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น้องแดงและผองเพื่อน
Nong Dang
and Friends

Common Problems in Hematology 2025

Educational Course Supported by Berlin

For Residency Training Program in Medicine

Sithakom Phusanti, M.D.
Hematology Consultant

Chakri Naruebodindra Medical Institute
Faculty of Medicine Ramathibodi Hospital,
Mahidol University

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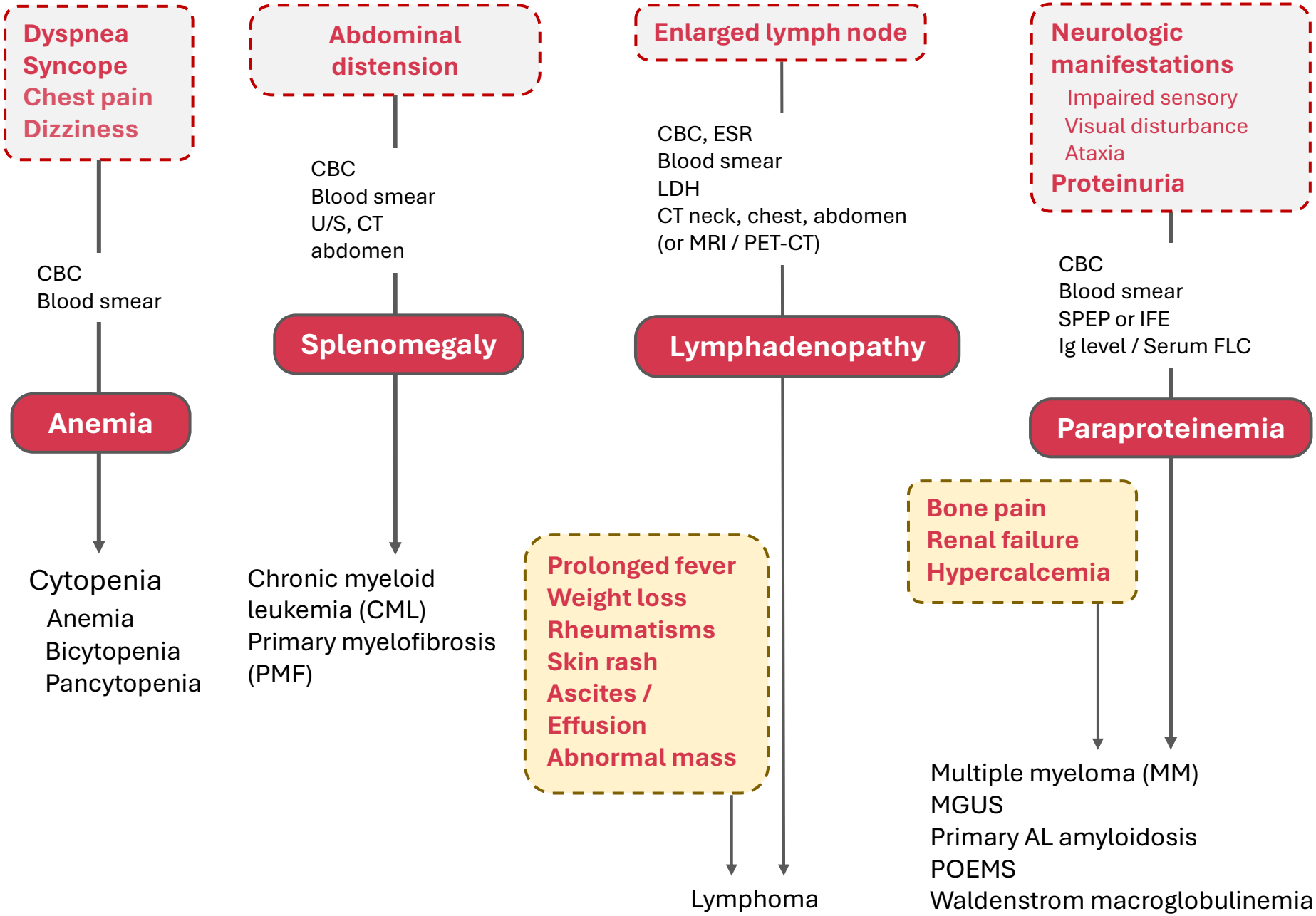
Outline

Case-based MCQs:

- ✓ **Case 1:** A 52 y.o. business owner presents with dyspnea on exertion for 3 months.
- ✓ **Case 2:** A 40 y.o. orchard farmer presents with progressive fatigue for 2 months.
- ✓ **Case 3:** A 20 y.o. hairdresser presents with cyanosis.
- ✓ **Case 4:** A 30 y.o. government officer presents with chronic diarrhea for 6 weeks.
- ✓ **Case 5:** A 72 y.o. retired teacher presents with multiple bruises for 1 week.
- ✓ **Case 6:** An 18 y.o. student presents with recurrent hypermenorrhea.
- ✓ **Case 7:** A 30 y.o. banker presents with sudden hemiparesis.
- ✓ **Case 8:** A 55 y.o. street vendor presents with acute dyspnea for 3 days.
- ✓ **Case 9:** A 50 y.o. lawyer presents with significant weight loss for 3 months.
- ✓ **Case 10:** A 35 y.o. TikToker presents with chronic cough for 2 months.

Symptomatology for Hematologic Problems in MCQs (1)



Symptomatology for Hematologic Problems in MCQs (2)

Petechiae
Purpura
Ecchymosis
Melena / hematochezia
Vaginal bleeding
Hemarthrosis
Hematomas

CBC
Blood smear
Coagulogram

Bleeding tendency

Cytopenia
- Thrombocytopenia

Bicytopenia
- Pancytopenia

Platelet dysfunction
Coagulopathy

Stroke
- Weakness / impaired sensory
- Visual disturbance
- Ataxia
- Memory defect

Coronary disease
- Chest pain
- Arrhythmia
- Syncope

Peripheral arterial disease
- Unilateral leg pain

Venous thrombosis
- Unilateral leg or arm swelling: DVT
- Dyspnea: PE
- Abdominal pain:
  - Splanchnic vein thrombosis
- Ascites / jaundice: Budd-Chiari
- Headache: CSVT

CBC
Imaging for thrombosis

Thrombosis

Myeloproliferative neoplasms (MPNs – ET, PV, PMF)
Leukostasis syndrome in leukemia
Cancer-associated thrombosis (CAT)
Antiphospholipid syndrome (APS)
Hereditary thrombophilia

Case 1

Q1

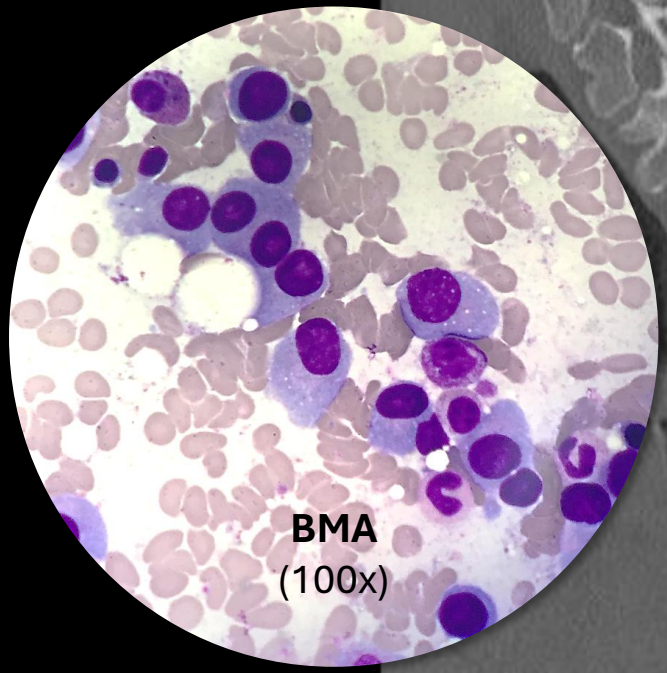
A 52-year-old male business owner presents to the emergency department with sudden paraplegia and back pain. Physical examination shows numbness and weakness in both lower extremities.

CBC reveals Hb 9.5 g/dL, Hct 29%, MCV 85 fL, WBC count 4,000/μL (N 45, L 45, M 5), platelet count 120,000/μL. Creatinine is 0.8 mg/dL. ALP is 126 IU/L.

MRI of the spine demonstrates L3 fracture and diffuse osteopenia with multiple osteolytic lesions.

What is the most likely diagnosis?

A. Extramedullary plasmacytoma
B. Multiple myeloma
C. Primary AL amyloidosis
D. Osteopetrosis
E. Splenic marginal zone lymphoma



CT spine (Bone window)

Angled kyphosis is centered at the T8 level, with a destructive soft tissue mass engulfing the T7, T8, and T9 vertebral bodies (near complete obliteration of the T8 vertebra).

There is no definite thoracic spinal canal tumor extension and minimal paravertebral soft tissue involvement. No focal abnormality was identified.

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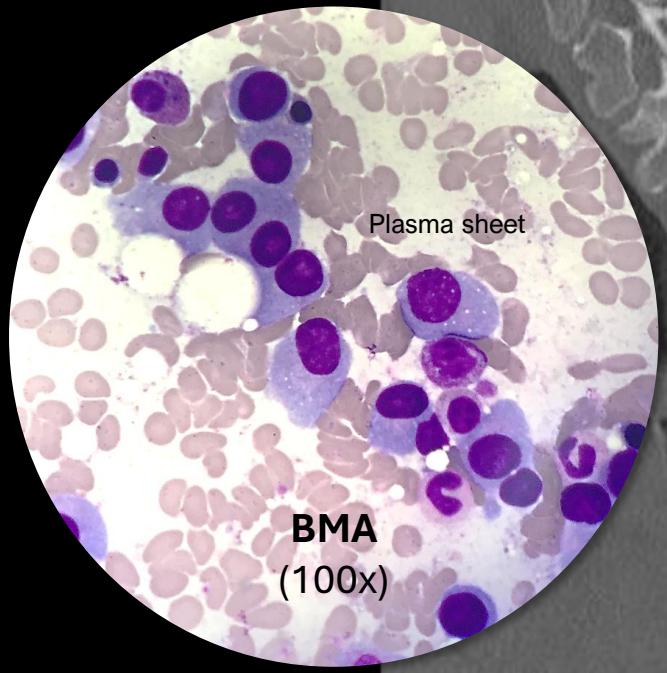

