contraindicated in pregnancy, extreme caution in end-stage renal disease (ESRD).	Daily subcutaneous injections, requires dose adjustment in CKD.	Narrow therapeutic index, requires frequent INR monitoring (Target 2.0-3.0), dietary interactions.

Anticoagulant Therapy Timeline



Reference: CHEST Guidelines 2021 Update

Thrombophilia: When to Test?

DO NOT TEST

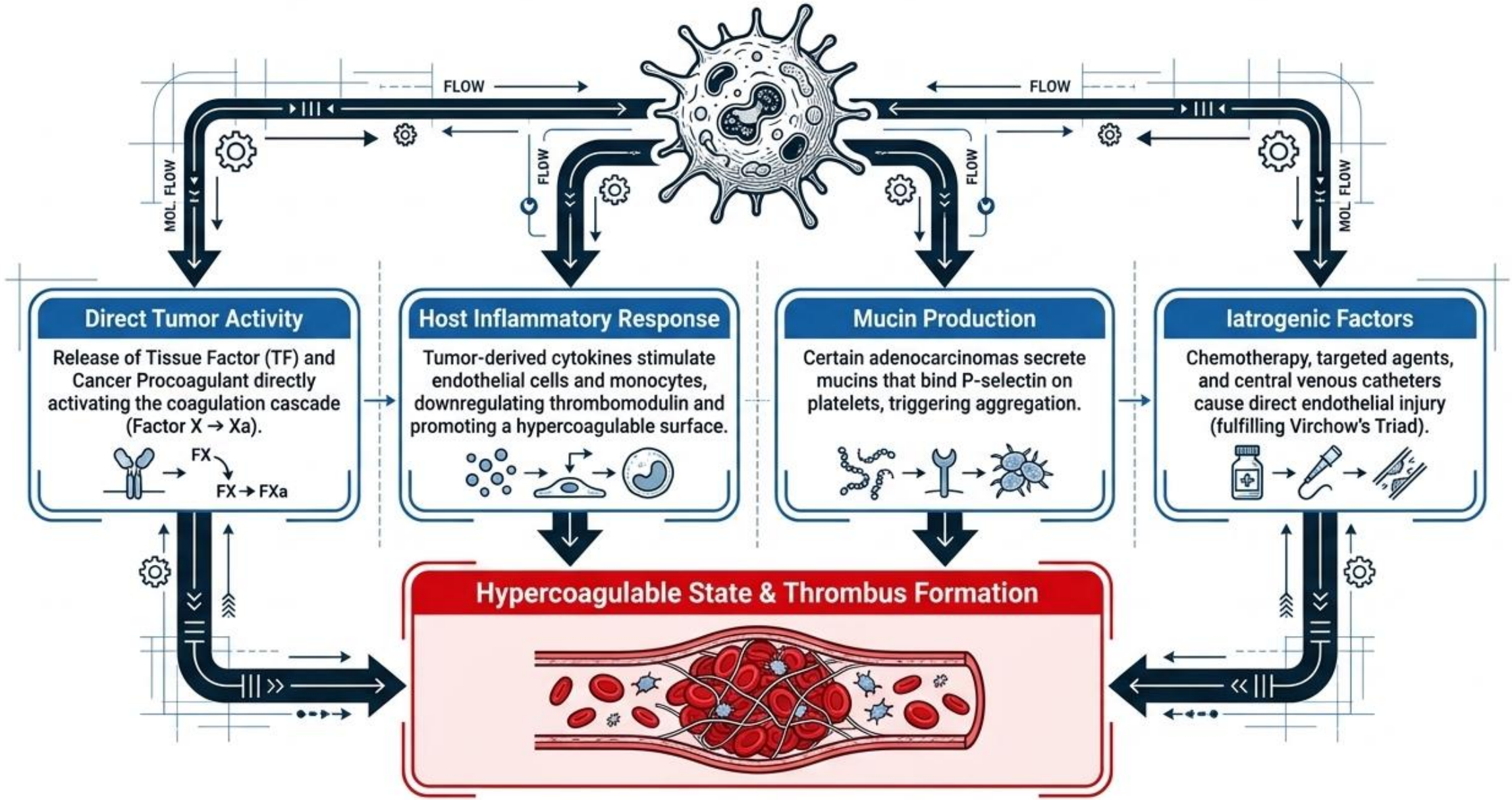
- During the acute thrombotic event (proteins consumed).
- While on active anticoagulation (alters assay results).
- In cases of provoked VTE with major transient risk factors (e.g., post-orthopedic surgery).

CONSIDER TESTING

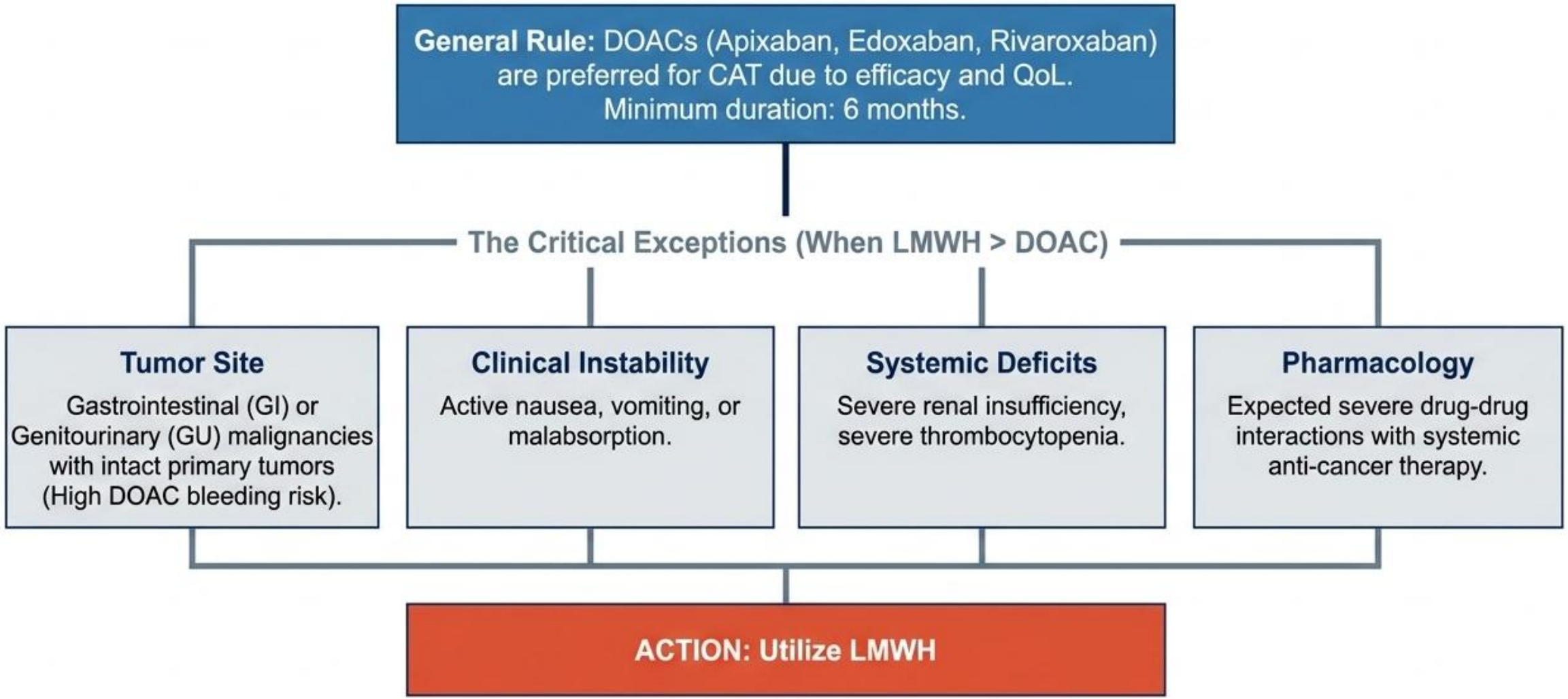
- Unprovoked VTE in young patients (< 50 years).
- Strong family history of unprovoked VTE.
- Thrombosis in unusual sites (e.g., splanchnic, cerebral veins).
- Recurrent VTE despite adequate anticoagulation.

High-Yield Knowledge: High-Risk Thrombophilias include Antithrombin/Protein C/Protein S deficiencies, Homozygous Factor V Leiden, and Antiphospholipid Syndrome (APS). Testing is only justified if it changes clinical management (e.g., duration of AC).

Pathophysiology of Cancer-Associated Thrombosis (CAT)



Cancer-Associated Thrombosis: Site-Specific Selection (NCCN/ESMO)



Case 7

Q7

A 40-year-old sportsman is brought to ED by his wife due to the sudden onset of profound right-sided weakness and an inability to speak. His wife states that he was entirely normal when they ate breakfast 3 hours ago. He has a history of poorly controlled hypertension and frequent complaints of severe itching after taking warm showers.

On physical examination, he appears markedly plethoric. He has dense right hemiplegia and global aphasia.

CBC shows Hb 19.8 g/dL, Hct 61%, MCV 90 fL, WBC count 15,200/µL (N 70, L 22, M 5, E 3), platelet count 610,000/µL.

A non-contrast CT scan of the brain is obtained immediately.

Which of the following is the most appropriate immediate management?

A. Administer rtPA followed by urgent therapeutic phlebotomy.
B. Perform urgent therapeutic phlebotomy and consult neurosurgery for mechanical thrombectomy.
C. Initiate a continuous intravenous heparin infusion
D. Administer rtPA and initiate high-dose hydroxyurea.
E. Administer dual antiplatelet therapy and defer phlebotomy until the neurological deficits stabilize.

CT brain shows hyperdense MCA sign (thrombus within the MCA) and peripheral low attenuation of the supplied MCA territory with loss of grey-white differentiation.

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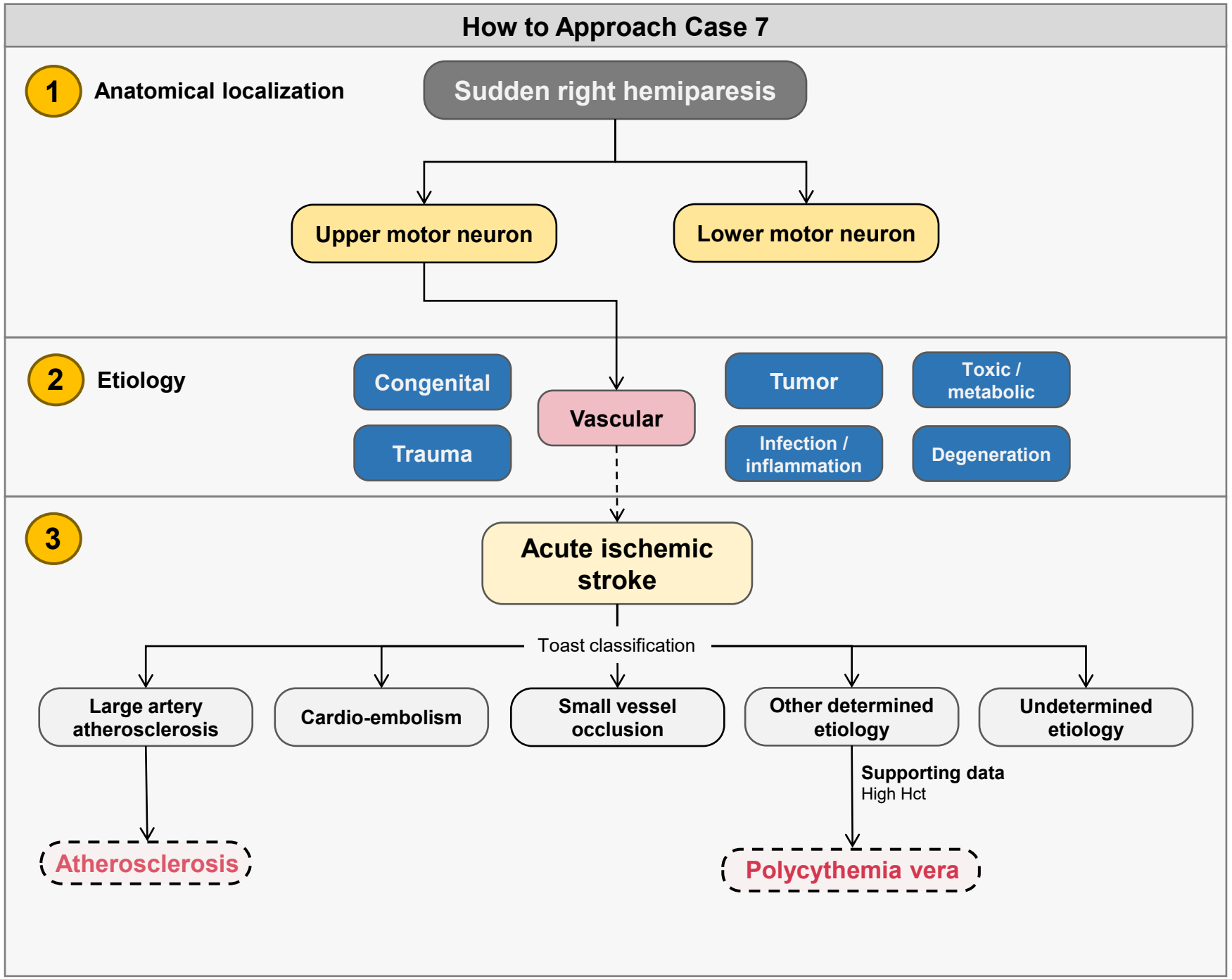
Polycythemia Vera


How to Approach Case 7
1
Anatomical localization
Sudden right hemiparesis
Upper motor neuron
Lower motor neuron
2
Etiology
Congenital
Trauma
Vascular
Tumor
Infection / inflammation
Toxic / metabolic
Degeneration
3
Acute ischemic stroke
Toast classification
Large artery atherosclerosis
Cardio-embolism
Small vessel occlusion
Other determined etiology
Undetermined etiology
Supporting data
High Hct
Atherosclerosis
Polycythemia vera

Clinical Approach to Erythrocytosis

Incidental Elevated Hgb / Hct

Relative (Spurious) Erythrocytosis

Normal RBC mass, decreased plasma volume.

Etiologies: Dehydration, excessive diuretic use.

Absolute (True) Erythrocytosis

Increased RBC mass

Proceed to Step 2: Assess Serum Erythropoietin (EPO).

High/Normal EPO (Secondary Erythrocytosis)

Hypoxia-driven: Cardiopulmonary disease, sleep apnea, high altitude, smoking/CO.

Pathologic: EPO-secreting tumors (Renal cell carcinoma, HCC).

Low EPO (Primary Erythrocytosis)

Bone marrow autonomous production.

Action: High suspicion for PV. Mandates JAK2 mutation testing and marrow biopsy.

⚠ Warning: Masked Polycythemia Vera

Concomitant iron deficiency can lower the Mean Corpuscular Volume (MCV) and mask the diagnostic parameters of PV. The hematocrit may appear strictly normal while the absolute RBC count is discordantly high. Always interpret Hgb/Hct in the context of ferritin and RBC counts.

Pathogenesis: From Clonal Mutation to Clinical Manifestation

The Molecular & Cellular Disruption	Systemic Consequences (The Hyper States)
The Driver Mutation: >98% of PV patients harbor the JAK2 V617F mutation. ~1-2% harbor JAK2 exon 12 mutations.	**Hyperviscosity:** Elevated hematocrit causes sluggish microvascular flow. **Clinical: Thrombosis** (arterial/venous), transient visual changes, headache, dizziness.
Mechanism: Causes constitutively active cytokine receptor signaling (JAK-STAT pathway).	**Hypercatabolism:** High cellular turnover rates. **Clinical: Hyperuricemia, secondary gout,** kidney stones.
Cellular Result: EPO-independent erythroid proliferation leading to **Panmyelosis** (hypercellular bone marrow with **trilineage proliferation**: erythroid, myeloid, and megakaryocytic).	**Inflammatory / Histamine Surge:** Mast cell and basophil degranulation. **Clinical: Aquagenic pruritus** (severe itching post-hot water contact), peptic ulcer disease.

Diagnostic Criteria Synthesis (WHO 2022 / ICC)

Major Criteria:

[1] Elevated Parameters: Hgb >16.5 g/dL (M) / >16.0 g/dL (F) OR Hct >49% (M) / >48% (F) OR increased red cell mass (>25% above normal).