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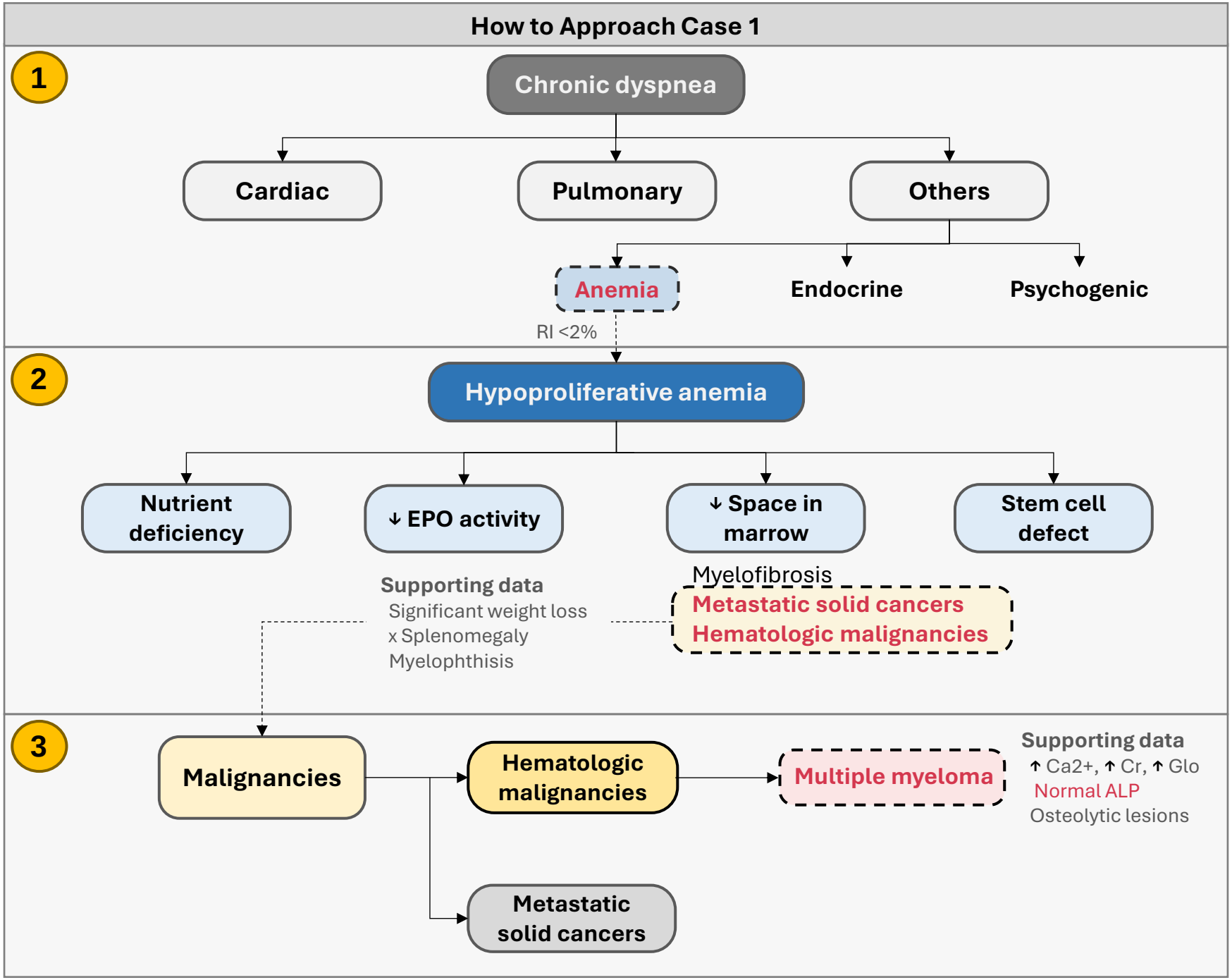
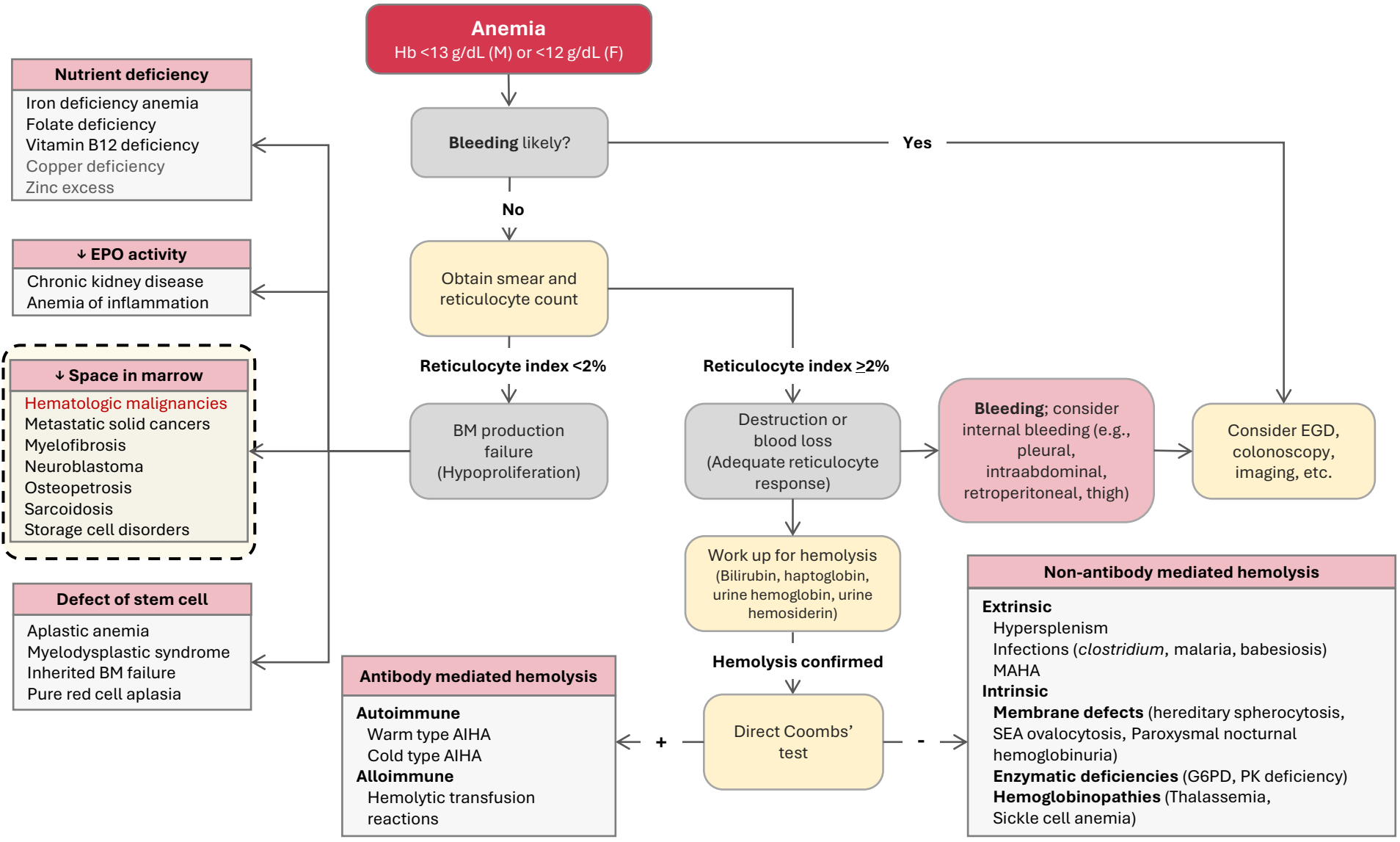

How to Approach Case 1
1
Chronic dyspnea
Cardiac
Pulmonary
Others
Anemia
Endocrine
Psychogenic
RI <2%
2
Hypoproliferative anemia
Nutrient deficiency
↓ EPO activity
↓ Space in marrow
Stem cell defect
Supporting data
Significant weight loss
x Splenomegaly
Myelophthisis
Myelofibrosis
Metastatic solid cancers
Hematologic malignancies
3
Malignancies
Hematologic malignancies
Multiple myeloma
Supporting data
↑ Ca2+, ↑ Cr, ↑ Glo
Normal ALP
Osteolytic lesions
Metastatic solid cancers

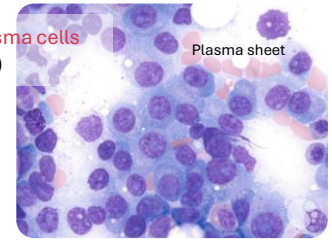
Approach Anemia



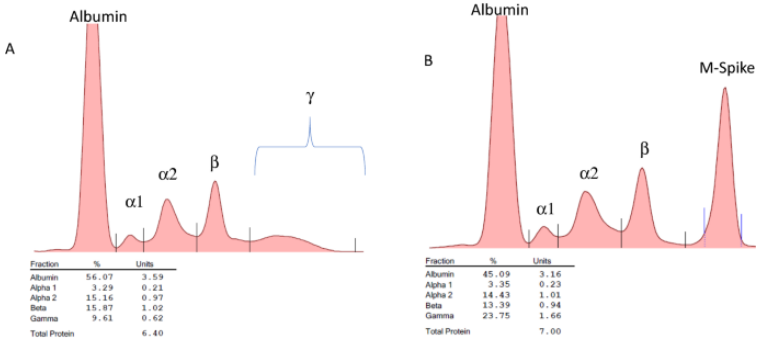
Multiple Myeloma

Diagnosis

Marrow findings: Infiltrated plasma cells (CD138+, CD45-, CD38+, CD19-)



Causes of false -ve SPEP:
- Non-secretory MM
- Light chain deposition disease
- Amyloidosis



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

Suspected MM

↓

Screening with SPEP +/- FLC

↓

Criteria

1. **Clonal marrow plasma cells ≥10%** or extramedullary plasmacytoma
2. Any 1 or more of myeloma defining events
   - **2.1 End-organ damage**
     - **Ca >11 mg/dL**
     - **Cr >2 mg/dL** (or CrCl <40)
     - **Hb <10 g/dL**
     - **Osteolytic lesion(s)** from imaging
   - 2.2 Biomarkers of malignancy
     - *Clonal marrow plasma cells ≥60%
     - Involved:uninvolved SFC ≥100
     - >1 focal lesions on MRI

*Clonality shows light chain restriction

↓

Serum IFE, M protein, Ig and FLC,
Bone marrow study (CD138, κ, λ)

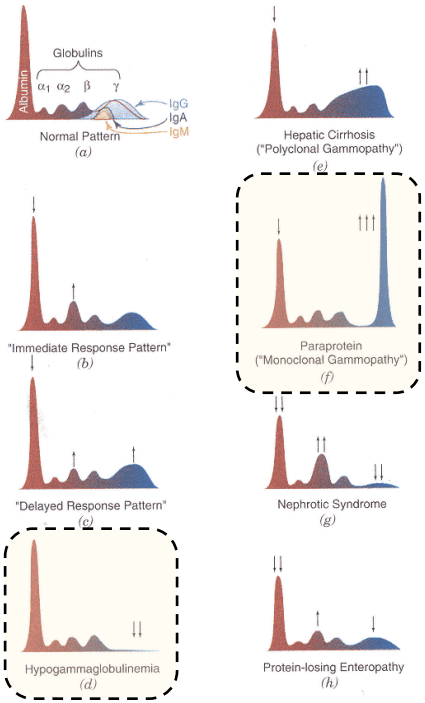
↓

Confirmed MM

Laboratory interpretation:

Serum protein electrophoresis (SPEP)

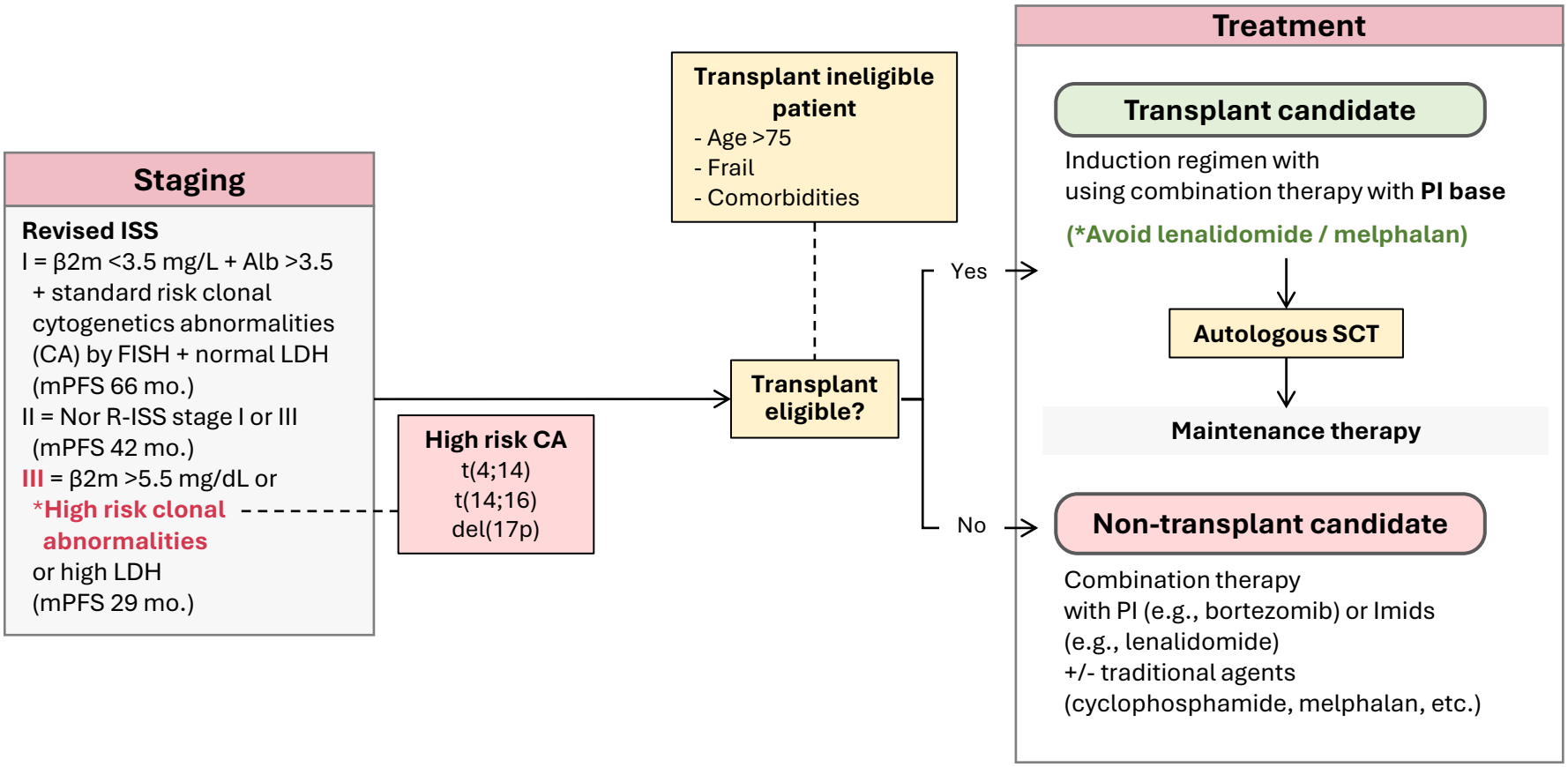
- 82% of MM: a spike or localized band (f)
- MM with hypogammaglobulinemia: (d)



Pathologic serum protein electrophoresis patterns

NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma. v.1.2023.

Multiple Myeloma



NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma. v.1.2023.

Supportive Care for Patients with Multiple Myeloma

Thromboembolic Events

- May occur when receiving IMiDs:
  - Low risk (<2 risk factors*): low-dose aspirin (81 mg)
  - High risk (≥2 risk factors*) or IMiD + high-dose dex: LMWH or therapeutic warfarin (target INR 2-3)
- Educate patients on preventive strategies and early detection
- Can consider DOACs, but not well studied in this population

Infection

- Stay current on appropriate vaccinations, including COVID-19 and annual flu vaccine
- Herpes prophylaxis when receiving PIs or mAbs and consider PJP prophylaxis if using high-dose dexamethasone
- Antibacterial and antifungal prophylaxis while neutropenic after CAR T-cell therapy
- Consider IVIG for recurrent, life-threatening infections

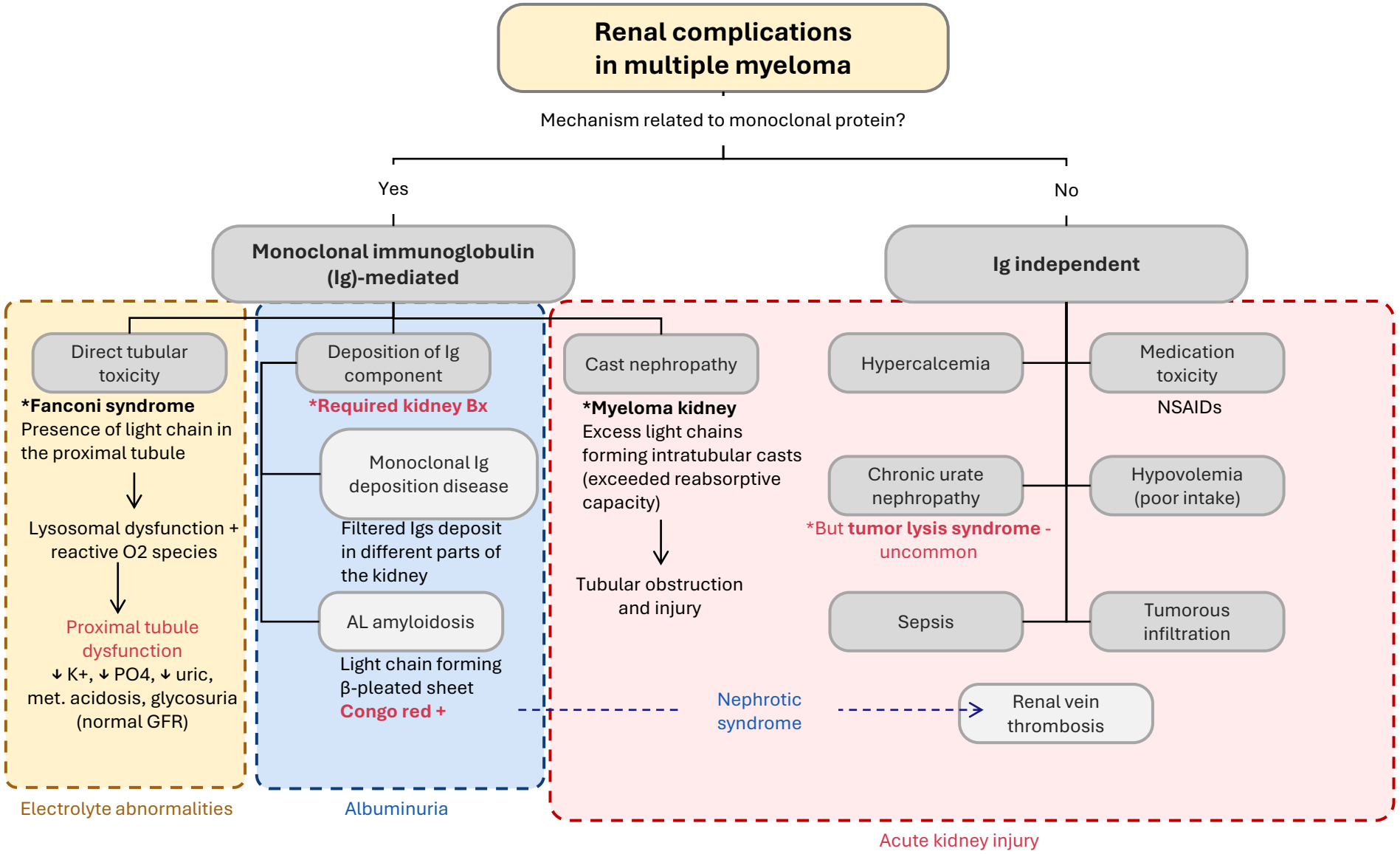
Bone Health

- All patients should receive bisphosphonates or denosumab
- Bisphosphonates: pamidronate and zoledronic acid (greater risk for osteonecrosis of jaw (ONJ) with zoledronic acid; monitor for renal impairment on bisphosphonates)
- SQ denosumab preferred when renal disease is present
- Baseline dental exam and ONJ monitoring while using bone-modifying therapy

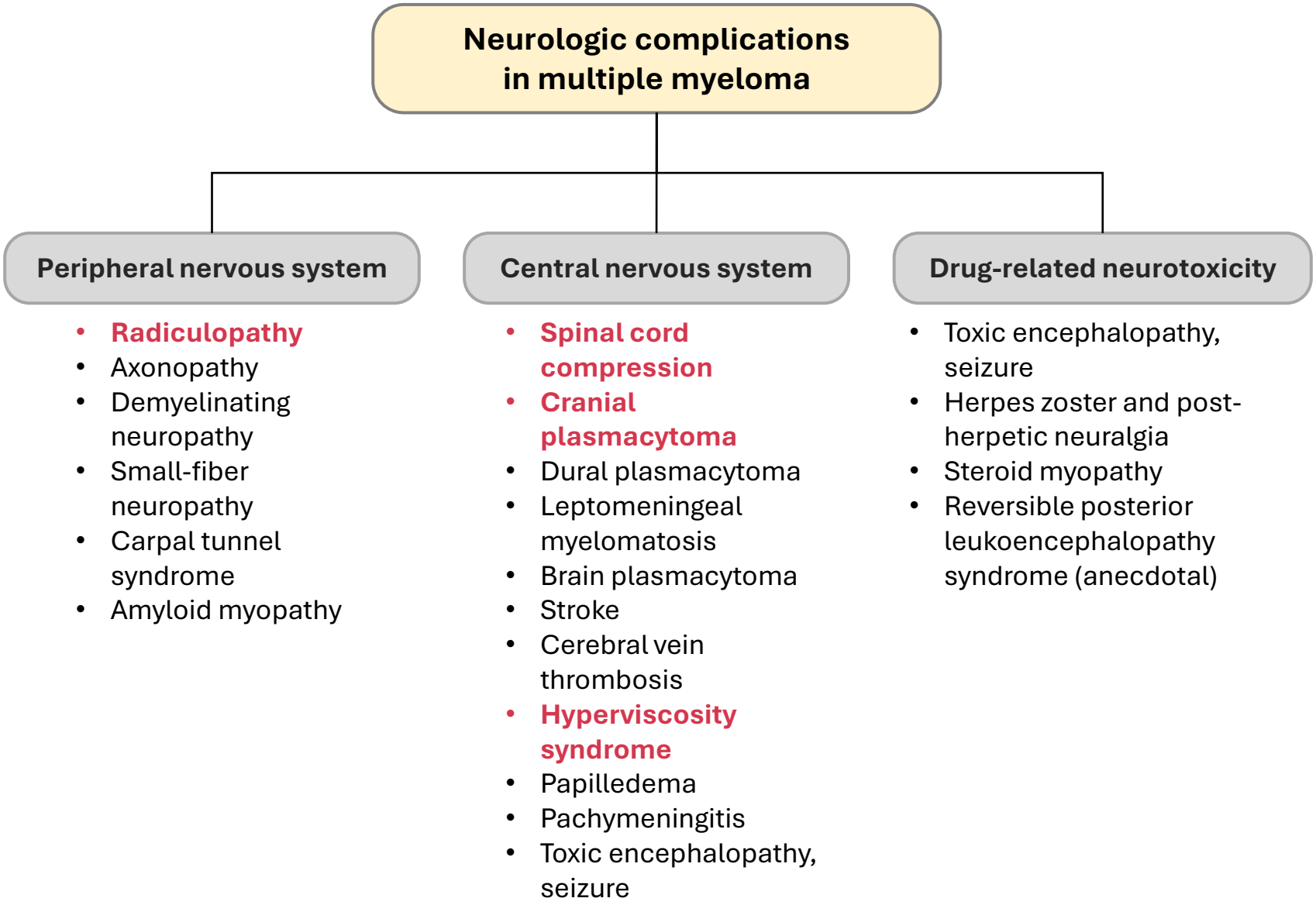
***Risk factors** include older age, history of thrombotic event, BMI ≥30 kgm^{-2}, prior central venous catheter or pacemaker, immobilization, CV/renal disease, diabetes, trauma, blood clotting disorders, hyperviscosity, acute infection.

Gleason. *J Adv Pract Oncol.* 2016;:53.
Kurtin. *J Adv Pract Oncol.* 2013;4:307.
Delforge. *Blood.* 2017;129:2359.
Noonan. *Clin J Oncol Nurs.* 2017;21:37.

Multiple Myeloma: Complications (1)



Multiple Myeloma: Complications (2)



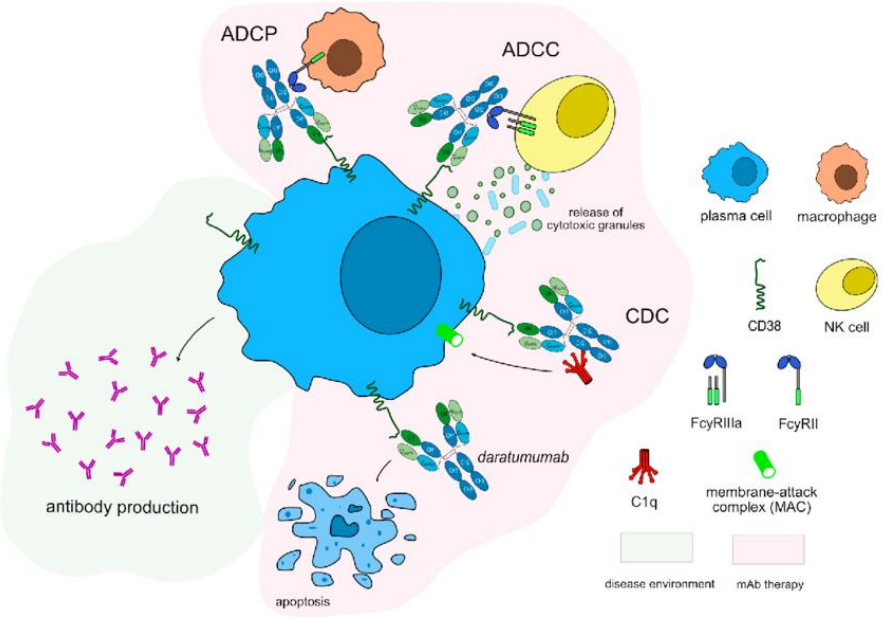
Suggested Empiric Age-Adjusted Dose Reductions in Patients with Multiple Myeloma