[2] Bone Marrow Morphology: Age-adjusted hypercellularity with trilineage growth (panmyelosis). Must show prominent erythroid, granulocytic, and pleomorphic mature megakaryocytes without atypia.

[3] Genetics: Presence of JAK2 V617F or JAK2 exon 12 mutation.

Minor Criterion:

[Minor] Subnormal serum erythropoietin (EPO) level.

CONFIRMED DIAGNOSIS REQUIRES:

(Major 1
+
Major 2
+
Major 3)
[OR]
(Major 1
+
Major 2
+
Minor)

Symptom Burden & Thrombotic Risk Stratification

Clinical Presentation & Symptom Burden

Microvascular Symptoms:

- **Erythromelalgia**: Burning pain, redness, and tingling in the extremities (hands/feet).
- Migraines, transient visual disturbances.

Constitutional / Disease Burden:

- **Aquagenic Pruritus**: Found in up to 68% of patients; severely impacts quality of life.
- **Splenomegaly**: Present in ~36%; causes early satiety and abdominal discomfort.
- **Severe Fatigue**: Reported by >90% of patients.

Prognostic Risk Stratification

Primary therapeutic goal is the prevention of major thrombosis.

Low-Risk Profile:

- **Age < 60 years AND No prior history of thrombosis.**
- Incidence: **~2.5** thrombotic events per 100 person-years.

High-Risk Profile:

- **Age > 60 years OR Prior history of thrombosis.**
- Incidence: **~5.0 - 10.9** thrombotic events per 100 person-years.

Prognostic Note

Cardiovascular events (ischemic stroke, MI, venous thromboembolism) remain the leading **cause of morbidity and mortality** in PV.

Management Phase I: Foundational Therapy & Low-Risk Strategy

Goal 1: Strict Hematocrit Control

Intervention: Therapeutic Phlebotomy

Target: Maintain Hematocrit strictly < 45% (standardized for both men and women).

Evidence Base (CYTO-PV Trial): Maintaining Hct <45% (vs. 45-50%) yields a nearly **4-fold decrease** in major cardiovascular deaths and thrombotic events.

Goal 2: Universal Thromboprophylaxis

Intervention: Low-dose Aspirin (81-100 mg/day) in the absence of absolute contraindications.

Benefit: Significantly reduces microvascular symptoms (e.g., erythromelalgia, ocular migraines) and prevents major arterial/venous events.

Clinical Caveat: Avoid Aspirin if extreme thrombocytosis is present (>1,000 x 10^9/L) due to the risk of bleeding from Acquired von Willebrand Syndrome.

Goal 3: Cardiovascular Risk Modification

Intervention: Aggressive primary care management.

Focus Areas: Strict smoking cessation (critical to lower thrombotic risk), aggressive management of hypertension, hyperlipidemia, and diabetes.

Management Phase II: Cytoreductive Therapy in High-Risk PV

Indications for Cytoreduction: High-Risk status (Age >60 or prior thrombosis), progressive splenomegaly, severe PV-related symptoms, or phlebotomy intolerance/refractoriness.

First-Line Option A
Hydroxyurea (HU)

Standard first-line agent.

Monitoring: Requires watch for cytopenias, mucocutaneous ulcers, and hyperpigmentation.

First-Line Option B
Interferon-alfa (e.g., Ropeginterferon alfa-2b)

Preferred in younger patients (Age <60) and during pregnancy.

Advantage: Capable of inducing molecular responses / lowering JAK2 allele burden.

If HU Resistance or Intolerance develops (ELN Criteria)

Second-Line Option A
Ruxolitinib (JAK1/2 Inhibitor)

Highly effective for achieving Hct control without phlebotomy.

Superior for symptom control (pruritus, severe fatigue) and reducing massive splenomegaly (RESPONSE / RELIEF Trials).

Second-Line Option B
Busulfan

Considered primarily in older patients. High efficacy but carries a leukemogenic risk with long-term use.

Disease Progression & Long-Term Monitoring

Post-PV Myelofibrosis (Post-PV MF)

Incidence: Occurs in ~10% of patients over a 10-15 year disease course.

Diagnostic Clues of Progression:

- Unexplained, progressive massive splenomegaly.
- Development of anemia (patient paradoxically no longer requires therapeutic phlebotomies).
- Peripheral blood leukoerythroblastosis.
- Bone marrow biopsy revealing Grade 2 or 3 reticulin/collagen fibrosis.

Leukemic Transformation

Incidence: Progression to Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS) occurs in <5% of patients.

Prognosis: Carries a very poor prognosis and high mortality.

Risk Factors: Advanced age, abnormal karyotype, and potentially decades of exposure to certain leukemogenic cytoreductive agents.

The Investigational Horizon

Rusfertide (Hepcidin Mimetic): Emerging targeted therapy (VERIFY Trial) showing high promise in controlling iron metabolism to effectively eliminate the need for routine phlebotomies.

Case 8

Q8

A 60-year-old previously healthy male shoemaker is brought to the emergency department by his partner. Over the past three weeks, he has experienced progressive fatigue, night sweats, and easy bruising. Over the last 24 hours, his condition rapidly deteriorated. He developed acute shortness of breath, a severe headache, blurred vision, worsening confusion, and rigors during the ambulance ride. He is diagnosed with hyperleukocytic AML.

Which of the following statements regarding the immediate management of his concurrent emergencies is correct?

A. Packed red cell transfusions should be administered to correct his anemia and improve cerebral oxygenation.
B. Intravenous calcium gluconate is indicated to correct his serum calcium to a normal physiological range.
C. A continuous therapeutic heparin infusion should be initiated to halt the consumptive microvascular thrombosis.
D. High-dose intravenous sodium bicarbonate infusion is the definitive primary therapy to resolve his severe Type B lactic acidosis.
E. Immediate administration of empiric broad-spectrum intravenous antibiotics with antipseudomonal coverage is required within the first hour of presentation, prior to the return of blood cultures.

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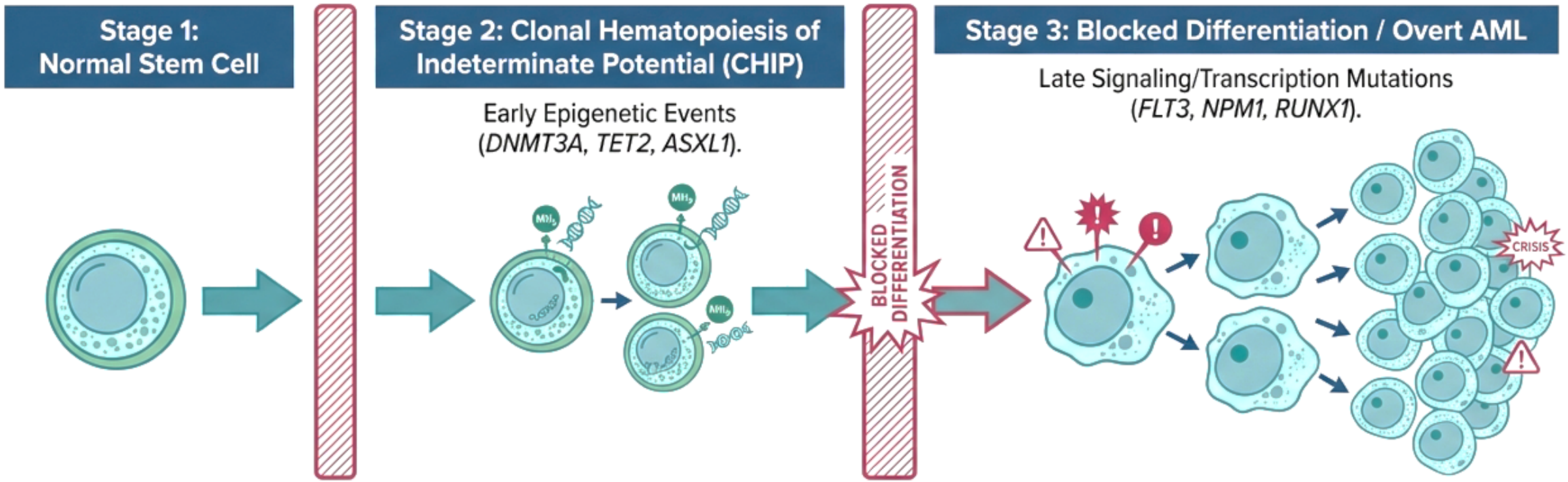
Acute Myeloid Leukemia with Oncologic Complications

Pathophysiology of AML (Leukemogenesis & Clonal Evolution)



AML is driven by the serial acquisition of somatic mutations, disrupting normal myeloid differentiation and causing life-threatening cytopenias.

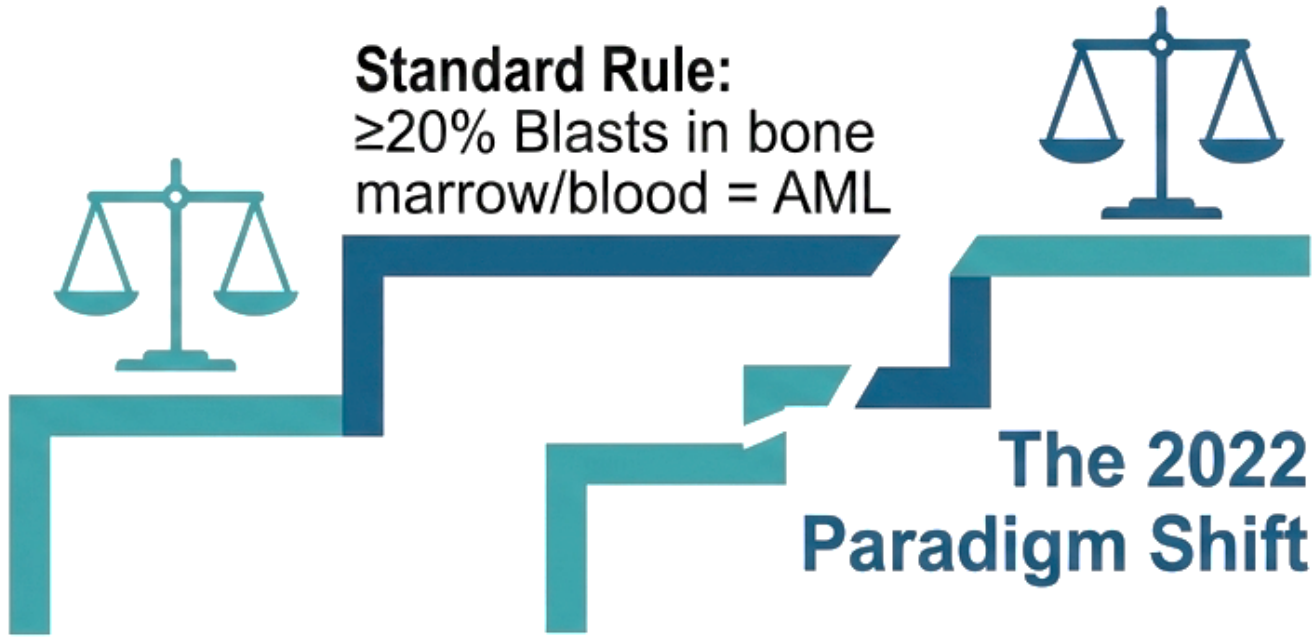
Clinical Manifestations & Modern Diagnosis

Clinical Signs

- Cytopenias (fatigue, infections)
- Coagulopathy & Bleeding
- Extramedullary involvement (myeloid sarcoma/chloroma)

Diagnostic Triad

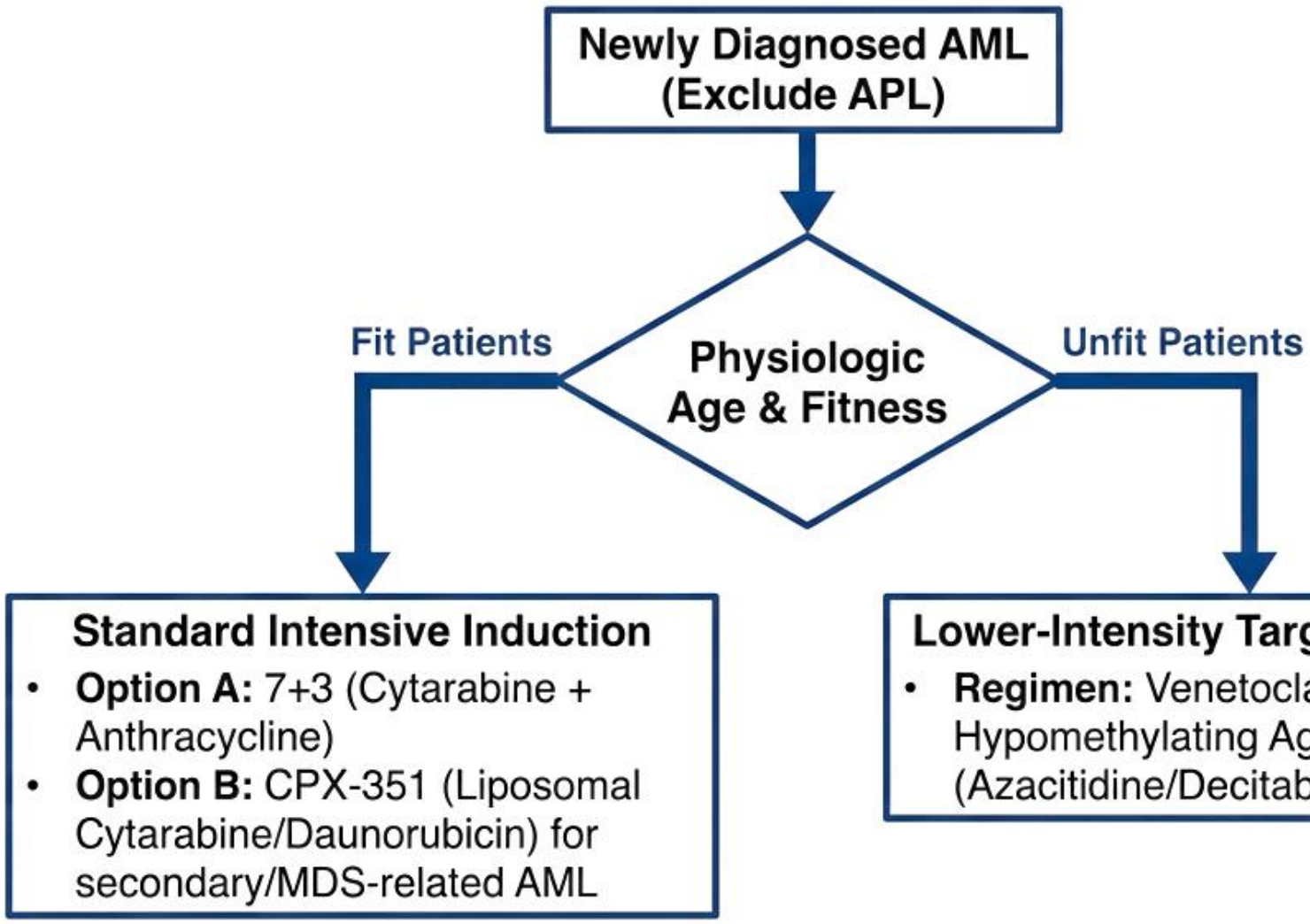
1) Morphology (Blood/Marrow)
2) Flow Cytometry (CD34, CD117, MPO)
3) Molecular Genetics



The 20% threshold is REMOVED (or lowered to 10% per ICC) **if specific AML-defining genetic abnormalities are present.**

PML::RARA, RUNX1::RUNX1T1, CBFB::MYH11

Management of AML (NCCN & TSH Harmonized Guidelines)