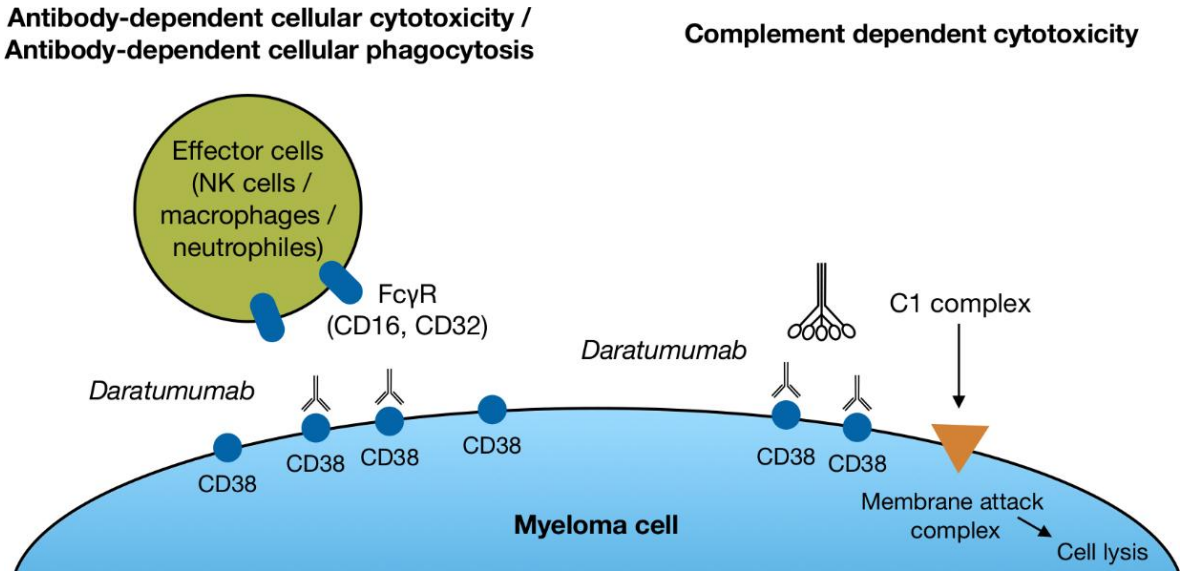
Agent	Younger Than 65 Yrs	65-75 Yrs	Older Than 75 Yrs
Dexamethasone	40 mg/day Days 1-4, 15-18 Q4W ***or*** Days 1, 8, 15, 22 Q4W	40 mg/day Days 1, 8,1 5, 22 Q4W	20 mg/day Days 1, 8, 15, 22 Q4W
Melphalan	0.25 mg/kg Days 1-4 Q6W	0.25 mg/kg Days 1-4 Q6W ***or*** 0.18 mg/kg Days 1-4 Q4W	0.18 mg/kg Days 1-4 Q6W ***or*** 0.13 mg/kg Days 1-4 Q4W
Cyclophosphamide	300 mg/day Days 1, 8, 15, 22 Q4W	300 mg/day Days 1, 8, 15 Q4W ***or*** 50 mg/day Days 1-21 Q4W	50 mg/day Days 1-21 Q4W ***or*** 50 mg/day QOD Days 1-21 Q4W
Thalidomide	200 mg/day	100 mg/day ***or*** 200 mg/day	50-100 mg/day
Lenalidomide	25 mg/day Days 1-21 Q4W	15-25 mg/day Days 1-21 Q4W	10-25 mg/day Days 1-21 Q4W
Bortezomib	1.3 mg/m^2 bolus Days 1, 4, 8, 11 Q3W	1.3 mg/m^2 bolus Days 1, 4, 8, 11 Q3W ***or*** Days 1, 8, 15, 22 Q5W	1.0-1.3 mg/m^2 bolus Days 1, 8, 15, 22 Q5W

Palumbo A. *N Engl J Med*. 2011.

Anti-CD38 Monoclonal Antibody

- New era of MM therapy
- **Mechanism of Action of Daratumumab**
  Three different effector mechanisms seem to be essential for the direct killing of malignant PCs by Daratumumab:
  1. Antibody-dependent cellular phagocytosis (ADCP)
  2. Antibody-dependent cellular cytotoxicity (ADCC)
  3. Complement dependent cytotoxicity (CDC)





Iversen KF. *Basic Clin Pharmacol Toxicol*. 2024.

Case 1: Multiple Myeloma

- ✓ Approach anemia
- ✓ Diagnosis and management of multiple myeloma
- ✓ Complications in multiple myeloma
- ✓ Pharmacology of anti-CD38 monoclonal antibody

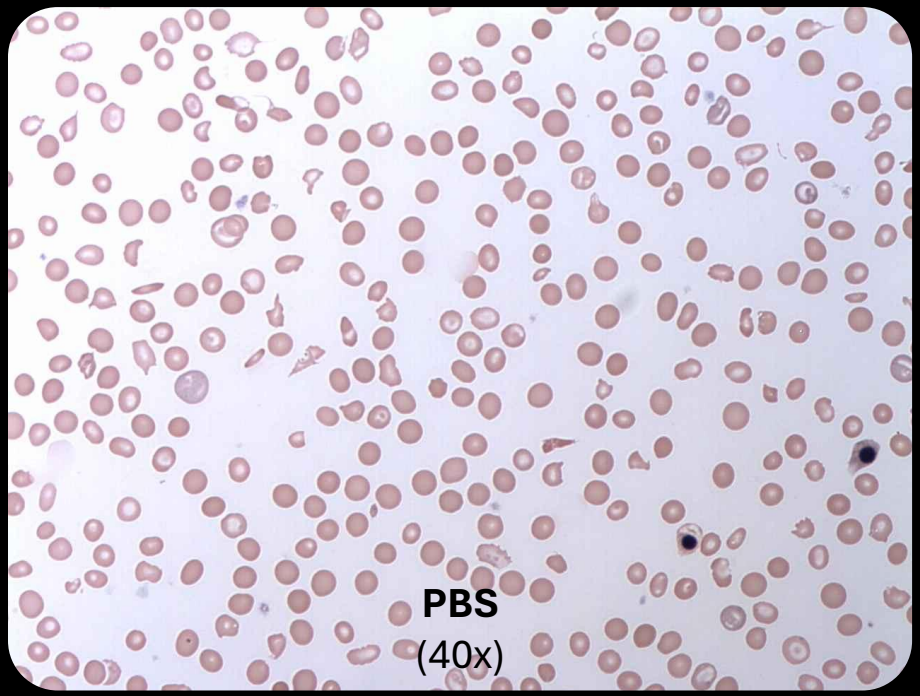
Case 2

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.

CBC reveals 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 and LDH are elevated. Ferritin and free haptoglobin are low. Direct Coombs test is negative. Urinalysis shows positivity for hemoglobin without red blood cells detected

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

Q2

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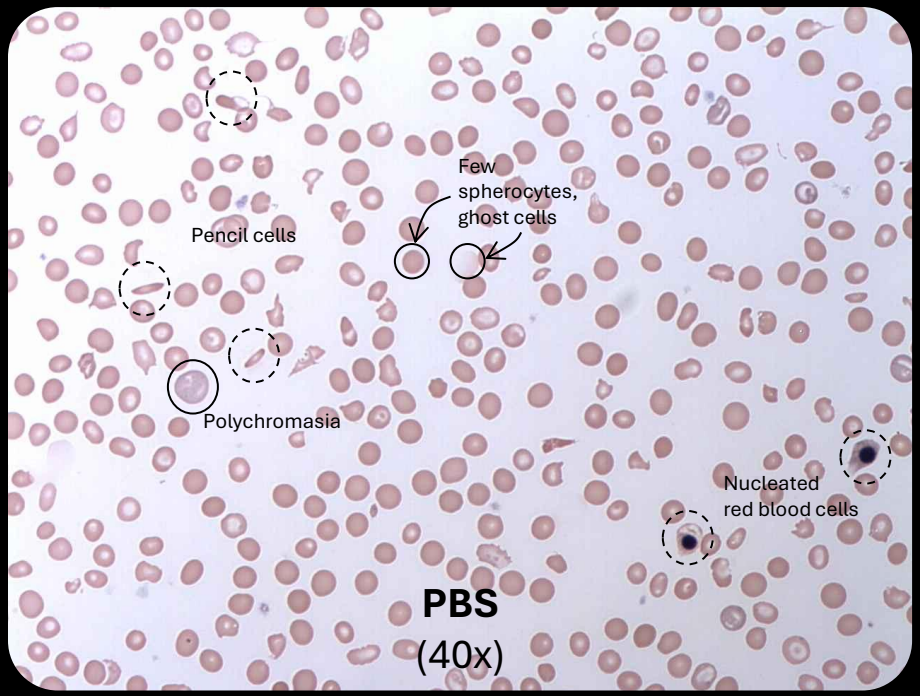
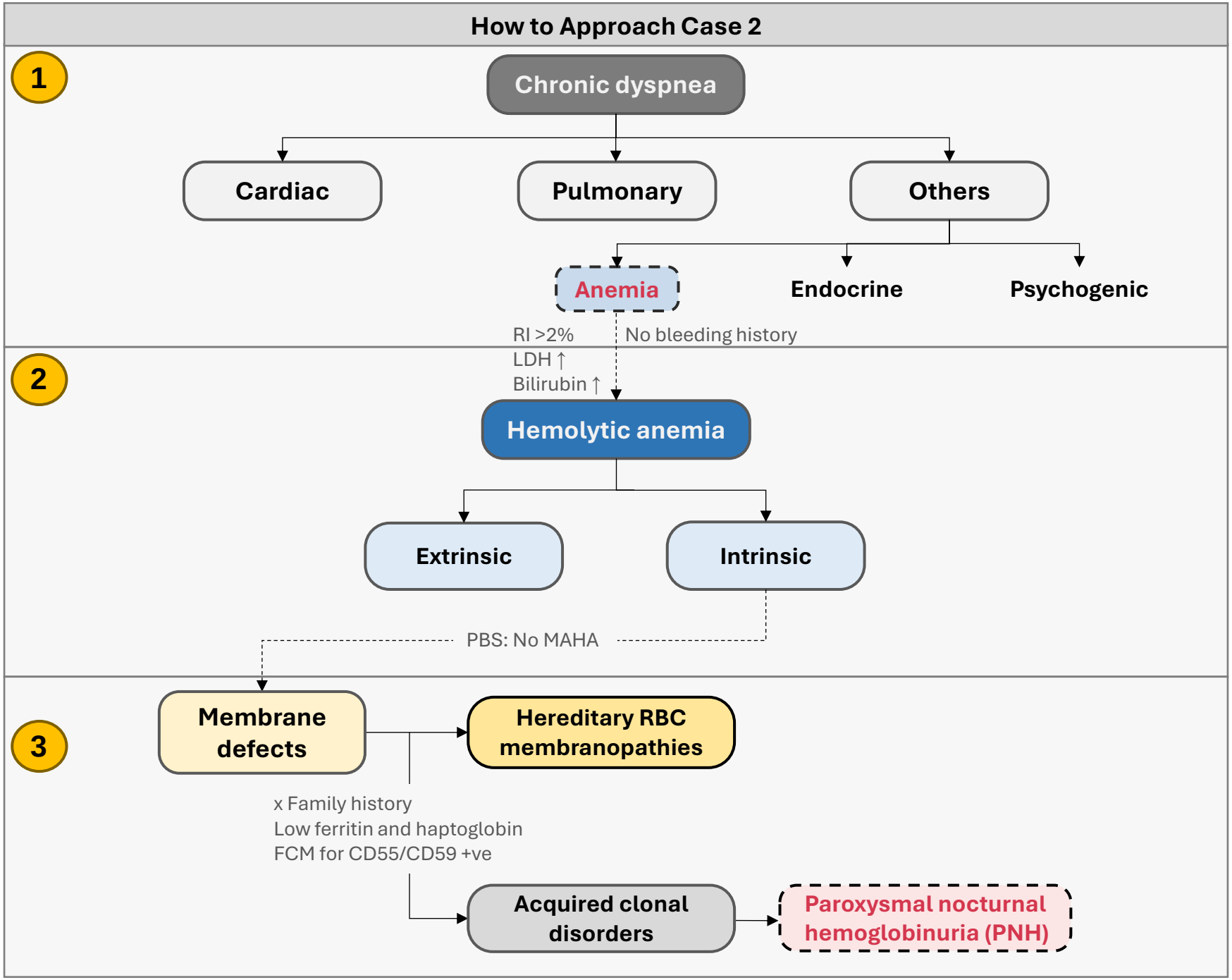
Microcytic 1+, Hypochromic 1+
Anisocytosis 2+
Poikilocytosis 1+



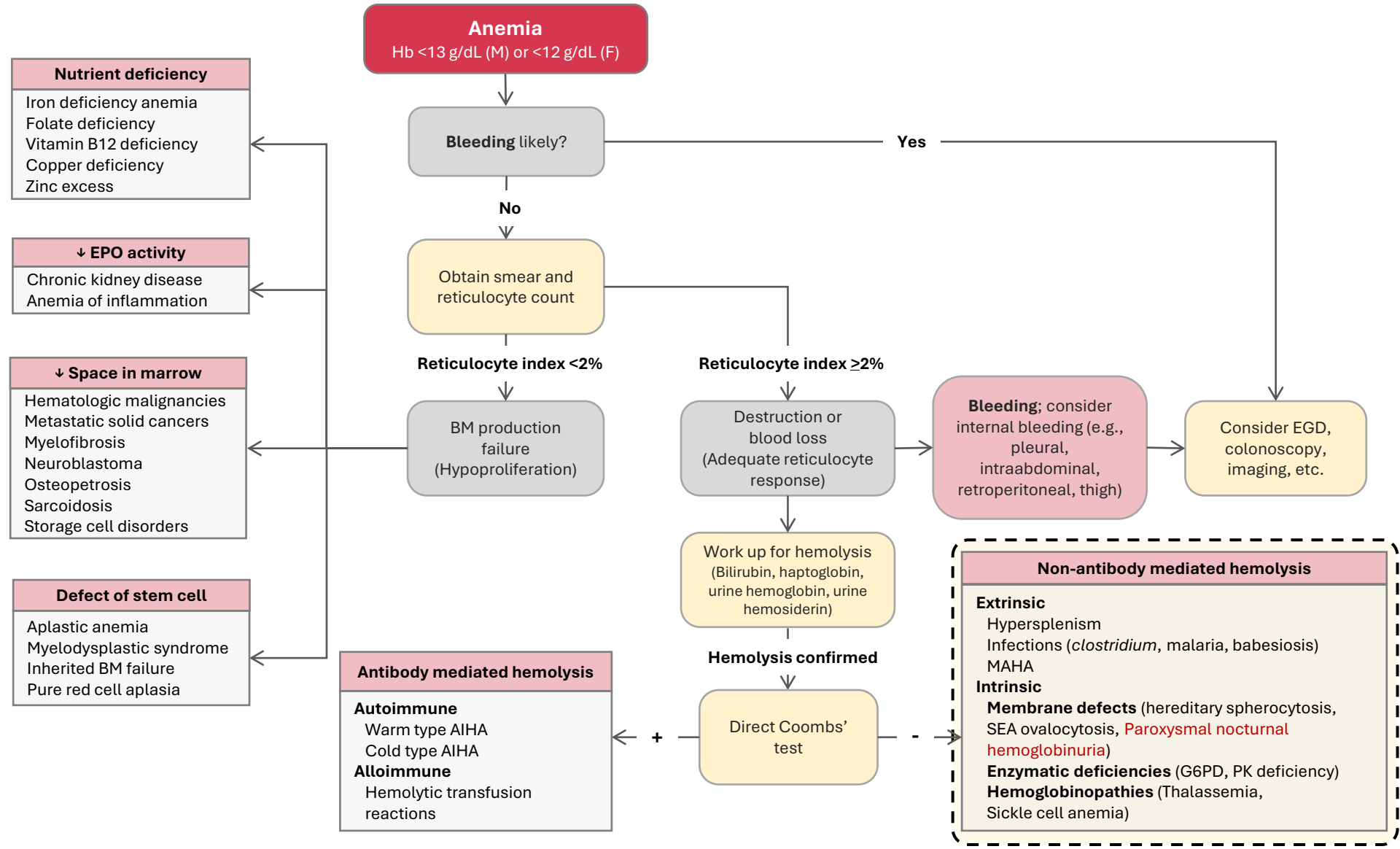
Blood smear interpretation:

1. intravascular hemolysis
2. Iron deficiency anemia

Paroxysmal nocturnal hemoglobinuria

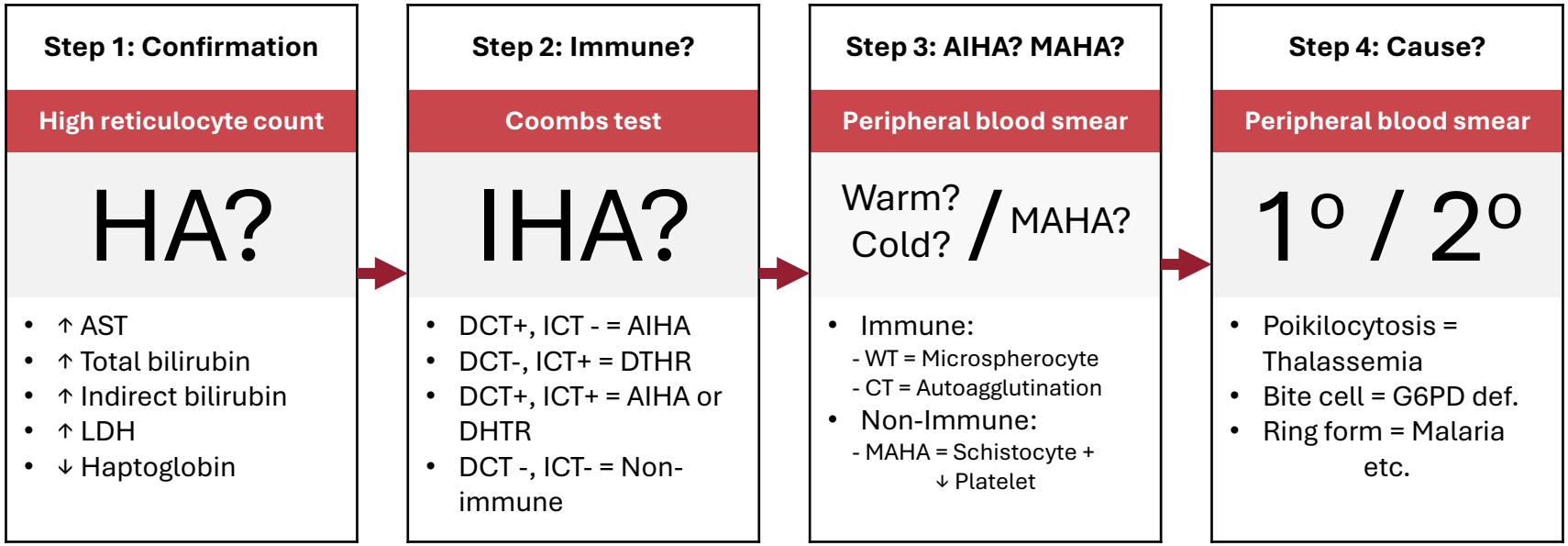

How to Approach Case 2
1
Chronic dyspnea
Cardiac
Pulmonary
Others
Anemia
Endocrine
Psychogenic
RI >2%
LDH ↑
Bilirubin ↑
No bleeding history
2
Hemolytic anemia
Extrinsic
Intrinsic
PBS: No MAHA
3
Membrane defects
Hereditary RBC membranopathies
x Family history
Low ferritin and haptoglobin
FCM for CD55/CD59 +ve
Acquired clonal disorders
Paroxysmal nocturnal hemoglobinuria (PNH)

Approach Anemia

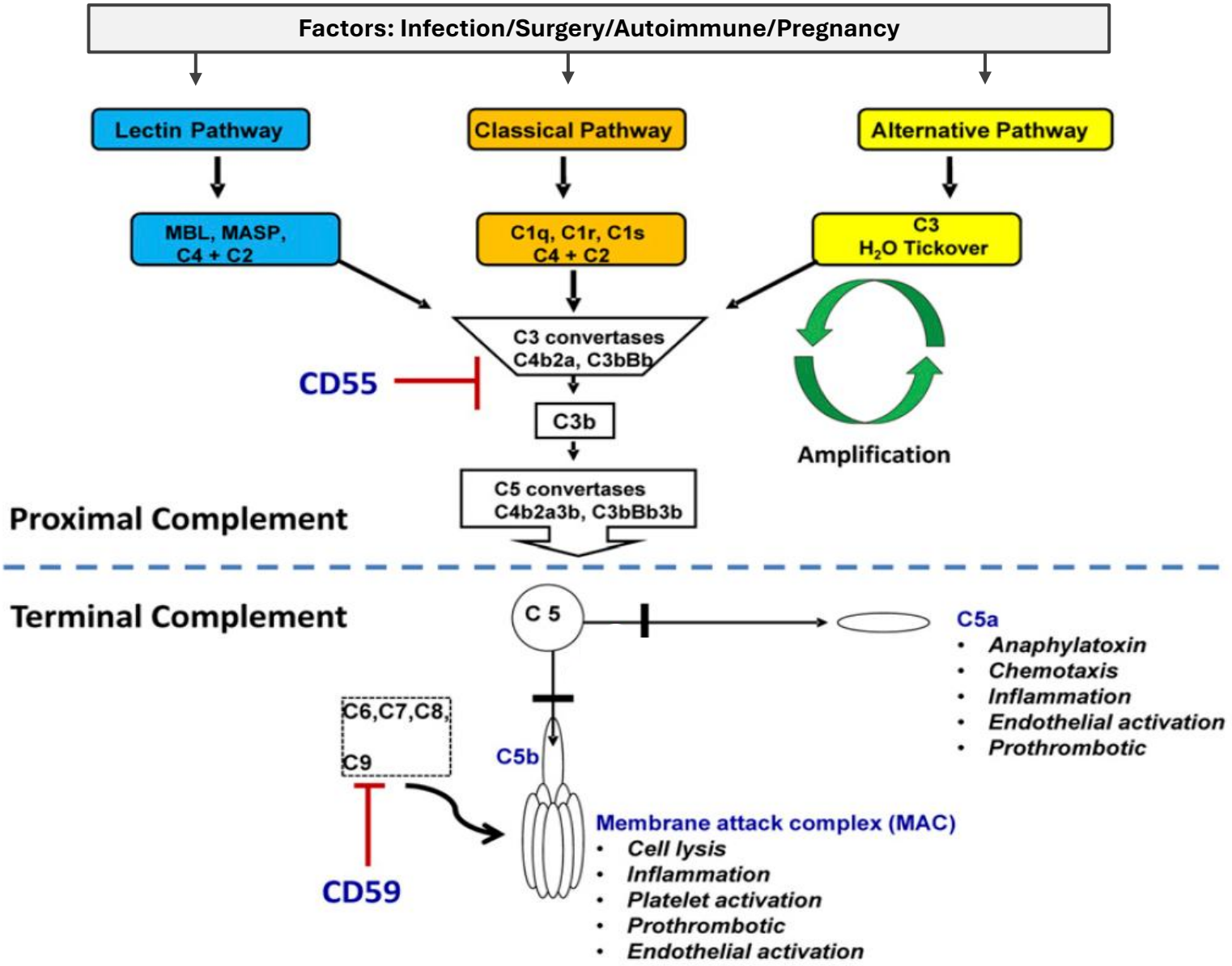


Stepwise Clinical Approach Hemolytic anemia

Most types of hemolytic anemia need peripheral blood smear to support diagnosis



Complement Systems



Paroxysmal Nocturnal Hemoglobinuria (PNH)

Pathogenesis

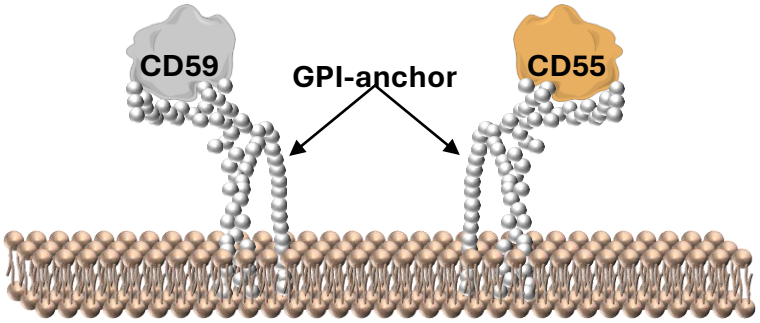
- PNH clones are defined as PNH cells with a deficiency of proteins that require a GPI anchor for attachment to the cell membrane.

CD59 (MIRL)

- Forms a defensive shield for red blood cells (RBCs) from complement-mediated lysis
- Inhibits the assembly of the membrane attack complex

CD55 (DAF)

- Prevents formation and augments instability of the C3 convertases, attenuating the complement cascade