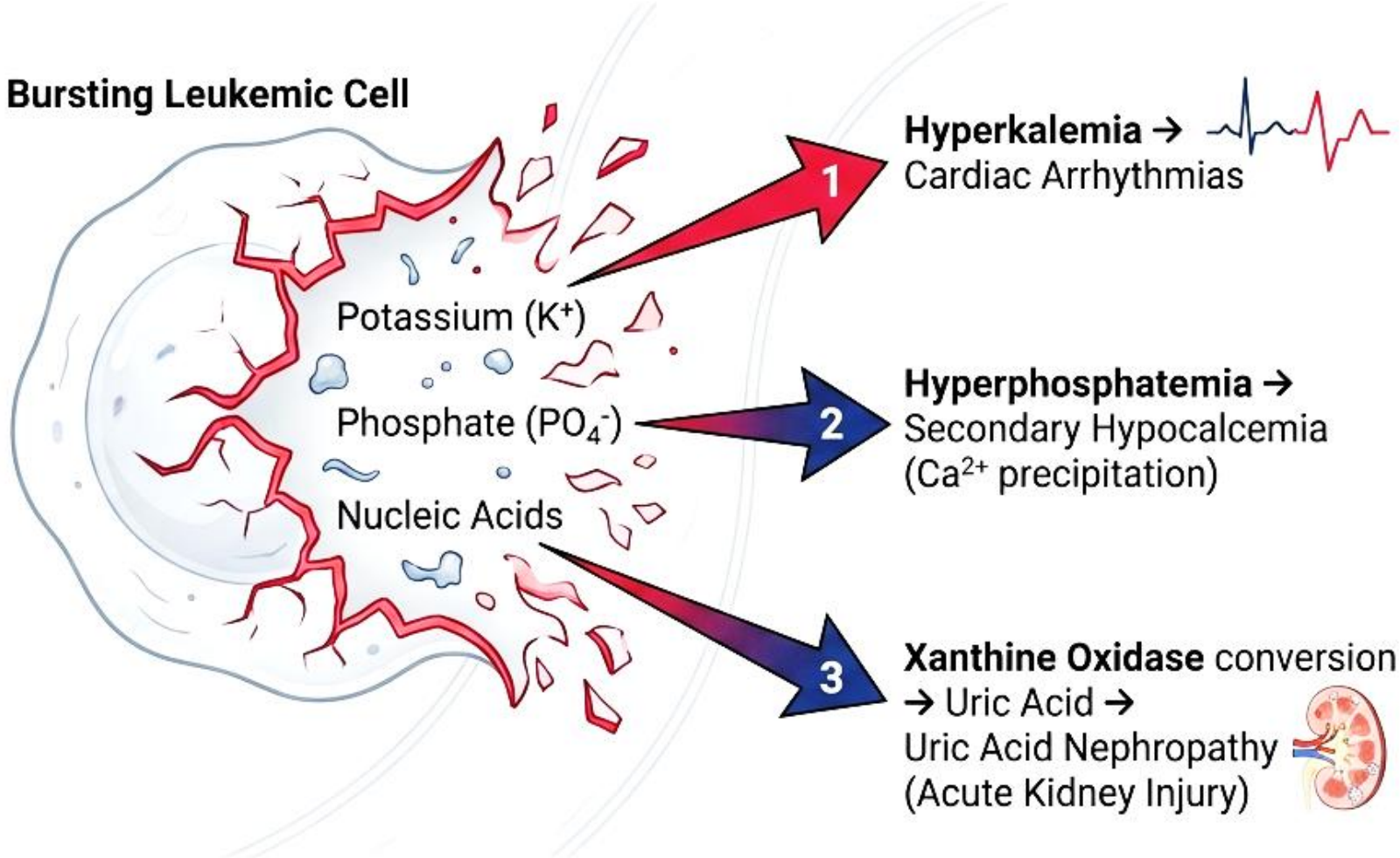
The APL Exception (PML::RARA)

The APL Exception (PML::RARA)

Regimen: ATRA + Arsenic Trioxide (ATO) - non-cytotoxic differentiation therapy.

TSH (Thai Society of Hematology) guidelines conceptually align with NCCN regarding the crucial intensive vs. non-intensive risk stratification.

Oncologic Emergency 1: Spontaneous & Therapy-Induced Tumor Lysis Syndrome (TLS)



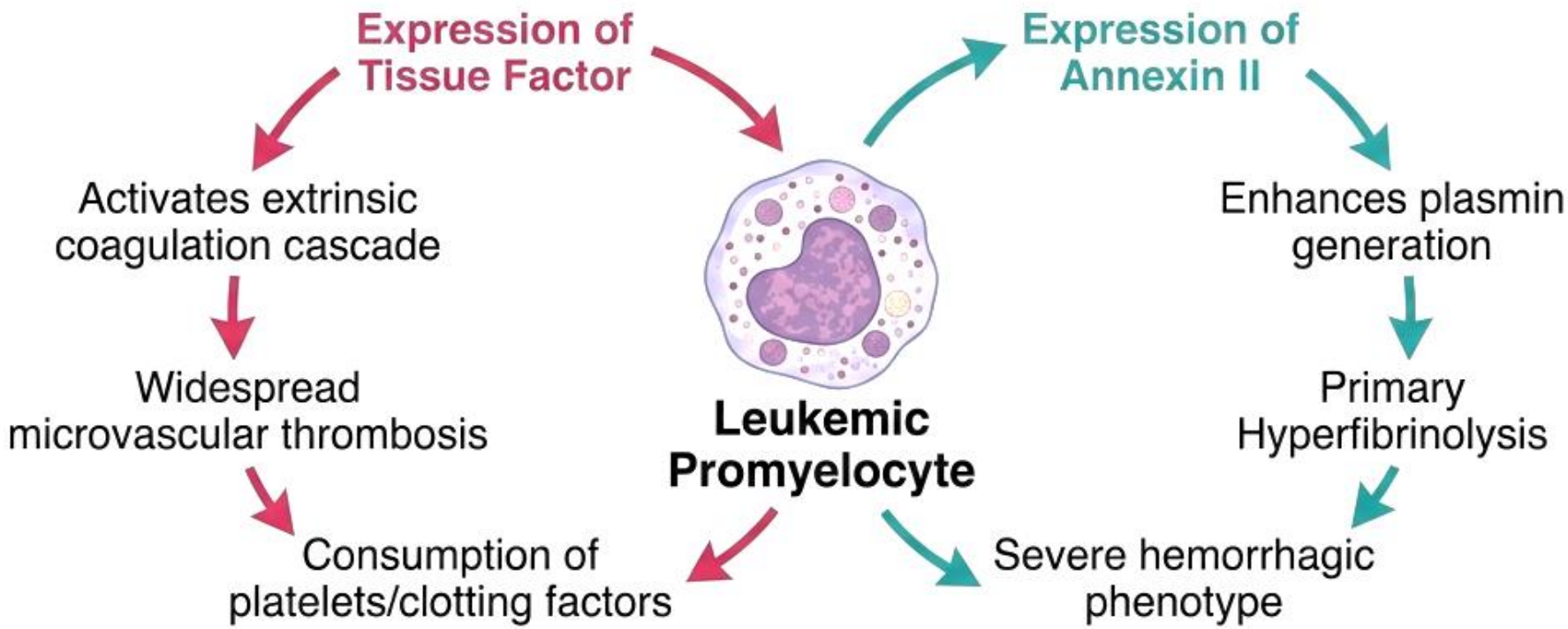
Clinical Context

Spontaneous (high tumor burden) or Therapy-Induced. High risk noted with initiation of Venetoclax regimens or high-burden aggressive phenotypes.

Diagnostic Criteria

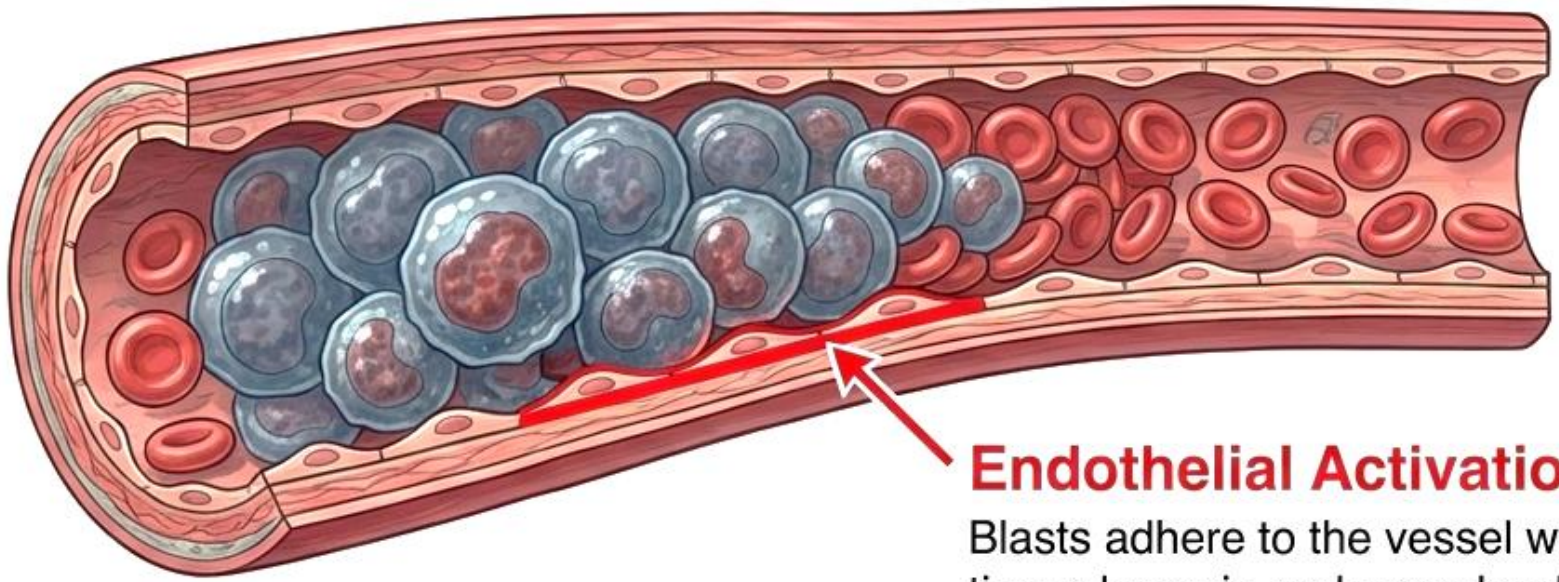
Distinguish between Cairo-Bishop (CB-TLS) and Howard criteria (H-TLS). Howard criteria are more stringent and identify clinically meaningful TLS requiring acute intervention.

Oncologic Emergency 2: Disseminated Intravascular Coagulation (DIC)



Clinical Correlate: High risk of early fatal pulmonary and intracranial hemorrhage. DIC in APL represents a dual-threat of thrombosis and profound bleeding.

Oncologic Emergency 3: Leukostasis Syndrome



Endothelial Activation

Blasts adhere to the vessel wall, causing localized tissue hypoxia and vascular damage.

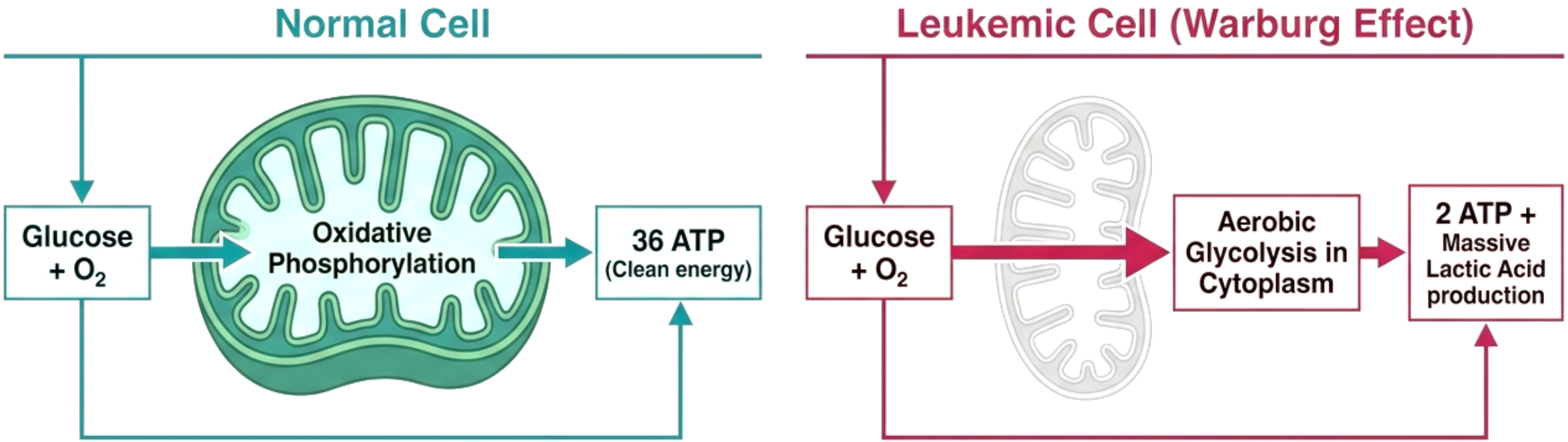
Key Threshold

Typically occurs with WBC > 100,000/mcL (Hyperviscosity).

Clinical Presentation

- Pulmonary distress: dyspnea, hypoxia, infiltrates.
- CNS manifestations: confusion, somnolence, stroke-like symptoms, visual changes.

Oncologic Emergency 4: Hyperwarburgism (Type B Lactic Acidosis)



Definition: Type B Lactic Acidosis. Occurs without tissue hypoperfusion or hypoxia.

Clinical Significance: Indicates a massive, rapidly dividing tumor burden. It is a severe prognostic sign requiring immediate intervention, not just supportive critical care. Cancer cells shift to high-rate aerobic glycolysis even in oxygen-rich states.

Pitfalls in Emergency Management

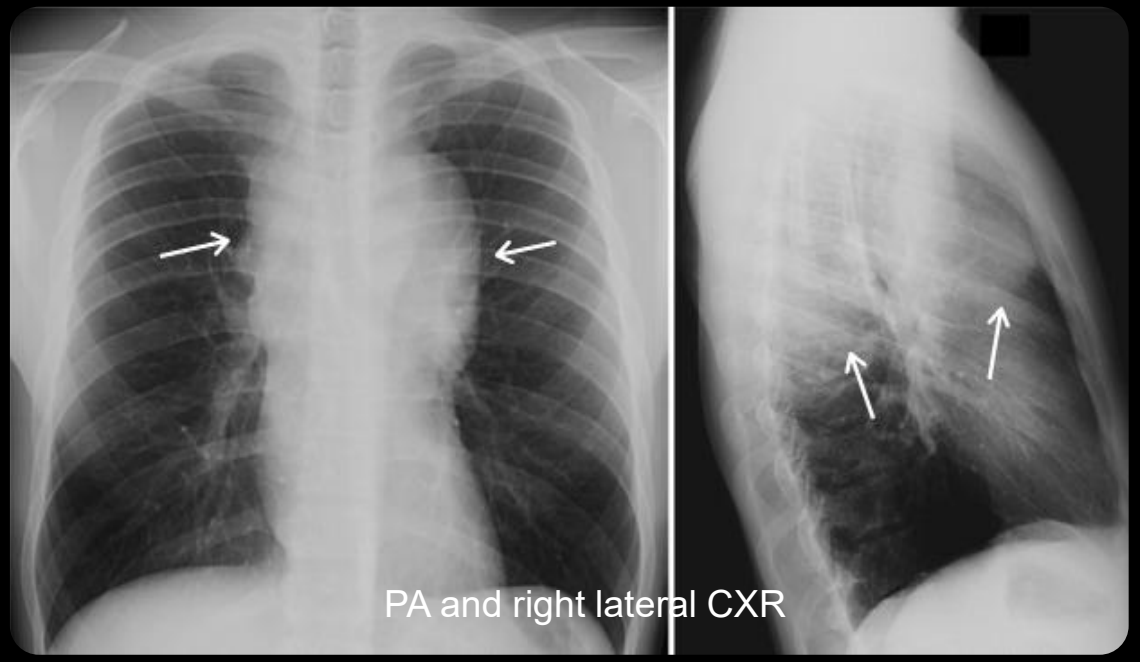
Emergency	Common Clinical Pitfall	Correct Action
Tumor Lysis Syndrome (TLS)	**Under-prophylaxis** when starting Venetoclax.	**Aggressive IV hydration, administer allopurinol or rasburicase prior to induction.**
DIC (in APL)	**Delaying ATRA therapy** while waiting for molecular/genetic confirmation.	**Start ATRA immediately upon morphological/clinical suspicion. Transfuse platelets/cryoprecipitate aggressively.**
Leukostasis	**Administering RBC transfusions** (worsens viscosity) or **diuretics** (causes dehydration).	**Urgent cytoreduction (apheresis, hydroxyurea); maintain euvolemia.**
Hyperwarburgism	**Administering continuous sodium bicarbonate** (worsens cardiac inotropy, ignores root cause).	**Urgent initiation of systemic chemotherapy to kill the lactate-producing blasts.**

Case 9

Q9

A 35-year-old female TikToker presents to the medicine clinic with persistent dry cough and progressive positional related SOB for 2 mo. She also had alcohol intolerance, and significant weight loss. Physical examination shows enlarged left cervical lymphadenopathies, and no adventitious lung sound.