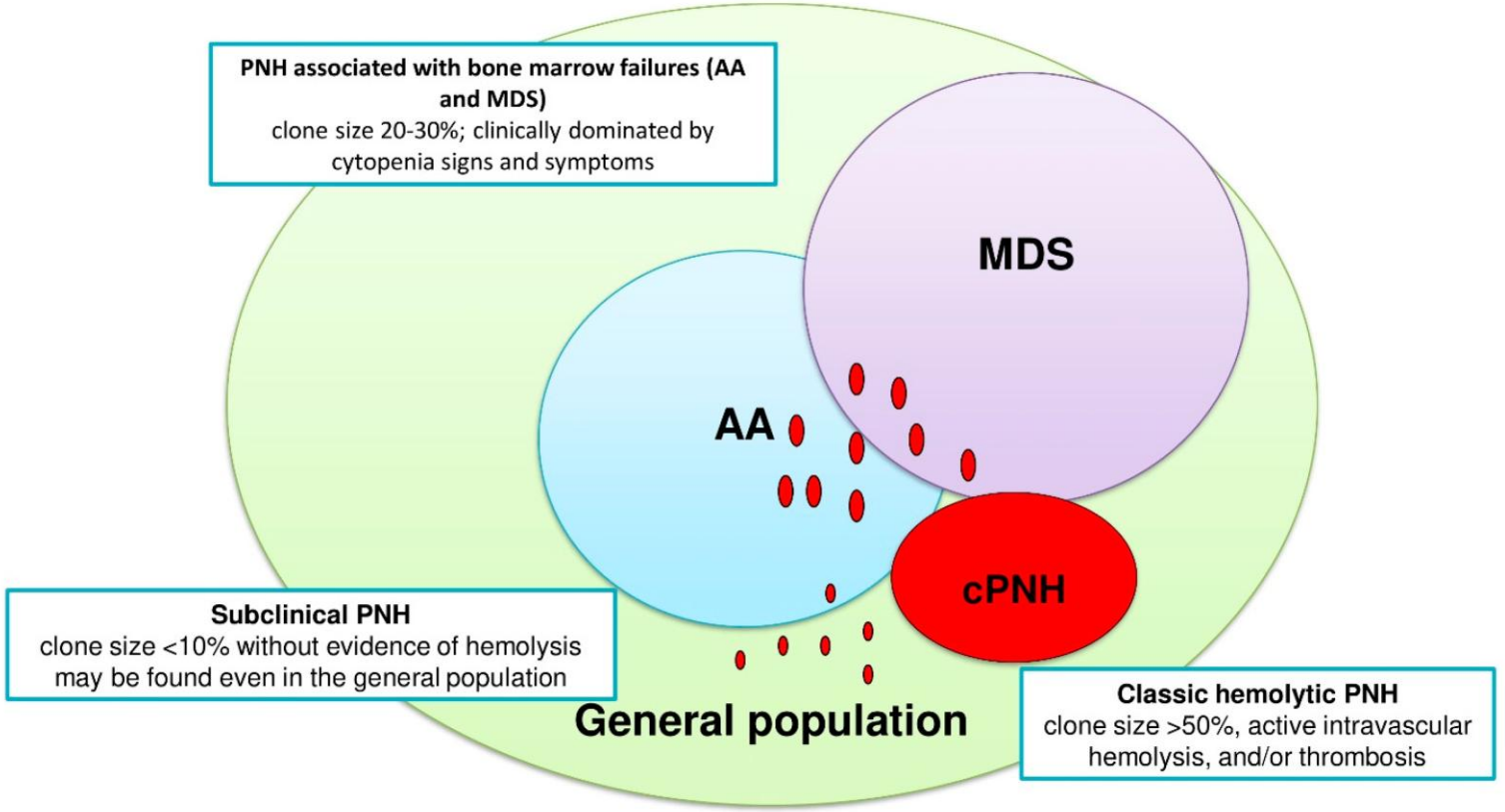
GPI = glycerophosphatidylinositol

Clinical manifestation

- Reactive BM with intravascular hemolysis
  - Normocellular to hypercellular BM with erythroid hyperplasia
  - elevated reticulocyte count
  - Large population of PNH cells (60% PNH granulocytes)
  - LDH = 2-10 x ULN
- Hemoglobinuria
- Smooth muscle dystonias (e.g. esophageal spasm, erectile dysfunction) and severe fatigue
- Thrombosis

PNH Subgroups

According to the International PNH Interest Group (IPIG) Classification



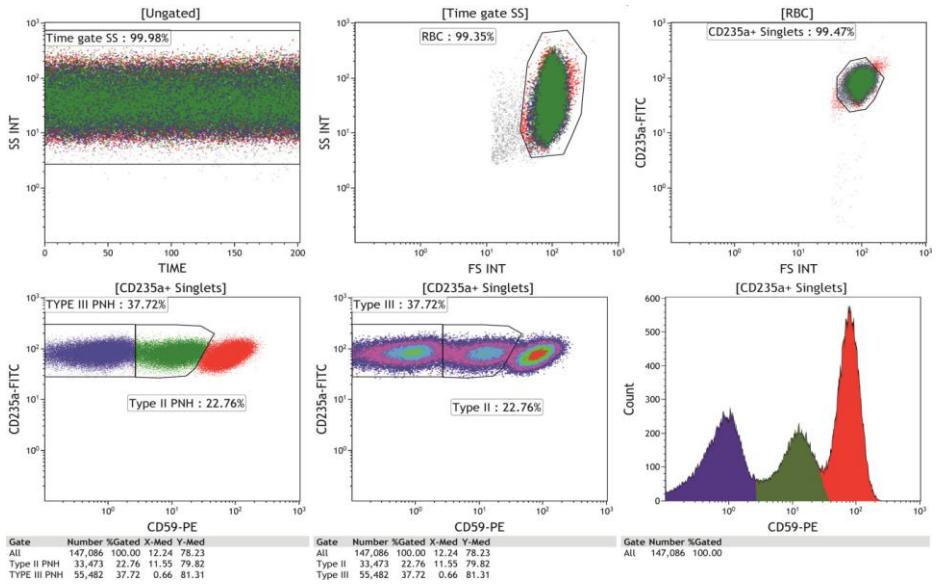
Types of PNH Cells

Abnormal cells

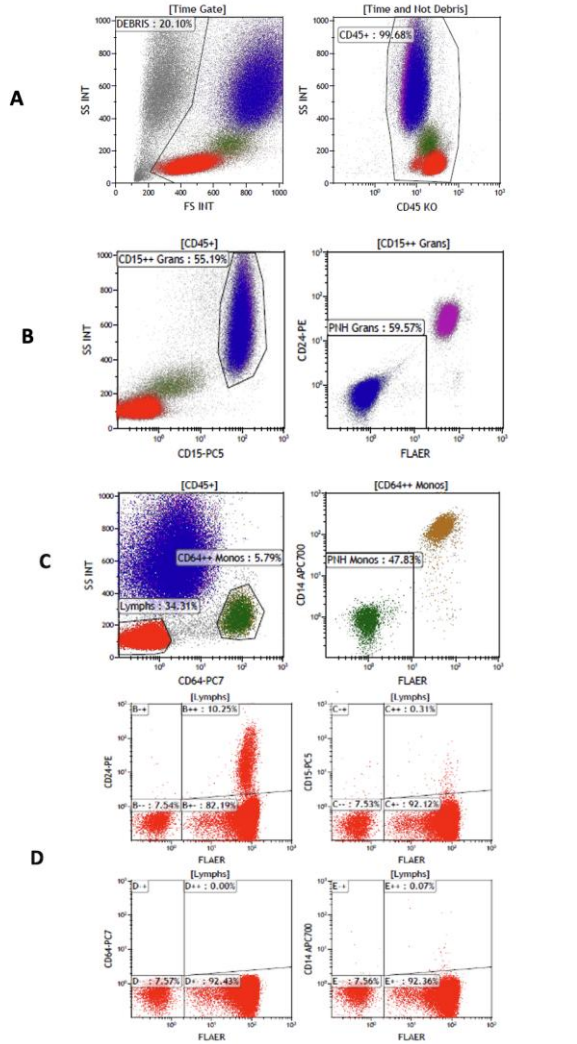
- PNH I cells normal in sensitivity to complement
- PNH II cells moderately more sensitive than normal cells (partial absence)
- PNH III cells marked sensitive, requiring one fifteenth t one twentieth of complement for an equal degree of lysis (complete absence).
    - This group is increased in patients with more severe PNH and is associated with a mean life span of 10-15 days

Diagnosis of PNH

- Flow cytometry detecting of CD55/CD59 on blood cells



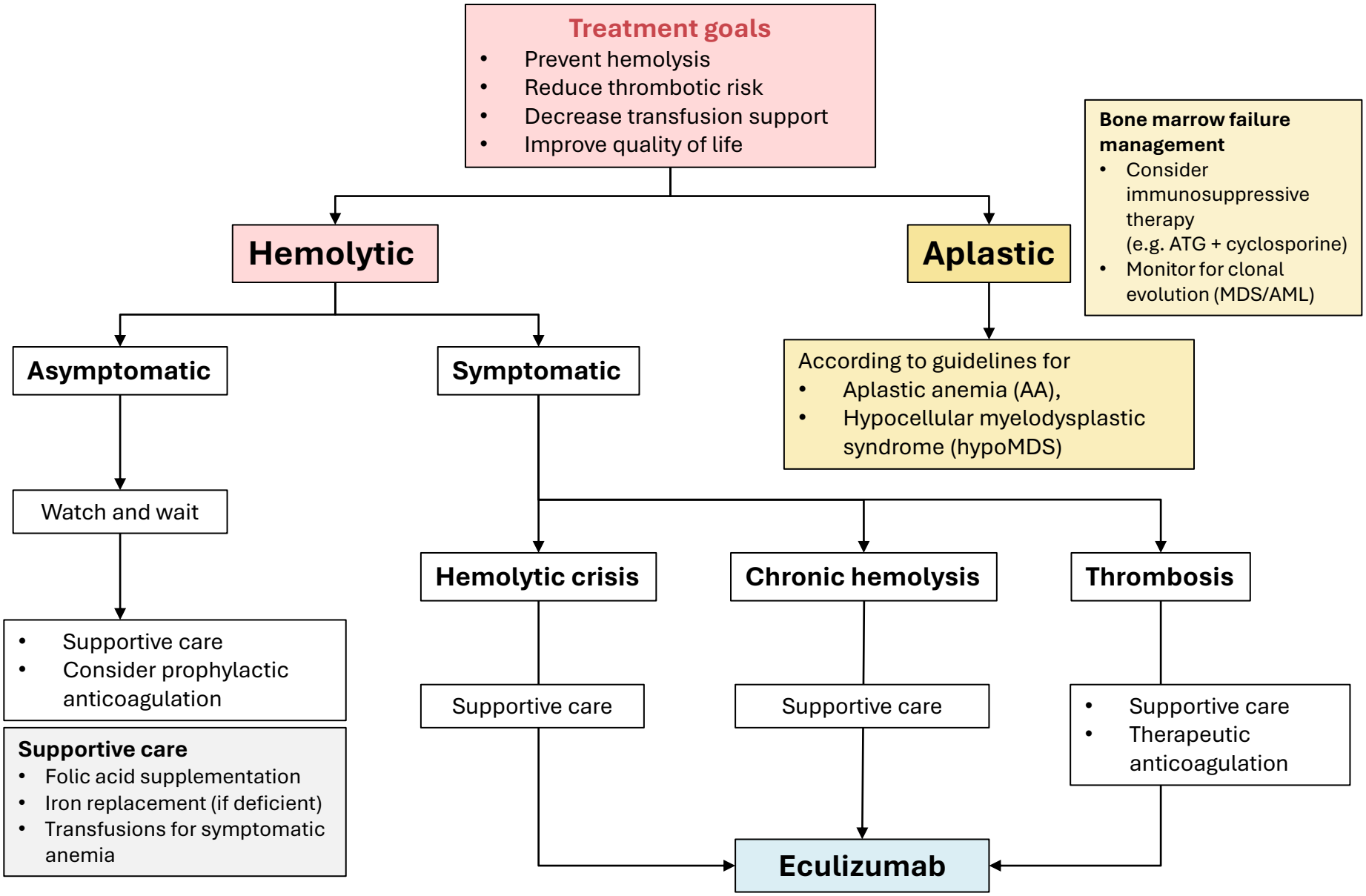
Red blood cell assay:
Patient with PNH RBC clone comprised of distinct Type II and Type III PNH RBC clones.



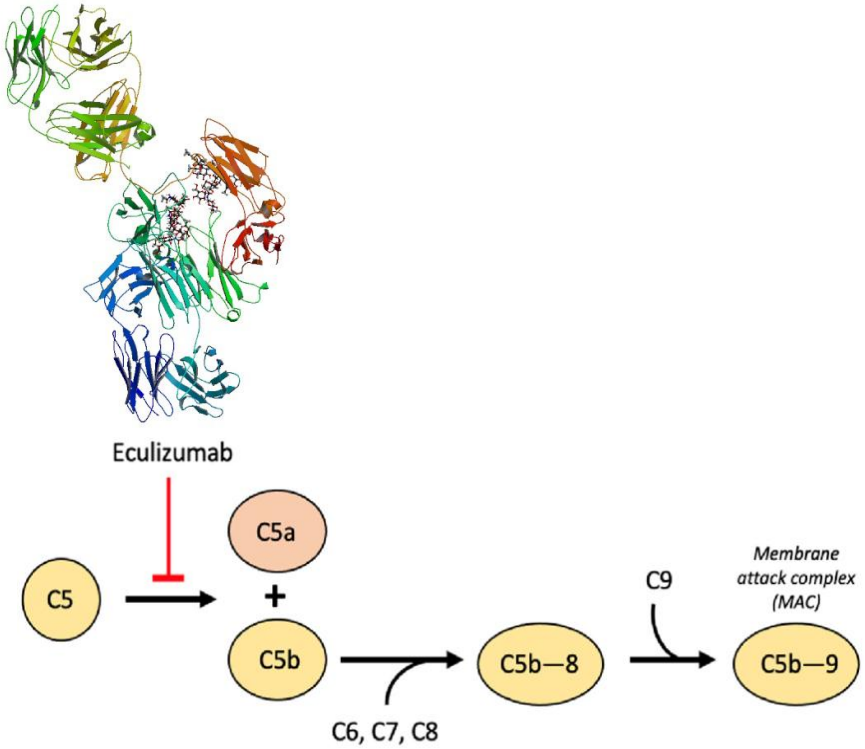
WBC panels:
A. CD45+ cells are gated on “Time” with the exclusion of the Debris (“Time” and “Singlets” plots are not shown).
B. CD45+ cells are gated lineage-specifically on **CD15++ neutrophils** and show a FLAER/CD24 negative PNH clone within the neutrophil population.
C. CD45+ cells are gated lineage-specifically on **CD64++ monocytes** and show a FLAER/CD14 negative PNH clone within the monocyte population.
D. Lymphocytes are not suitable targets for PNH clone evaluation due to the long lifespan of memory cells, but they do serve as excellent internal controls for instrument setup & compensation.

Cytometry Part B Clinical, Volume: 94, Issue: 1, Pages: 49-66, First published: 13 December 2017, DOI: (10.1002/cyto.b.21609)

Management of PNH



C5 Inhibitor



- **Targeted therapy: Eculizumab (C5 inhibitor)**
  - Reduces intravascular hemolysis
  - Prevents thrombosis
  - Improves fatigue, and quality of life

Future and emerging therapies: Pegcetacoplan, Danicopan, Gene therapy

Case 2: Paroxysmal Nocturnal Hemoglobinuria

- ✓ Approach hemolysis
- ✓ Diagnosis and management of PNH
- ✓ Pharmacology of C5-inhibitor

Case 3

Q3

A 20-year-old female hairdresser with systemic lupus erythematosus (SLE) presents to the emergency department with bluish discoloration of her lips and fingers. She is not in respiratory distress. Pulse oximetry shows an oxygen saturation of 85% on room air, but her arterial blood gas reveals a normal PaO_2. She is currently on immunosuppressive therapy and was recently started on prophylactic medication to prevent opportunistic infection.

Which of the following medications is the most likely causative agent of her symptoms?

A. Dapsone
B. Hydroxychloroquine
C. Mycophenolate mofetil
D. Trimethoprim-sulfamethoxazole
E. Pneumocystis jirovechii infection

Q3

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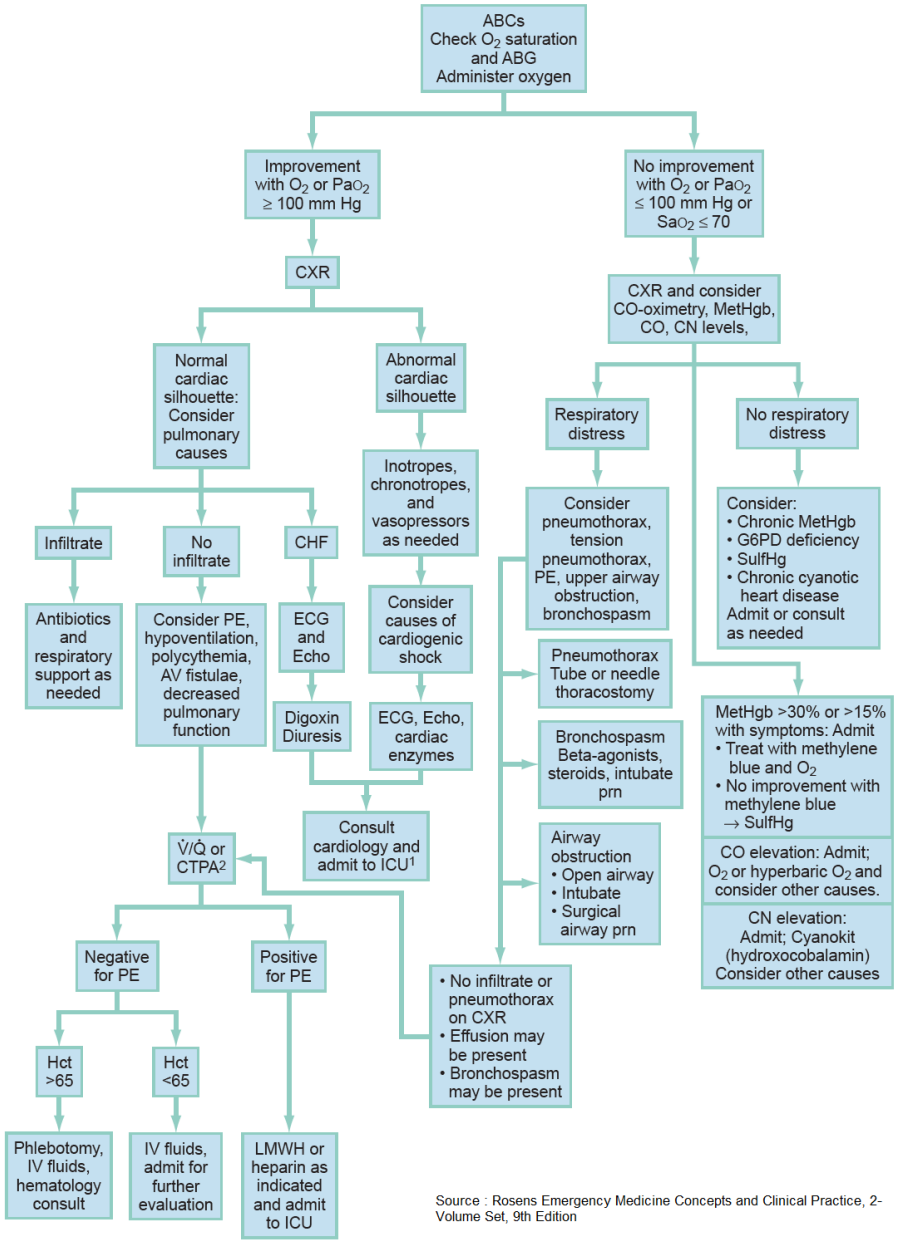
E. Pneumocystis jirovechii infection

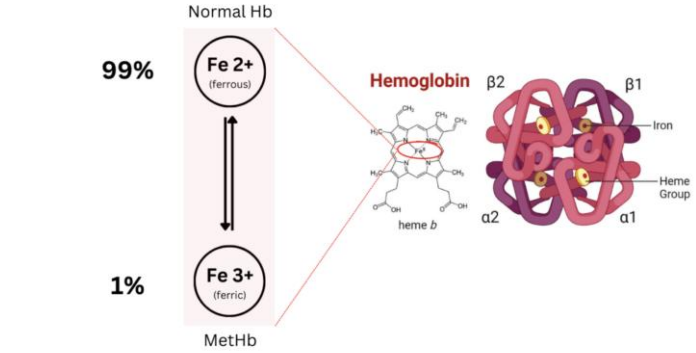
Approach Cyanosis

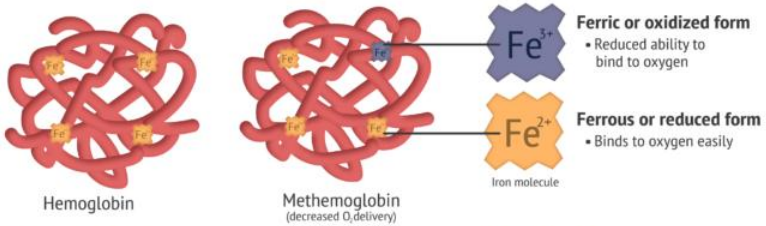


Source : Rosens Emergency Medicine Concepts and Clinical Practice, 2-Volume Set, 9th Edition

Fig. 11.4. An algorithmic approach to central cyanosis. *ABCs,* Airway, breathing, circulation; *ABG,* arterial blood gas; *AV,* arteriovenous; *CHF,* congestive heart failure; *CN,* cyanide; *CO,* carbon monoxide; *CTPA,* computed tomography pulmonary angiography; *CXR,* chest radiograph; *ECG,* electrocardiography; *Echo,* echocardiography; *G6PD,* glucose-6-phosphate dehydrogenase; *Hct,* hematocrit; *ICU,* intensive care unit; *IV,* intravenous; *LMWH,* low-molecular-weight heparin; *MetHgb,* methemoglobin; O_2, oxygen; PaO_2, partial pressure of arterial oxygen; *PE,* pulmonary embolus; *prn,* as needed; *RA,* room air; SaO_2, arterial oxygen saturation; *SulfHg,* sulfhemoglobin; V̇/Q̇, ventilation-perfusion scan. [1]Patients with chronic cyanotic heart disease may not require ICU care or even hospital admission. Disposition should be discussed with the patient's cardiologist.[2] The V̇/Q̇ ratio may be determined when CTPA is unavailable or contraindicated.

Methemoglobinemia





Congenital Methemoglobinemia

- Cyb5R deficiency
- Hemoglobin M disease

VS.

Acquired Methemoglobinemia

- Drugs
  e.g. dapsone (think G6PD deficiency), chloroquine, nitrates & nitrites, some topical anesthetics

Diagnosis and Symptoms

- Arterial blood gas methemoglobin < 5%

MILD:

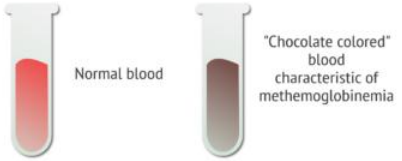
- 3-20% may be asymptomatic

MODERATE:

- 20-50% dyspnea, fatigue, headache

SEVERE:

- 50-70% shock, severe respiratory depression



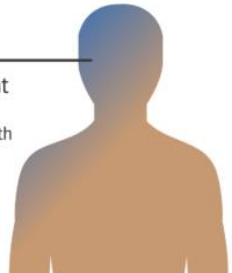
Investigations

CBC	ABG	G6PD deficiency testing
Normal or elevated HgB	Methemoglobin levels Normal or elevated PaO_2	

Physical Exam

- Cyanosis
- Pulse oximetry might show O_2 sat ~85%
  - Failing to improve with supplemental O_2

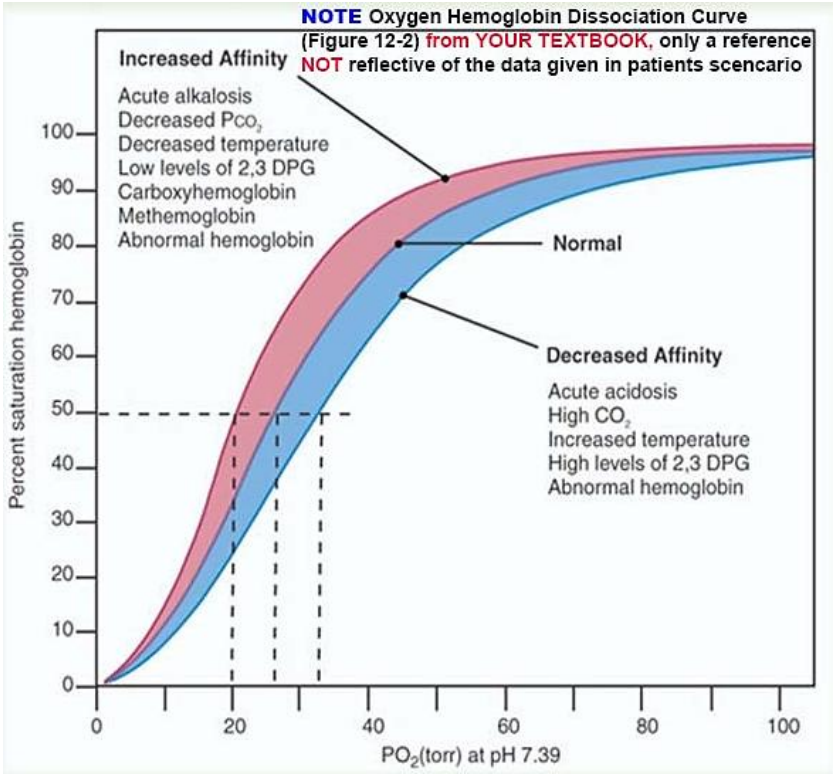
*Routine pulse oximetry unable to distinguish methemoglobin and oxy/deoxy-hemoglobin



Treatment

If methemoglobin levels are **> 30%** or **symptomatic**:

1. **Methylene Blue**
   - Caution in G6DP deficiency - hemolysis
   - Can cause serotonin syndrome if taken with serotonergic medication
2. **Ascorbic Acid**
   - For those with G6DP deficiency
3. **Avoiding oxidant substances**