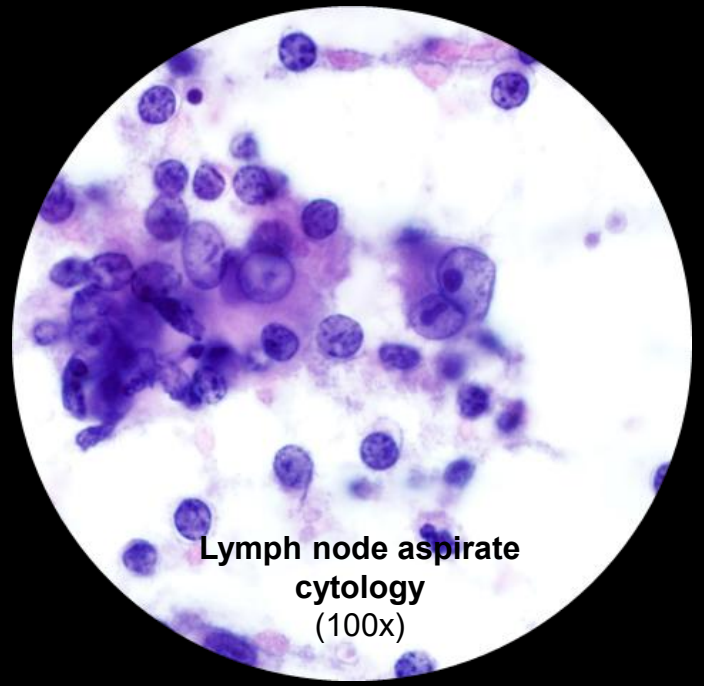
CBC reveals Hb 12.8 g/dL, Hct 39%, WBC count 10,000/μL (N 60, L 30, M 8), platelet count 550,000/μL. Chest X-ray demonstrates as a shown figure. Cervical lymph node aspiration is performed.



PA and right lateral CXR

What is the most likely diagnosis?

A. Bronchogenic adenocarcinoma
B. Hodgkin lymphoma
C. Ovarian germ cell tumor
D. Primary mediastinal B cell lymphoma
E. Thymoma



Lymph node aspirate cytology
(100x)

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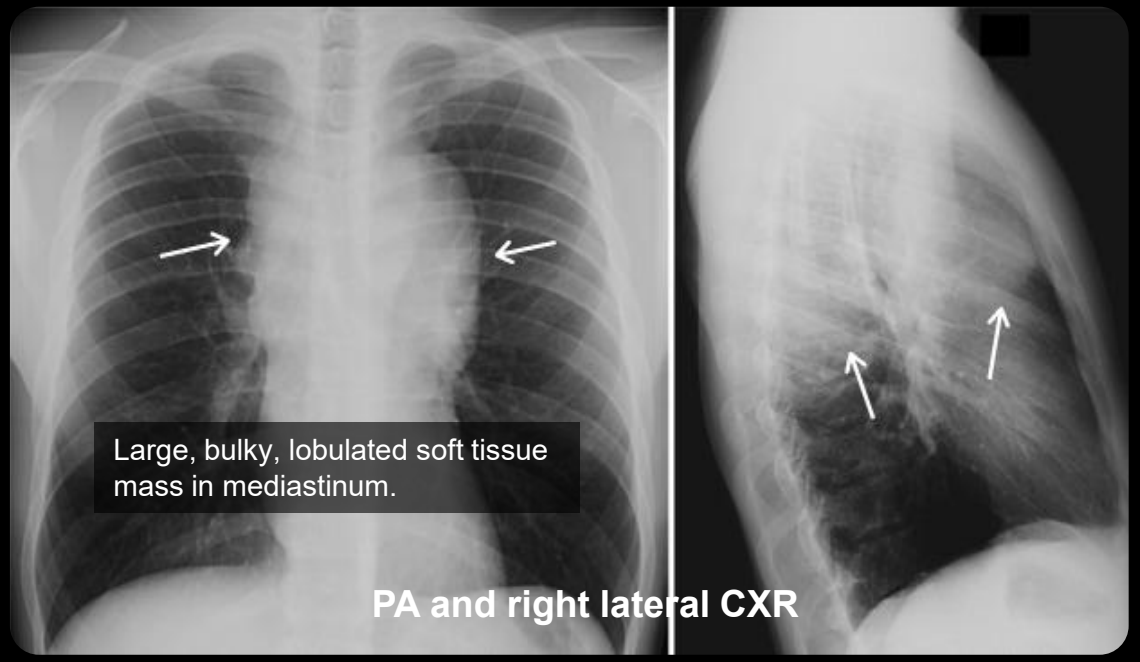

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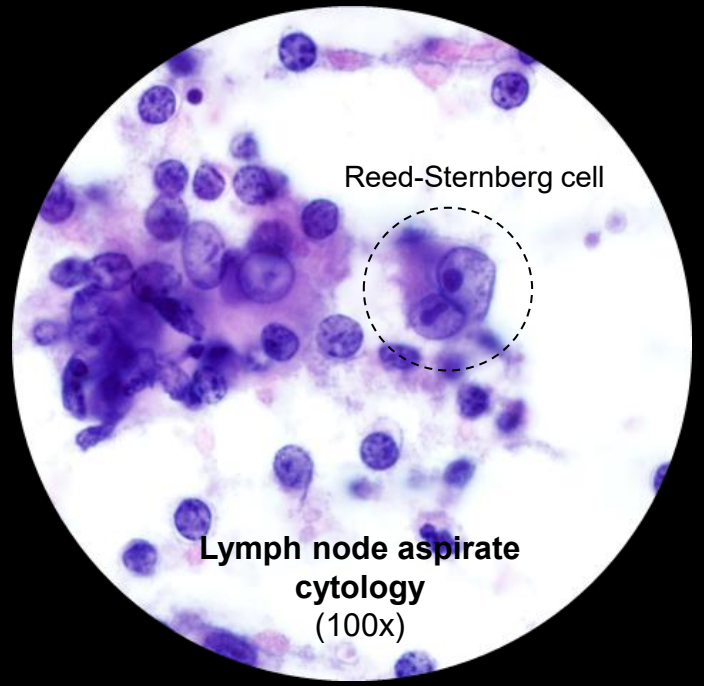
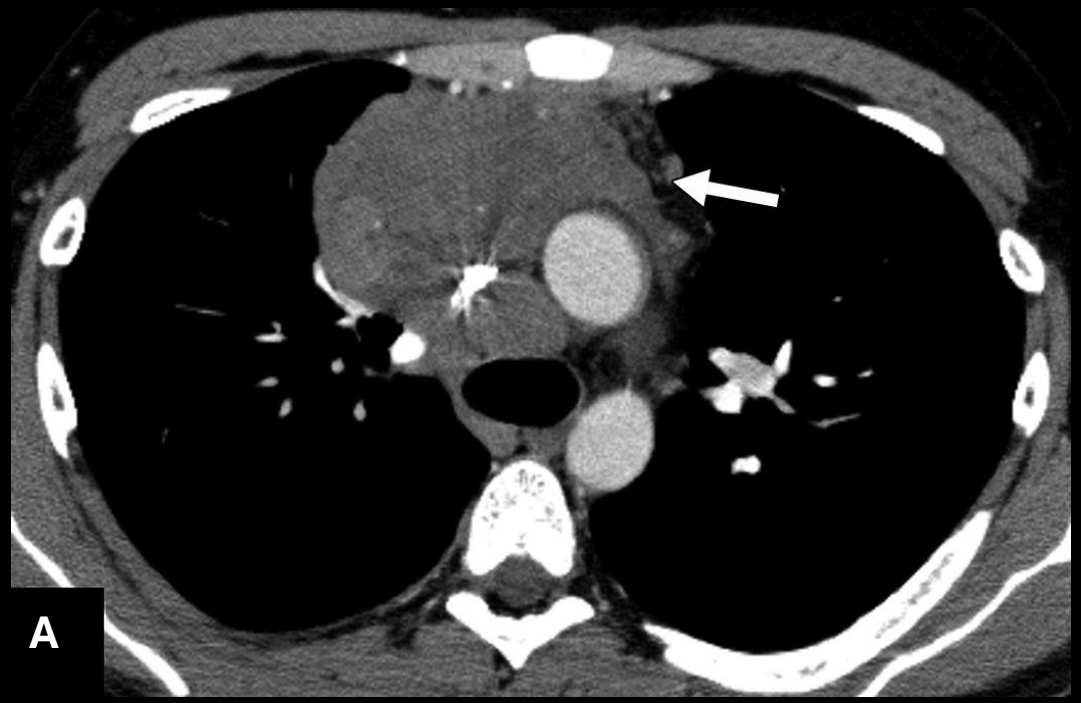
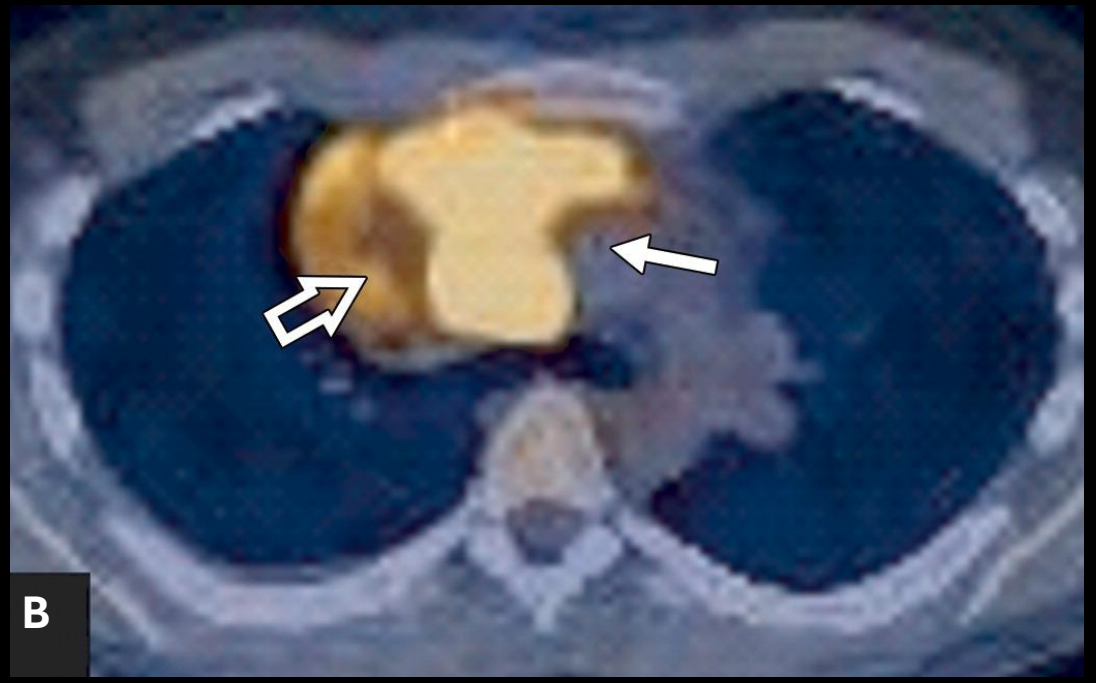


Lymph node aspirate cytology
(100x)

^{18}F-FDG PET-CT Scan

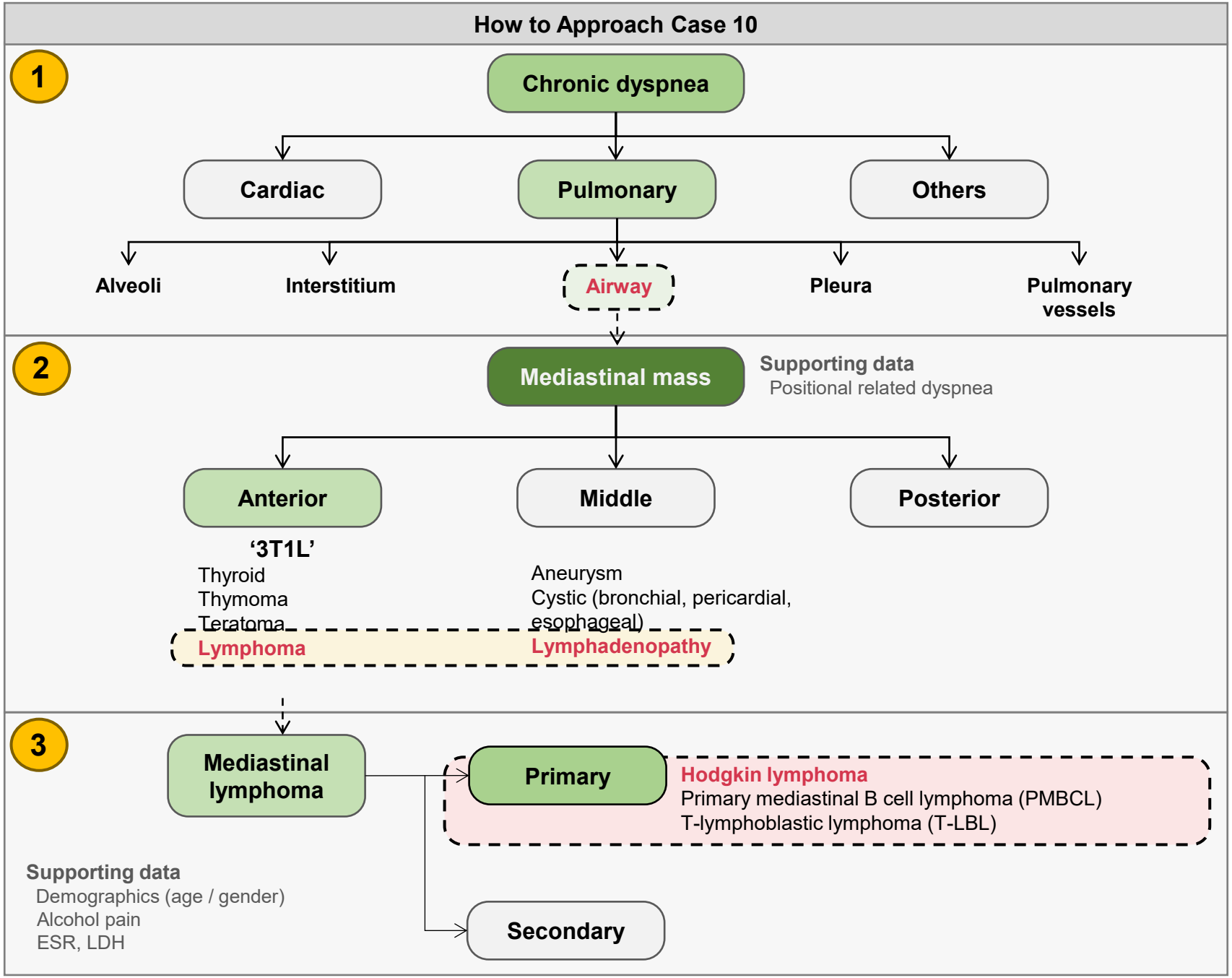


A: Transverse enhanced CT image of chest shows bulky mass of heterogeneous density (arrow) in anterior mediastinum. Encasement and compression of mediastinal veins are caused by growing mass.

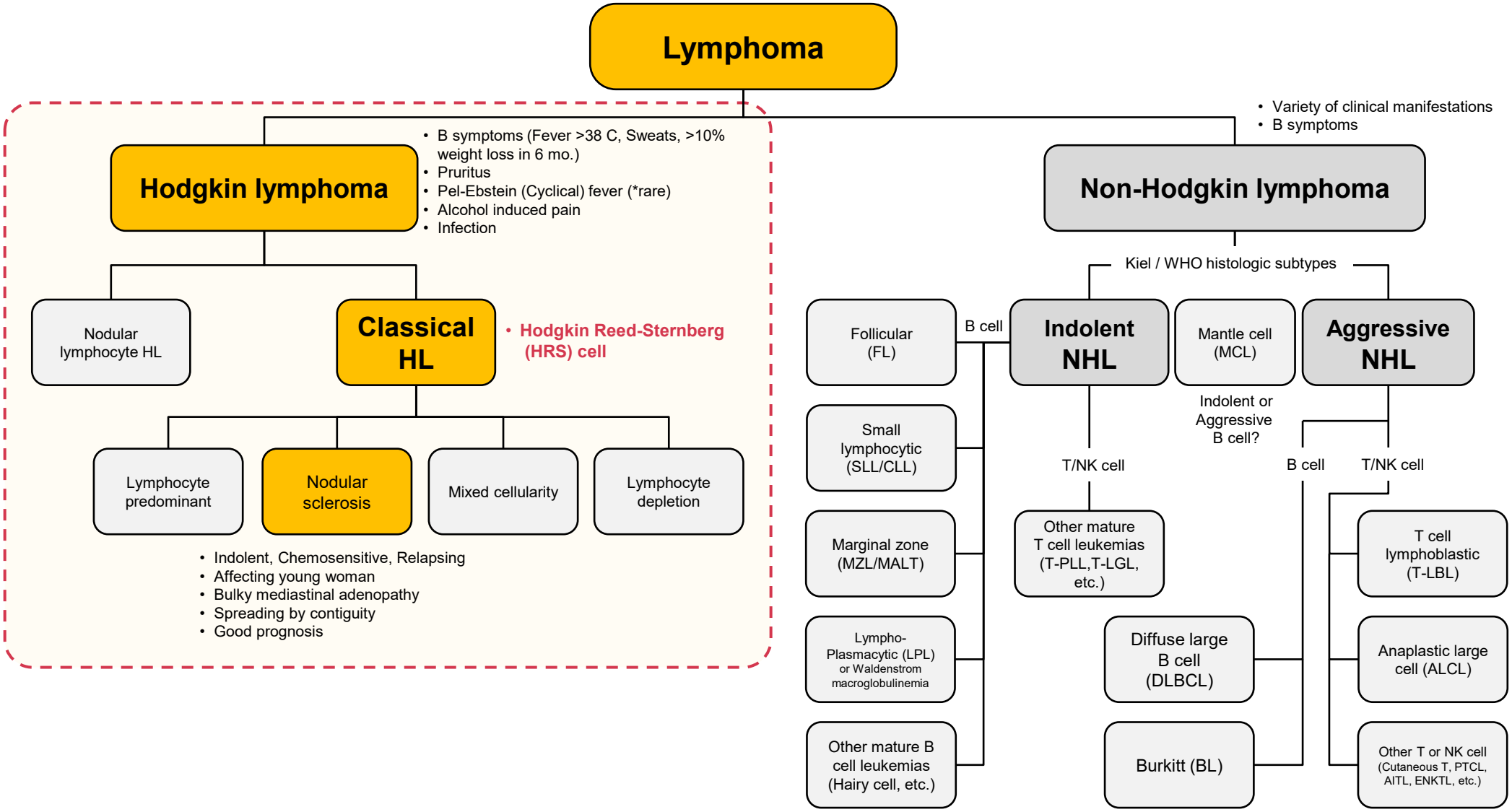


B: Transverse fused FDG PET/CT image of chest shows FDG-avid structure (*solid arrow*) corresponding to lymphoma. Signal heterogeneity reflecting necrosis of lesion is clearly detectable (*open arrow*).

Hodgkin Lymphoma


How to Approach Case 10
1
Chronic dyspnea
Cardiac
Pulmonary
Others
Alveoli
Interstitium
Airway
Pleura
Pulmonary vessels
2
Mediastinal mass
Supporting data
Positional related dyspnea
Anterior
Middle
Posterior
'3T1L'
Thyroid
Thymoma
Teratoma
Lymphoma
Aneurysm
Cystic (bronchial, pericardial, esophageal)
Lymphadenopathy
3
Mediastinal lymphoma
Primary
Hodgkin lymphoma
Primary mediastinal B cell lymphoma (PMBCL)
T-lymphoblastic lymphoma (T-LBL)
Secondary
Supporting data
Demographics (age / gender)
Alcohol pain
ESR, LDH

Classification of Lymphoma



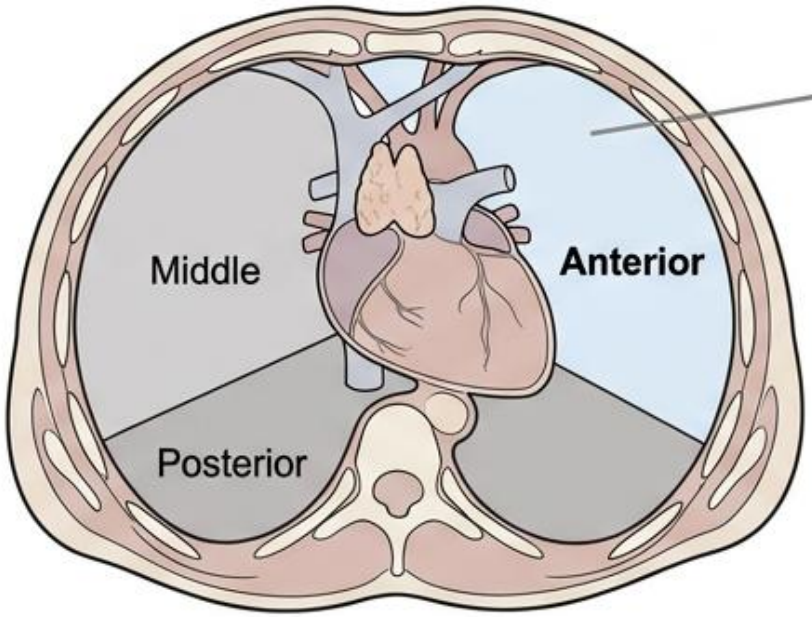
MALT = Mucosa-associated lymphoid tissue lymphoma, PLL = Prolymphocytic leukemia, LGL = Large granular lymphocyte leukemia
PTCL = Peripheral T cell lymphoma, AITL = Angioimmunoblastic T cell lymphoma, ENKTL = Extranodal NK/T cell lymphoma

Differential Diagnosis: Lymphoma in Different Settings

Young adult	Mediastinal mass	HIV related	Primary BM (+/- splenomegaly)	HLH associated	HyperIg
HL	HL (F, Y)	PCNSL	LPL or WM	DLBCL or IVL	LPL or WM (IgM)
DLBCL	PMBCL (F, 35 y/o)	Burkitt	MZL	ALCL	MZL (IgG)
Burkitt	ALCL (M/F, Y)	DLBCL (Imm.)	MCL	SPTCL	AITL (Polyclonal)
ALCL	T-LBL (M,Y)	PBL	SMZL	T-LBL	
T-LBL	DLBCL (M/F, E)	PEL	HCL	1º cut. Γδ-T-cell	
		Hodgkin (MC/LD)	T-LGL	Hodgkin (MC/LD)	

HL = Hodgkin lymphoma, ALCL = Anaplastic large cell lymphoma, T-LBL = T cell lymphoblastic lymphoma, PMBCL= Primary mediastinal B cell lymphoma, T-LGL = Large granular lymphocyte leukemia, SPTCL = Subcutaneous panniculitis like T cell lymphoma, 1o cut. Γδ-T-cell = Primary cutaneous gamma-delta T cell lymphoma, SMZL = Splenic marginal zone lymphoma, MCL = Mantle cell lymphoma, PBL = Plasmablastic lymphoma, PEL = Primary effusion lymphoma, LPL = lymphoplasmacytic lymphoma, AITL = Angioimmunoblastic T cell lymphoma, HCL = Hairy cell leukemia, IVL = Intravascular lymphoma

Approach to the Anterior Mediastinal Mass



ANTERIOR MEDIASTINAL MASS

- Thymoma
- Teratoma
- Thyroid (goiter/neoplasm)
- **Terrible** Lymphoma

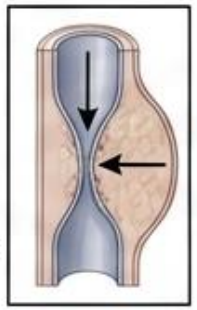
Clinical Presentation: **Hodgkin Lymphoma** typically presents in young adults (20-39 years) with bulky anterior mediastinal lymphadenopathy. May include "B symptoms" (unexplained fever >100.4°F, drenching night sweats, weight loss).

Diagnostic Imperative: **Tissue is the issue**. Avoid Fine-Needle Aspiration (FNA) due to loss of architectural information. Excisional biopsy is the gold standard; core needle biopsy is acceptable if excisional is not feasible.

Emergency Management: SVC Obstruction

Pathophysiology

Bulky anterior mediastinal mass compresses the Superior Vena Cava, impeding venous return from the head, neck, and upper extremities.



Clinical Signs

Facial plethora, jugular venous distension (JVD), dyspnea, and upper extremity edema.

The Hematology/ Oncology Dilemma

Securing a tissue diagnosis BEFORE initiating empirical steroids or radiation is critical.

Premature administration of steroids can cause tumor lysis or necrosis, obscuring the delicate pathology of lymphoma and delaying definitive curative therapy.

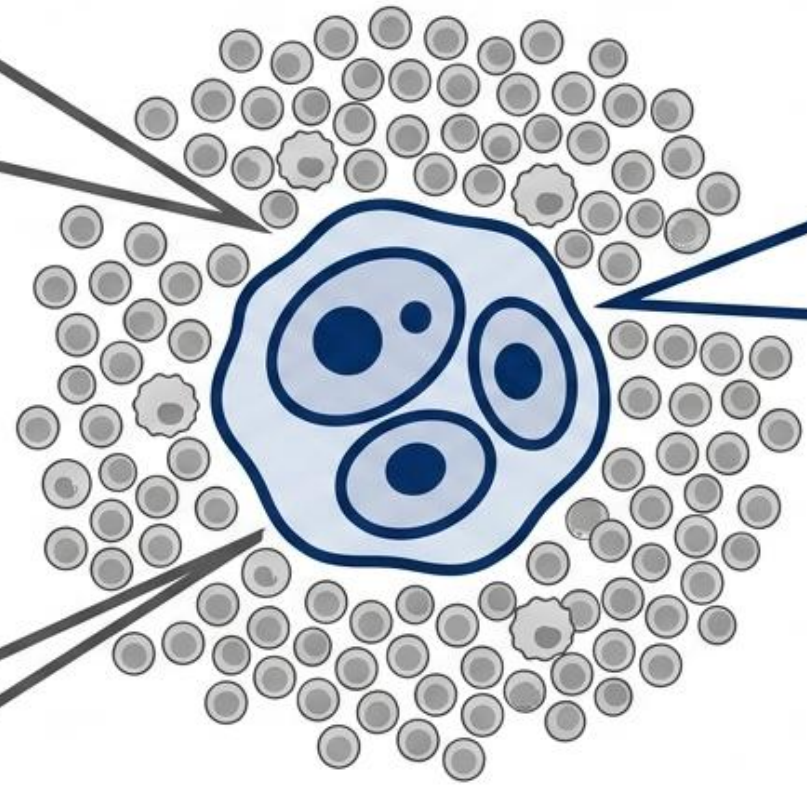
Pathophysiology: The Unique Tumor Microenvironment

The 1% Rule

Malignant Hodgkin and Reed-Sternberg (HRS) cells account for only 1% to 10% of the tumor mass. The remaining 90%+ is a non-neoplastic inflammatory background (T-cells, eosinophils, macrophages).

Origin

Derived from crippled germinal center B-cells.



Immune Evasion (The Therapeutic Target)

HRS cells inherently **overexpress PD-L1** and **PD-L2** (driven by 9p24.1 amplification). This exhausts surrounding T-cells, **cells, evading immune surveillance** (the biological rationale for **PD-1 inhibitors like Nivolumab).**

Pathology & WHO Classification

Classification	Classic Hodgkin Lymphoma (cHL) (~95%)	Nodular Lymphocyte-Predominant (NLPHL) (~5%)
Malignant Cell	Reed-Sternberg (HRS) cells	Lymphocyte Predominant (LP) / “Popcorn” cells
Immunophenotype	**CD15+**, **CD30+**, CD20-, CD45-	**CD20+**, **CD45+**, CD15-, CD30-
Subtypes	Nodular Sclerosis (most common), Mixed Cellularity (EBV associated), Lymphocyte-Rich, Lymphocyte-Depleted	Distinct entity (variant growth patterns D/E carry higher transformation risk)
Clinical Note	Bimodal age distribution. Strong EBV association in mixed cellularity.	Indolent course, localized peripheral adenopathy, risk of transformation to DLBCL.

Comprehensive Diagnostic Workup

Tissue (Gold Standard)

- Excisional lymph node biopsy (or adequate core needle).

Alert: FNA is definitively inadequate due to scarcity of HRS cells.

Imaging & Staging

- **PET/CT Scan**: Skull to mid-thigh (Gold standard for baseline and response).
- Diagnostic CT with contrast for precise mass measurement and XRT planning.

Labs & Organ Baseline

- **CBC, ESR, LDH** (Key prognostic markers).
- **HIV**, Hep B/C serologies.
- **Echocardiogram/MUGA**: Required baseline prior to Anthracyclines (Doxorubicin).
- **PFTs / DLCO**: Required baseline prior to Bleomycin.
- **Fertility** preservation counseling.

Lugano Classification (Modified Ann-Arbor Staging)

Stage IV
Diffuse/disseminated involvement of ≥1 extralymphatic organs (e.g., liver, bone marrow, lung).

Stage III
Lymph node regions on both sides of the diaphragm (III). May include spleen (IIIS).

Stage II
≥2 node regions on the same side of the diaphragm (II), or with localized extralymphatic involvement (IIE).

Stage I
Single lymph node region (I) or single extralymphatic organ/site (IE).

Modifiers (B Symptoms):

A: Asymptomatic.

B: Unexplained weight loss (>10% in 6 months), Fevers (>38°C), or Drenching night sweats.

Risk Stratification Framework

Early-Stage Favorable
(Stage I-IIA)

- No adverse risk factors present.

Early-Stage Unfavorable
(Stage I-II)

- Presence of any adverse factor:
  - Bulky mediastinal disease (>1/3 intrathoracic diameter or >10 cm).
  - Age > 50 years.
  - ESR >50 (without B symptoms) or >30 (with B symptoms).
  - >3 nodal sites involved.

Advanced-Stage
(Stage III-IV) - IPS

- Evaluated via the International Prognostic Score (IPS) (1 point each):
  - Albumin < 4.0 g/dL
  - Hb < 10.5 g/dL
  - Male sex
  - Age > 45
  - Stage IV
  - WBC > 15k/mcL
  - ALC < 600/mcL (or <8%)

Baseline Management Principles (TSH / Standard Care Alignment)

Disease Stage	Primary Goal	Standard Regimen
Early-Stage Favorable	**Goal:** Maximize cure, minimize late toxicity.	**Standard:** ABVD x 2 cycles → 20 Gy Involved-Site Radiation Therapy (ISRT). ***PET-Adapted:*** *Interim PET (PET-2) used to drop Bleomycin if negative.*
Early-Stage Unfavorable		**Standard:** ABVD x 4 cycles → 30 Gy ISRT.
Historical Advanced-Stage (Stage III-IV)		**Standard:** ABVD x 6 cycles (PET-adapted to AVD). **High-Risk Alternative:** Escalated BEACOPP for IPS > 2 (balances higher efficacy with severe toxicity).

Note: Thai Society of Hematology (TSH) guidelines broadly align with these ESMO/NCCN risk-adapted paradigms, prioritizing ABVD as the foundational backbone.

NCCN 2025 Updates: The Shift in Advanced cHL Frontline Therapy

Regimen 1: BV-AVD

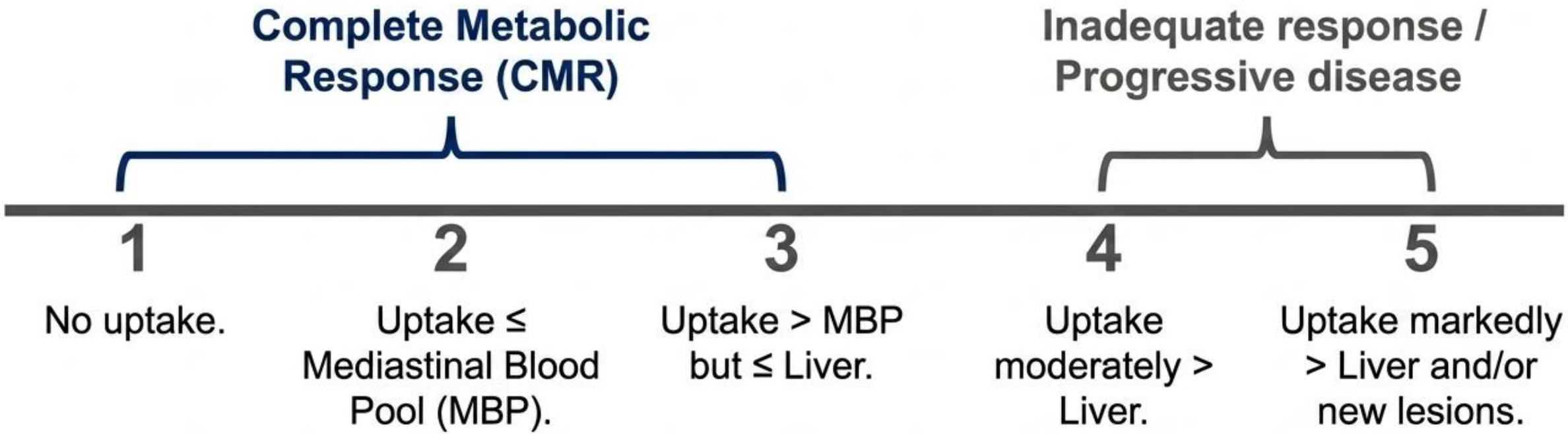
- **Drug:** Brentuximab Vedotin (Anti-CD30 antibody-drug conjugate) + AVD.
- **Trial:** ECHELON-1 (Proved superiority over ABVD).
- **Clinical Caveats:** Higher rates of
of peripheral neuropathy. Strictly contraindicated with Bleomycin (severe pulmonary toxicity).

Regimen 2: N-AVD – The New Preferred Standard

- **Drug:** Nivolumab (PD-1 Checkpoint Inhibitor) + AVD.
- **Trial:** SWOG S1826 (Proved superiority over BV-AVD).
- **NCCN 2025 Status:** Preferred for adolescents and adults. ener adults with previously untreated Stage III/IV cHL.

Ref: NCCN Clinical Practice Guidelines in Oncology: Hodgkin Lymphoma, V.2.2025.

Response Assessment: The Deauville Scale



Clinical Application:
Drives PET-adapted therapy (e.g., performing an interim PET-2 to safely drop Bleomycin if Deauville 1–3 is achieved).

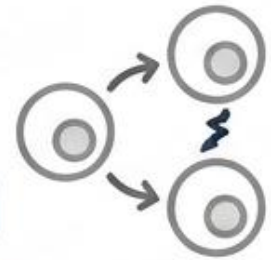
Ref: Cheson BD, et al. J Clin Oncol 2014;32:3059-68.

Survivorship & Management of Late Effects

Cardiovascular

High risk of premature CAD, valvular disease, and heart failure due to Doxorubicin and chest radiation (ISRT). Requires lifelong ECHO/lipid monitoring.

Secondary Malignancies

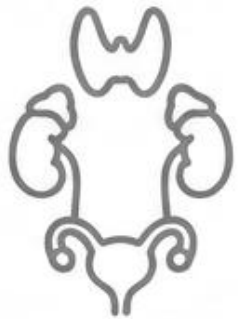


High risk of solid tumors. **Critical Alert: Women treated with chest radiation <30 years old require annual breast MRI starting 8-10 years post-therapy.**

Pulmonary

Bleomycin-induced pulmonary toxicity (fibrosis). Avoid high FiO2 if possible.

Endocrine & Fertility



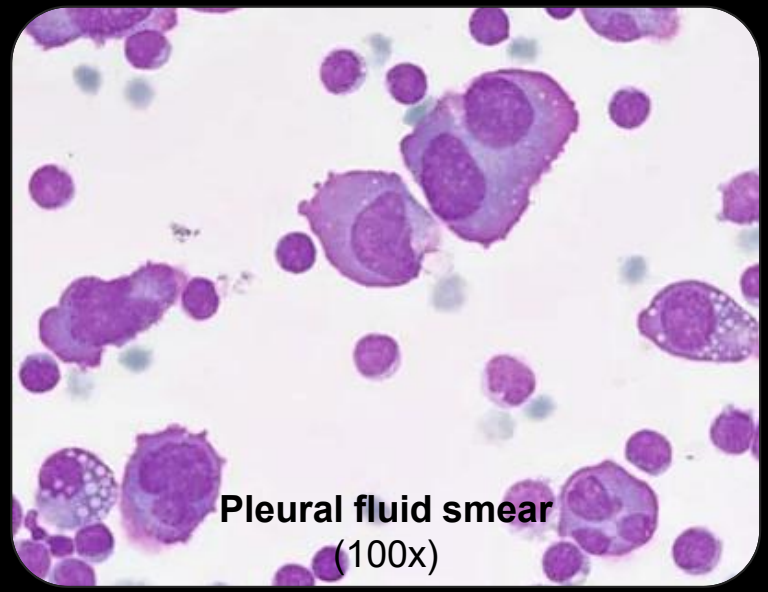
Hypothyroidism (from neck radiation). Premature ovarian failure or azoospermia (from alkylating agents).

Case 10

Q10

A 62-year-old male university lecturer presents to the emergency department with a 2-week history of acute, progressively worsening dyspnea. He also reports a recent onset of constipation, and a dull pain in his mid-back. On physical examination, he appears pale. Chest examination reveals dullness to percussion and decreased breath sounds over the right lower lung field.

Laboratory evaluation is notable for a serum calcium level of 13.2 mg/dL(normal: 8.4 - 10.2 mg/dL), a serum creatinine of 1.8 mg/dL, and a normocytic anemia. A chest radiograph demonstrates a large right-sided pleural effusion with an incidentally noted lytic lesion in the 8th rib. Diagnostic thoracentesis yields an exudative fluid; cytologic evaluation of the pleural fluid reveals a proliferation of cells as the figure.



Pleural fluid smear
(100x)

What is the most likely diagnosis?

A. Multiple myeloma
B. Primary effusion lymphoma
C. Pulmonary alveolar proteinosis
D. Squamous cell lung carcinoma
E. Waldenström macroglobulinemia

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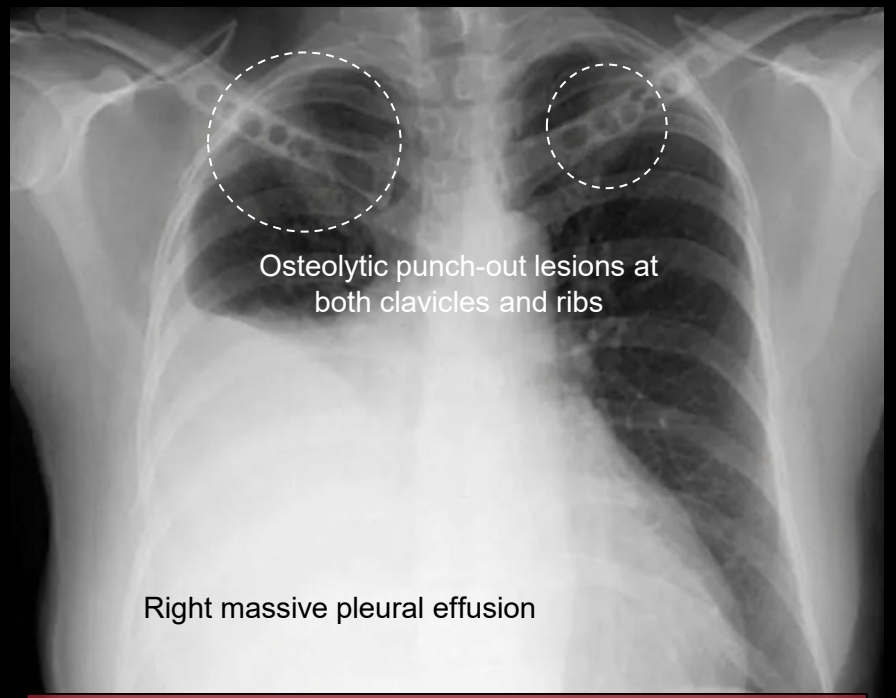
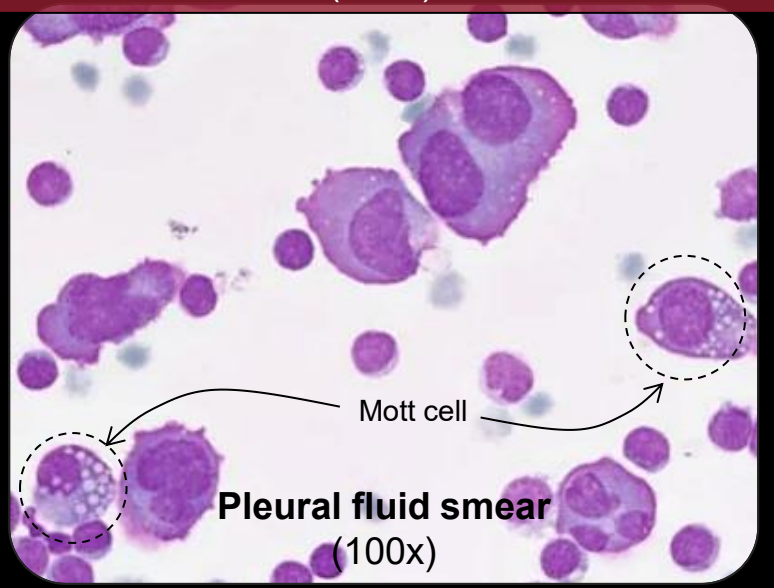
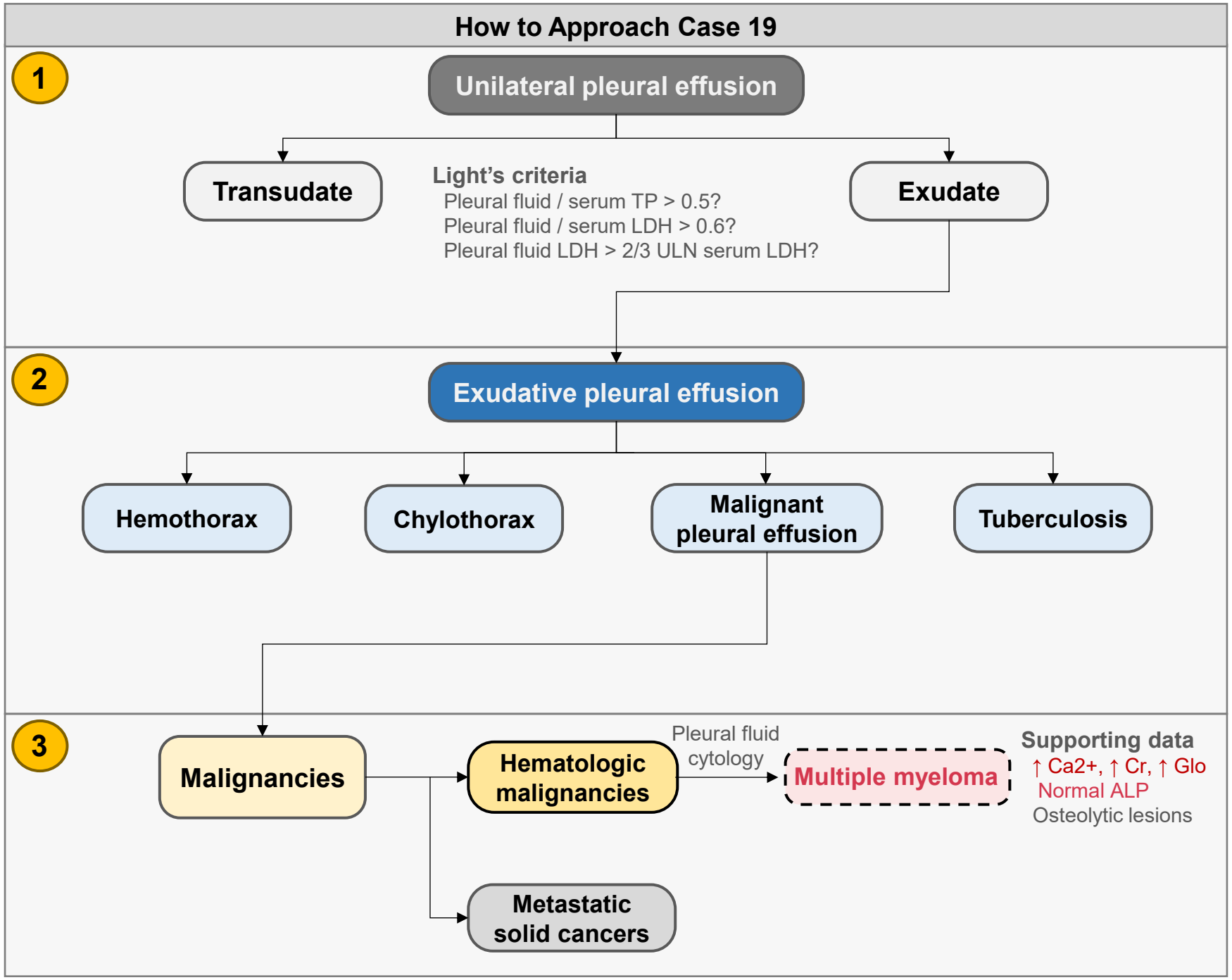


Primary malignant myelomatous pleural effusion (MPE)

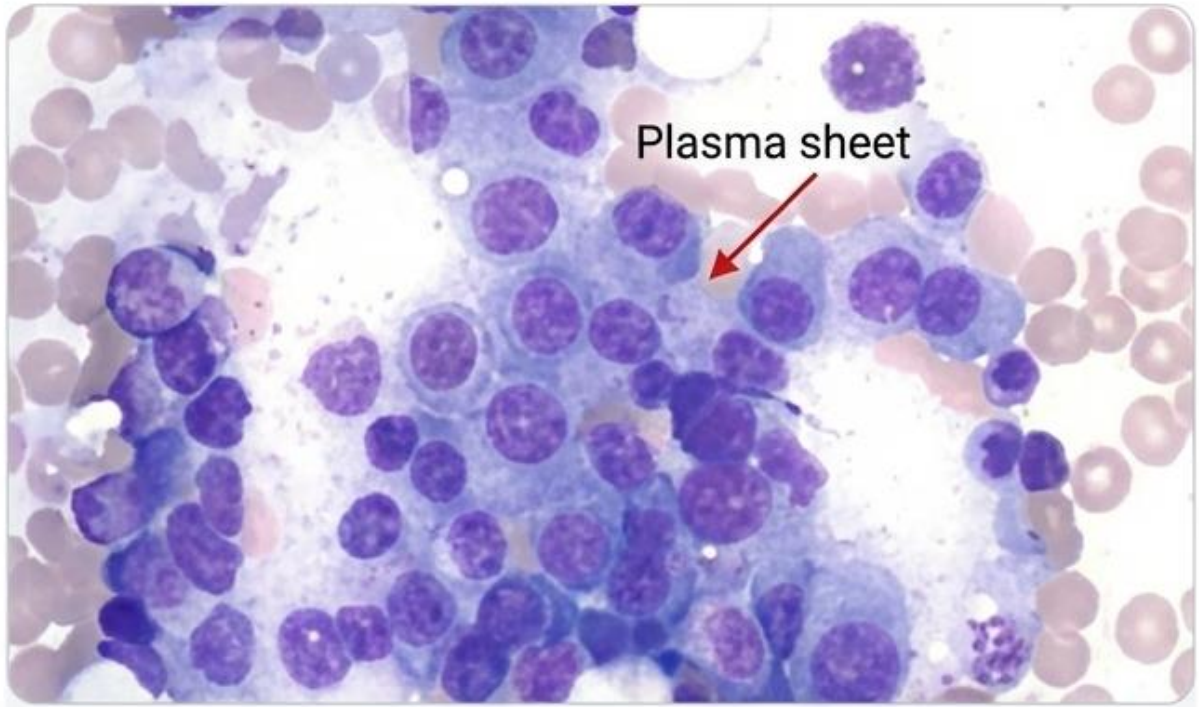


Myeloma plasma cells:
Round to irregular, rich cytoplasm with a purplish-red periphery and a bluish-purple perinuclear area, often containing numerous vacuoles.

Multiple Myeloma

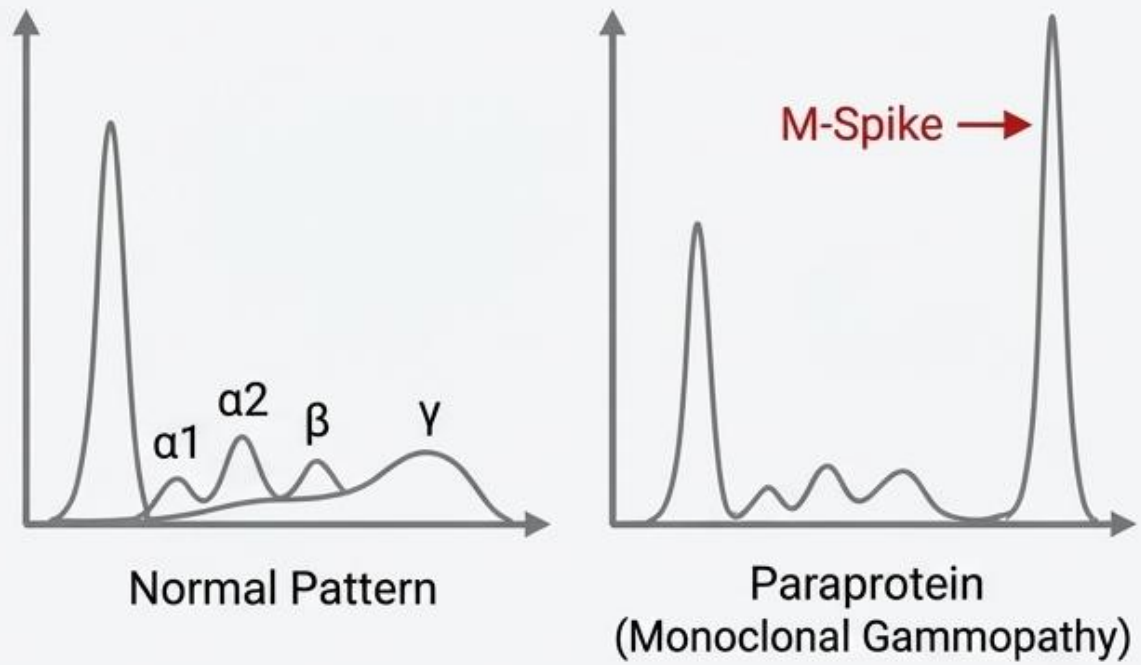

How to Approach Case 19
1
Unilateral pleural effusion
Transudate
Light's criteria
Pleural fluid / serum TP > 0.5?
Pleural fluid / serum LDH > 0.6?
Pleural fluid LDH > 2/3 ULN serum LDH?
Exudate
2
Exudative pleural effusion
Hemothorax
Chylothorax
Malignant pleural effusion
Tuberculosis
3
Malignancies
Hematologic malignancies
Pleural fluid cytology
Multiple myeloma
Supporting data
↑ Ca2+, ↑ Cr, ↑ Glo
Normal ALP
Osteolytic lesions
Metastatic solid cancers

Bone Marrow Pathology



Infiltrated plasma cells
(CD138+, CD45-, CD38+, CD19-).

SPEP Patterns



Note: 82% of MM cases present with
a localized band.

Alert Box

Causes of **false-negative SPEP:** Non-secretory MM, Light chain deposition disease, Amyloidosis.

The Disease Spectrum

Disease	M protein	BM PCs	CRABs
MGUS	<3 g/dL	<10%	No
Smoldering Myeloma	>3 g/dL or κ/λ (Urinary FLCM protein >500 mg/24 hr)	10-59%	No
MG of Renal Significance	<3 g/dL	<10%	Renal (requires kidney biopsy for Dx)
Active MM	**Present (exception non-secretory)**	**>10%**	**Yes**

Confirming Active Multiple Myeloma

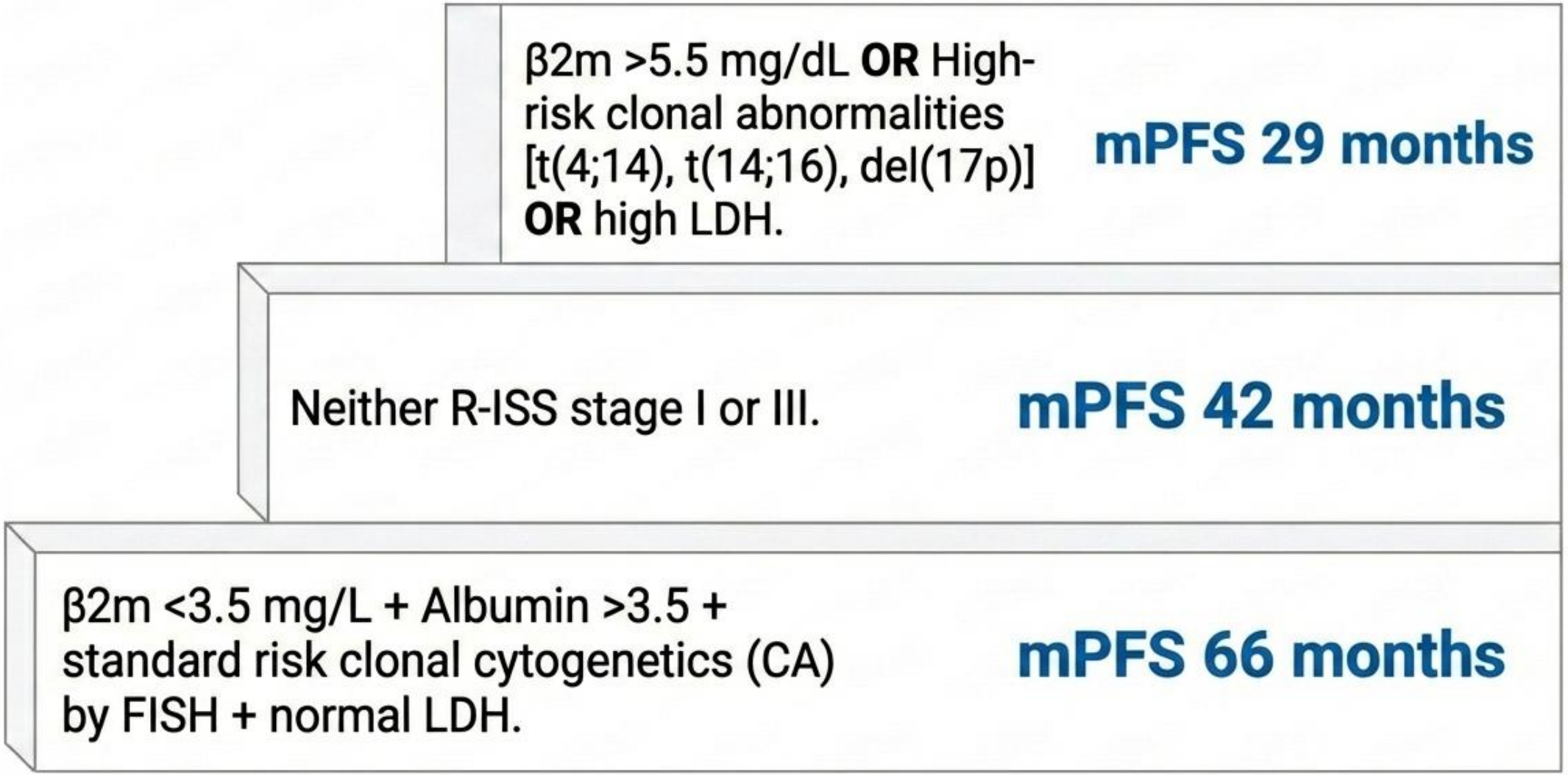
1. Clonal marrow plasma cells >10% **OR** extramedullary plasmacytoma.

+

End-organ damage / CRAB		Biomarkers of malignancy / SLiM
• Ca >11 mg/dL • Cr >2 mg/dL (or CrCl <40) • Hb <10 g/dL • Osteolytic lesion(s) from imaging	**OR**	• Clonal marrow plasma cells ≥60% • Involved:uninvolved SFC ≥100 • >1 focal lesions on MRI

*Clonality must show light chain restriction.

Prognostication: Revised ISS Staging



Risk Stratification: Redefining ‘High Risk’ in 2026

R2-ISS Additive Points System

Variables: ISS Stage, LDH, high-risk chromosomal abnormalities, 1q gain.

Stages: Stage I (0 pts) to Stage IV (3.0-5.0 pts).

Purpose: Refines the heterogeneous “Stage II” group from older systems.

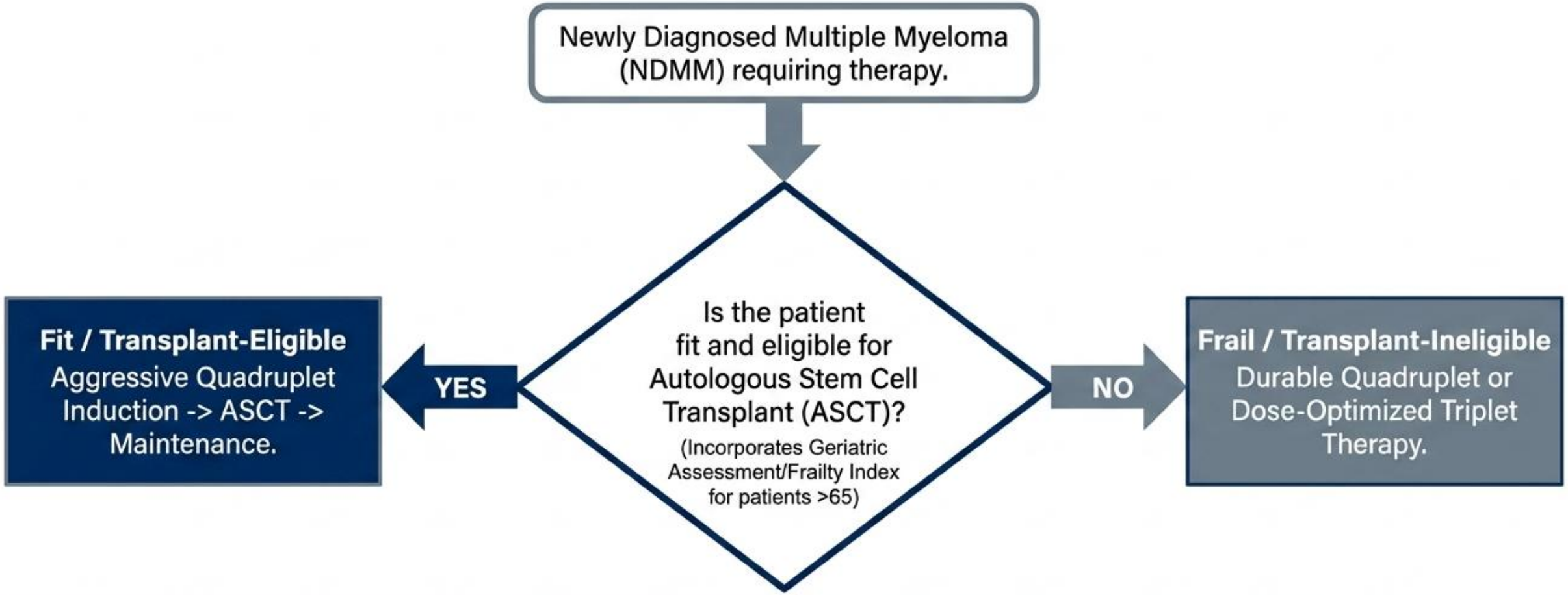
2025 IMS-IMWG Consensus Genomic Staging (CGS)

Context: Validated in >6,500 patients; defines ~23% of newly diagnosed as High Risk.

- del(17p) and/or TP53 mutation
- IgH translocations: t(4;14), t(14;16), t(14;20) concurrent with 1q gain or del(1p)
- Biallelic del(1p32)

Accurate genomic profiling via Next-Generation Sequencing (NGS) or FISH is now a mandatory prerequisite for treatment planning.

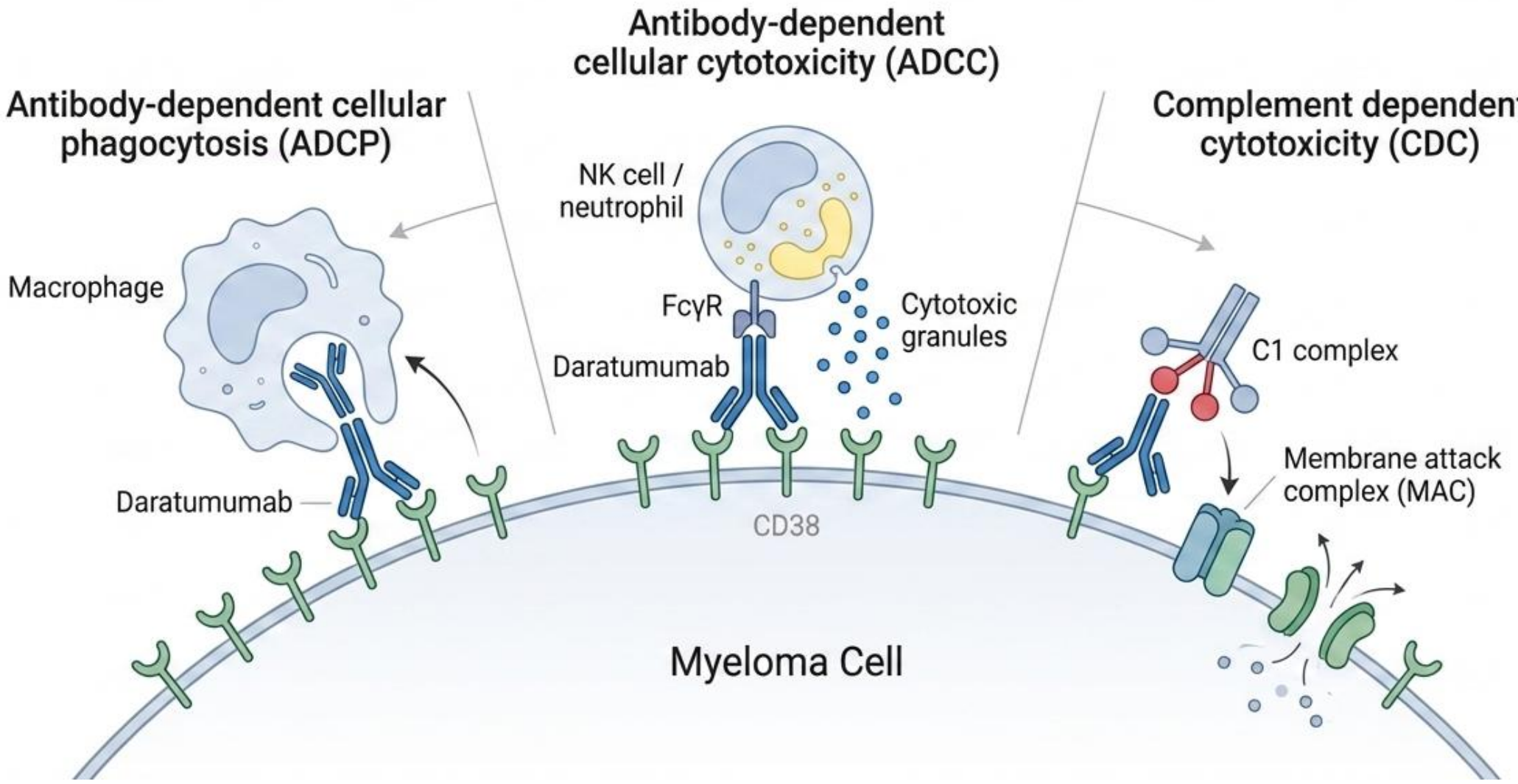
2026 Frontline Standard of Care: The Quadruplet Era



Core Principle:

ASCO/EHA-EMN guidelines universally prioritize the addition of an anti-CD38 monoclonal antibody (Daratumumab or Isatuximab) to standard backbones for all suitable patients.

Pharmacology Spotlight: Anti-CD38 (Daratumumab)



Transplant-Eligible (Fit) Pathway

Step 1: Induction (At least 4 cycles)

Quadruplet Standard: Anti-CD38 mAb + Proteasome Inhibitor + IMiD + Steroid.

Specific Regimens: Dara-VRd or Isa-VRd (Daratumumab/Isatuximab, Bortezomib, Lenalidomide, Dexamethasone).

Substitute Carfilzomib for high-risk (Dara-KRd/Isa-KRd).

Step 2: Consolidation

High-Dose Melphalan + Autologous Stem Cell Transplant (ASCT).

Step 3: Maintenance

Standard: Lenalidomide monotherapy.

2026 Update: Conditional recommendation for Lenalidomide + Daratumumab or Carfilzomib for deep, sustained response (based on PERSEUS data).

Transplant-Ineligible (Frail) Pathway

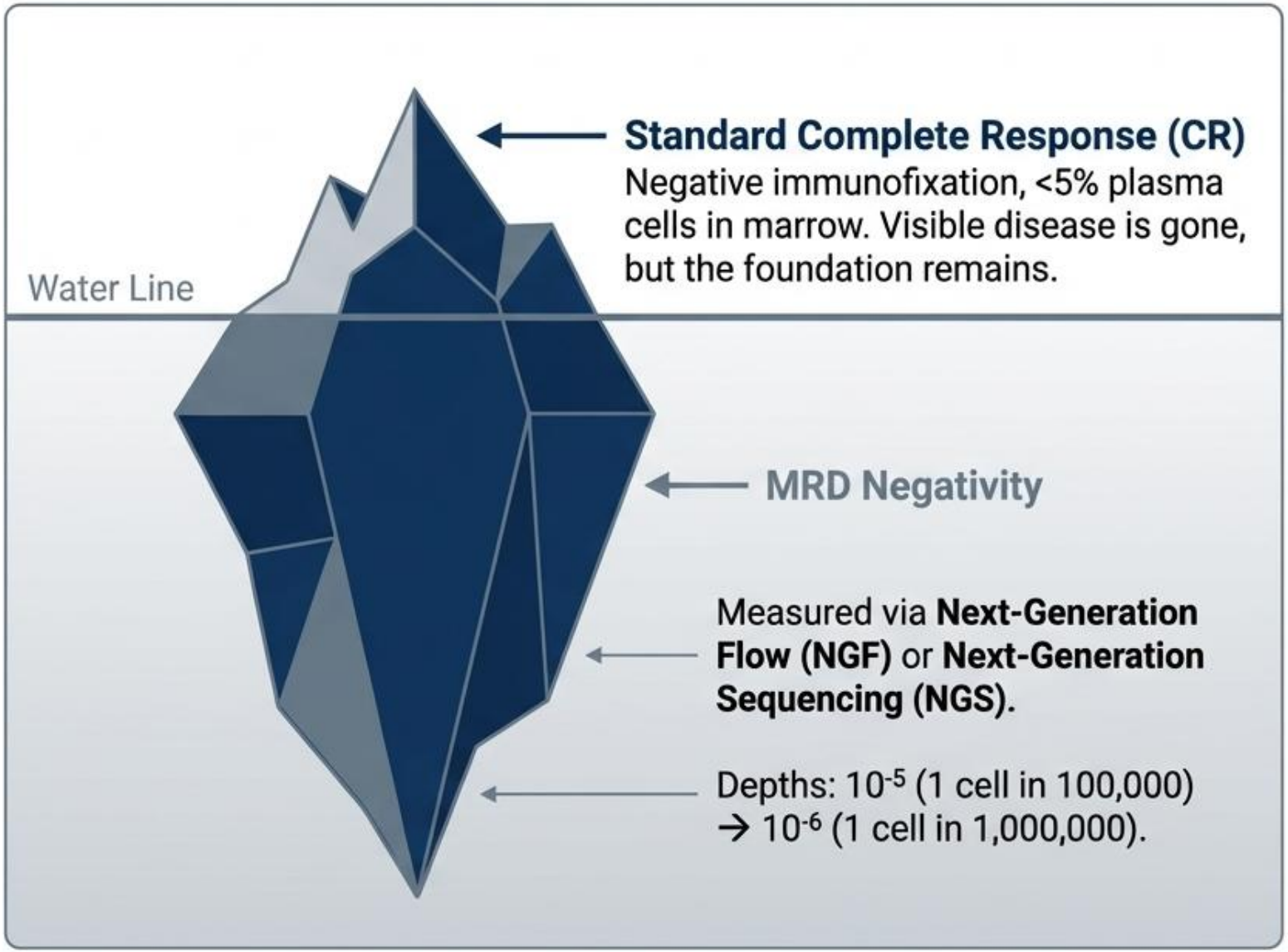
Tier 1: Older but Fit (Transplant Ineligible)

Regimen: Quadruplet Therapy (Dara-VRd or Isa-VRd) or Triplet (Dara-Rd).
Goal: Maximize Progression-Free Survival (PFS).
Trials (IMROZ, CEPHEUS) show ~73% alive at 5 years with quads vs 67% with triplets.

Tier 2: Very Elderly (>75/80) or Frail

Regimen: Dose-optimized Triplets.
Specifics: Dara-Rd (MAIA trial) or VRd-lite.
Critical Adjustments: Strict avoidance of high-dose dexamethasone (reduce to 20 mg or 8-12 mg weekly); weekly bortezomib to minimize neuropathy and infection risk.

Minimal Residual Disease (MRD): The Ultimate Response Endpoint



Clinical Implications

- The FDA now accepts undetectable MRD as an early endpoint for accelerated approvals.
- **MRD-Guided Discontinuation (Investigational)**
  Trials like MASTER and MRD2STOP show that patients achieving sustained MRD negativity (10^{-6}) for 12+ months may safely discontinue maintenance therapy (85% remain progression-free at 1 year).

Geriatric & Frailty Dosing Modifications

	Younger Than 65 Yrs	65-75 Yrs	Older Than 75 Yrs
Dexamethasone	40mg (D1-4, 15-18 or D1,8,15,22)	40mg (D1,8,15,22)	20mg (D1,8,15,22)
Melphalan	0.25 mg/kg (D1-4 Q6W)	0.25 or 0.18 mg/kg	0.18 or 0.13 mg/kg
Cyclophosphamide	300 mg/day (D1,8,15,22)	300 mg/day (D1,8,15) or 50mg (D1-21)	50 mg/day (D1-21)
Thalidomide	200 mg/day	100 or 200 mg/day	50-100 mg/day
Lenalidomide	25 mg/day	15-25 mg/day	10-25 mg/day
Bortezomib	1.3 mg/m2 (D1,4,8,11)	1.3 mg/m2 (various schedules)	1.0-1.3 mg/m2

Supportive Care Blueprint: Managing Myeloma Bone Disease

All newly diagnosed active MM patients require bone-targeted antiresorptive therapy (regardless of visible lytic lesions).

Renal Function Assessment

CrCl >= 30 mL/min

Bisphosphonates

Drug: Zoledronic acid or Pamidronate.

Duration: Up to 2 years, then extend intervals if stable.

Severe Renal Impairment / CrCl < 30

RANK-L Inhibitor

Drug: Denosumab (120 mg monthly). Non-nephrotoxic.

Warning: High risk of severe hypocalcemia. Requires strict calcium/Vitamin D monitoring. Discontinuation causes rapid rebound bone loss.

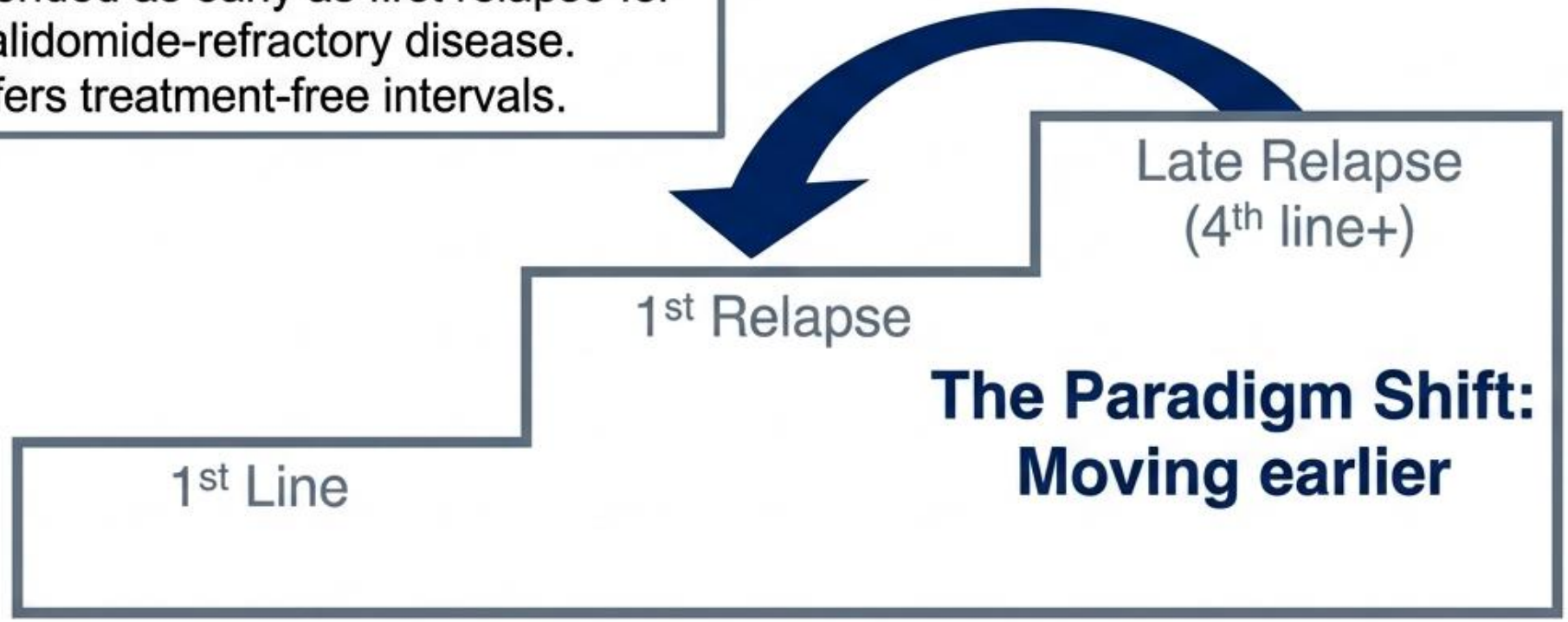
Relapsed & Refractory: The Earlier Ascent of T-Cell Redirection

CAR T-Cell Therapy

Ciltacabtagene autoleucel (Cilta-cel) or Idecabtagene vicleucel (Ide-cel). Now recommended as early as first relapse for lenalidomide-refractory disease. Offers treatment-free intervals.

Bispecific Antibodies (BsAbs)

Teclistamab (BCMA-targeted). High efficacy even in heavily pre-treated patients.



Managing Complications: Renal

Renal complications in multiple myeloma

Monoclonal Ig-Mediated

Direct tubular toxicity	→	Fanconi syndrome: ↓ K+, ↓ PO4, ↓ uric, met. acidosis
Deposition of Ig component	→	AL amyloidosis (Congo red +), Monoclonal Ig deposition disease
Cast nephropathy	→	Myeloma kidney: excess light chains form intratubular casts causing obstruction

Ig-Independent

- Hypercalcemia
- Medication toxicity (NSAIDs)
- Chronic urate nephropathy

(Note: Tumor lysis syndrome is uncommon).

Holistic Supportive Care

Thromboembolic Events	Infection	Bone Health
IMiD risks. Low risk (<2 factors) = low-dose aspirin (81mg). High risk (≥2 factors or high-dose dex) = LMWH or therapeutic warfarin (INR 2-3).	Current vaccinations (COVID-19, annual flu). Herpes prophylaxis with PIs/mAbs. Consider PJP prophylaxis with high-dose dexamethasone.	All patients should receive bisphosphonates (pamidronate/zoledronic acid) or denosumab. Monitor for renal impairment and osteonecrosis of the jaw (ONJ).

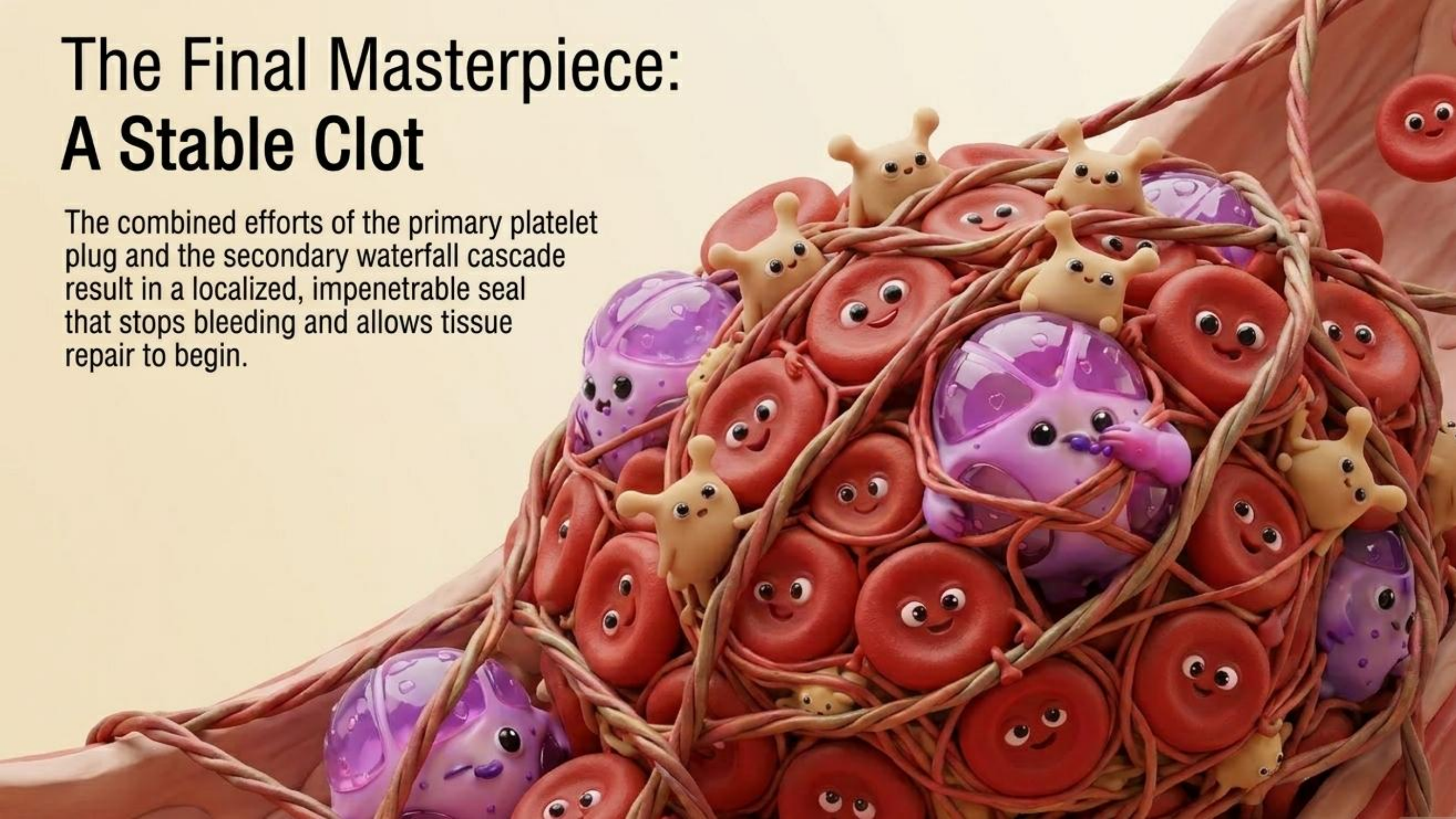
What Have We Learned Today

Approach a Patient with…

- ✓ **Q1** Chronic underproductive anemia
  Pernicious anemia
- ✓ **Q2** Chronic hemolytic anemia
  Paroxysmal nocturnal hemoglobinuria
- ✓ **Q3** Subacute fever
  Thrombotic thrombocytopenic purpura
- ✓ **Q4** Bleeding and bruising
  Acquired factor VIII deficiency
- ✓ **Q5** Antenatal consultation
  Obstetric antiphospholipid syndrome
- ✓ **Q6** Acute pulmonary embolism
  Cancer associated thrombosis
- ✓ **Q7** Acute ischemic stroke
  Polycythemia vera
- ✓ **Q8** Oncologic complications:
  (1) Tumor lysis syndrome,
  (2) Disseminated intravascular coagulation,
  (3) Leukostasis syndrome
  (4) Hyper-Warburgism
  Acute myeloid leukemia
- ✓ **Q9** Mediastinal mass
  Hodgkin lymphoma
- ✓ **Q10** Pleural effusion with hypercalcemia
  Multiple myeloma

The Final Masterpiece: **A Stable Clot**

The combined efforts of the primary platelet plug and the secondary waterfall cascade result in a localized, impenetrable seal that stops bleeding and allows tissue repair to begin.



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