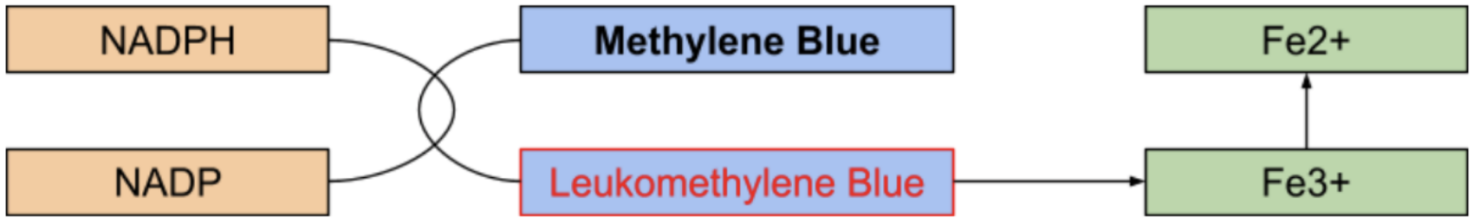


Drug-Induced Methemoglobinemia

Potential drugs known to induce methemoglobinemia	Potential toxins to induce methemoglobinemia
Antimalarials Primaquine Chloroquine	Aniline dyes Nitrobenzene Naphthalene (moth balls) Nitroethane (nail polish remover) Mushrooms Well water Antifreeze Frozen-dried foods Root vegetables
Antineoplastic agents Cyclophosphamide Ifosfamide	
Analgesics Celecoxib	
Antibiotics Sulfonamides Nitrofurans	
Anesthetics Benzocaine Prilocaine	
Others Phenazopyridine Dapsone Nitroglycerin Metoclopramide	

Diagnosis and Management of Methemoglobinemia

Mechanism of Action of Methylene Blue



Pharmacokinetics of methylene blue

- Onset of action: 30-60 minutes
- Time to peak: 30 minutes
- Protein binding: 94%
- Metabolism: first-pass metabolism
- Half-life: 5-7 hours
- Excretion: bile, feces, and urine

Treatmen		Role in Therapy
Supportiv Care		**rst-Line** for **ALL** cases of methemoglobinemia: • Immediate cessation of the offending agent • IV hydration should be implemented on a case to case basis • Oxygen supplementation should be instituted • If necessary, cardiopulmonary support with mechanical ventilation may be appropriate • Glucose supplementation may be needed
Methylene Blue	1-2 mg/kg infused over 3-5 minutes; may repeat dose if no significant improvement is seen within 30-60 minutes (max total dose: 7 mg/kg)	**First-Line** pharmacologic agent for patients with: • MetHb level > 30% • MetHb level 20-30% who are symptomatic and/or have underlying cardiac or pulmonary disease
Ascorbic Acid	1-10 grams every 6 hours until MetHb levels normalize	**Second-Line** pharmacologic option for patients who have: • Severe or symptomatic methemoglobinemia when methylene blue is unavailable or contraindicated

Contraindications of Methylene Blue

- **Active use of serotonergic agents**
  - Methylene blue shares a similar chemical structure to monoamine oxidase inhibitors (MAOIs).
  - Increase the risk of developing serotonin syndrome.
- **Pregnancy**
  - Lead to intestinal atresia.
- **Renal failure**
  - Be avoided in patients with severe renal impairment.
  - Be administered cautiously in patients with mild to moderate renal impairment.
- **Active hemolysis**
- **G6PD deficiency**

Case 3: Drug-Induced Methemoglobinemia

- ✓ Approach cyanosis
- ✓ Diagnosis and management of methemoglobinemia
- ✓ Methylene blue

Case 4

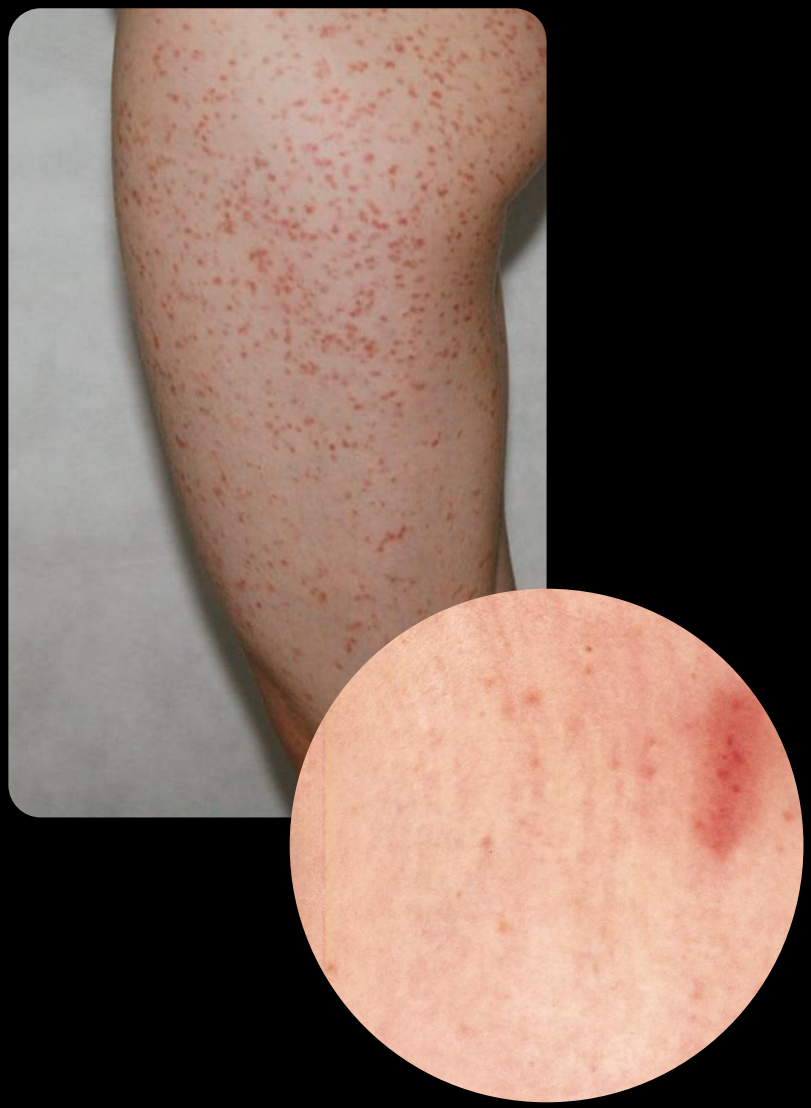
Q4

A 30-year-old male government officer presents with chronic diarrhea for the past 6 weeks. He also reports episodic facial flushing, abdominal cramping, nausea, and lightheadedness. He denies recent travel, antibiotic use, or blood in stool. On physical examination, he has multiple hyperpigmented macules on his trunk that become erythematous and pruritic when rubbed.

CBC reveals Hb 11 g/dL, MCV 74 fL, WBC count 12,000/µL (N 50, L 20, M 5, E 25), platelet count 450,000/µL. Stool studies shows negativity for ova, parasites, leukocytes, and culture.

Serum tryptase is 45 ng/mL (elevated). IgE is mildly elevated. 24-hour urinary 5-hydroxyindoleacetic acid is normal.

What is the most likely diagnosis?



A. Capillariasis
B. Carcinoid syndrome
C. Primary AL amyloidosis
D. Intestinal MALT lymphoma
E. Systemic mastocytosis

Q4

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Darier's sign

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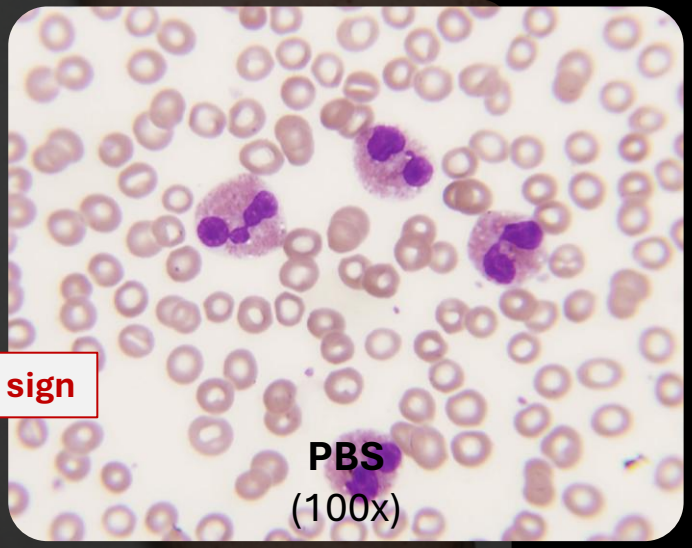
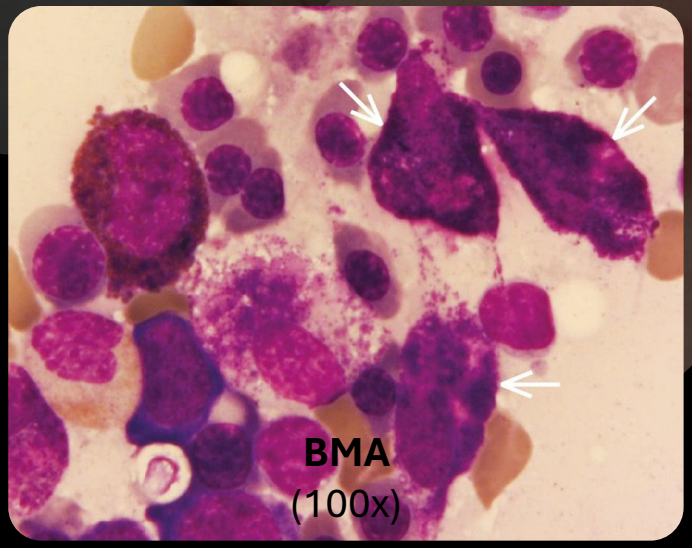
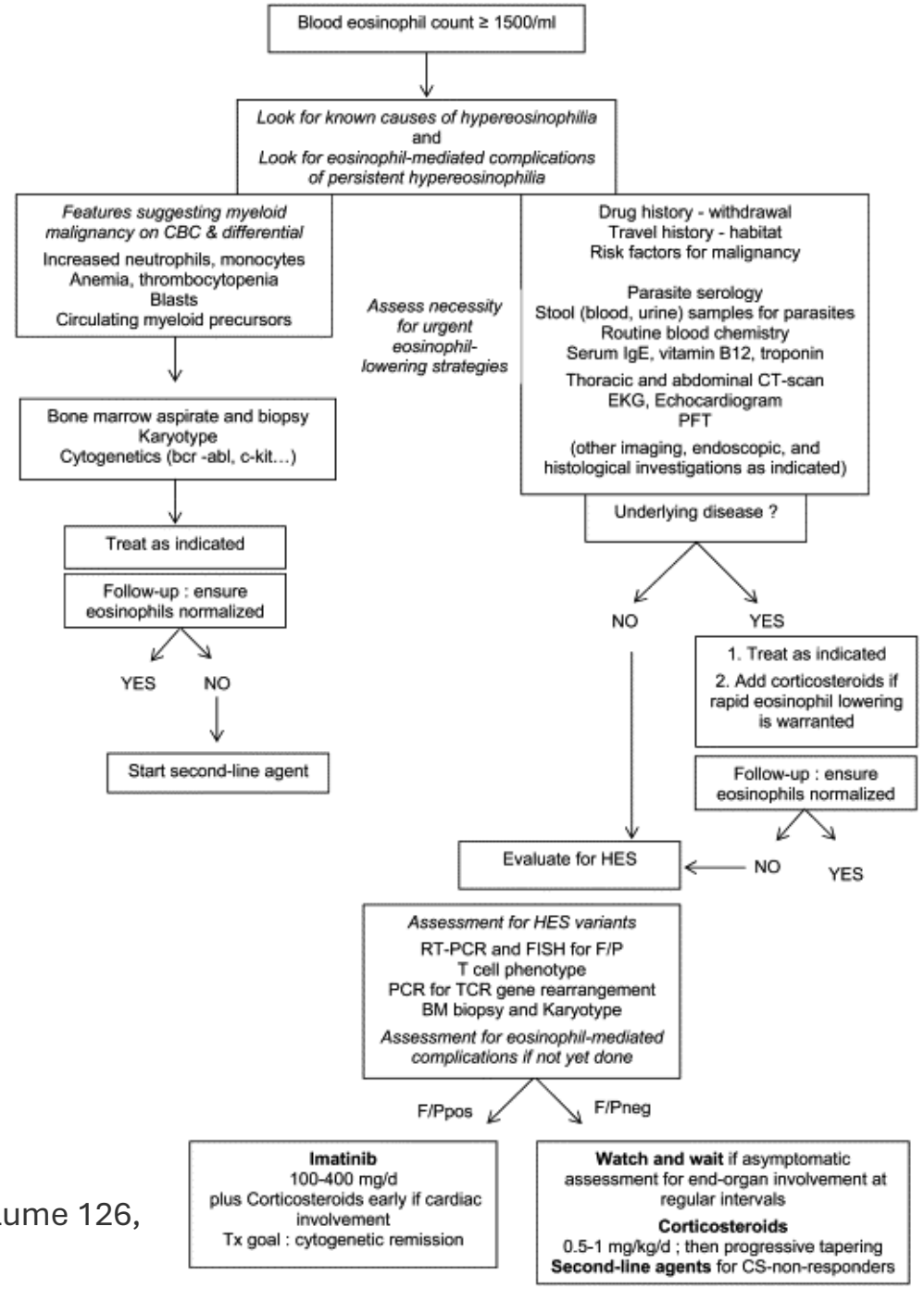


Eosinophilia



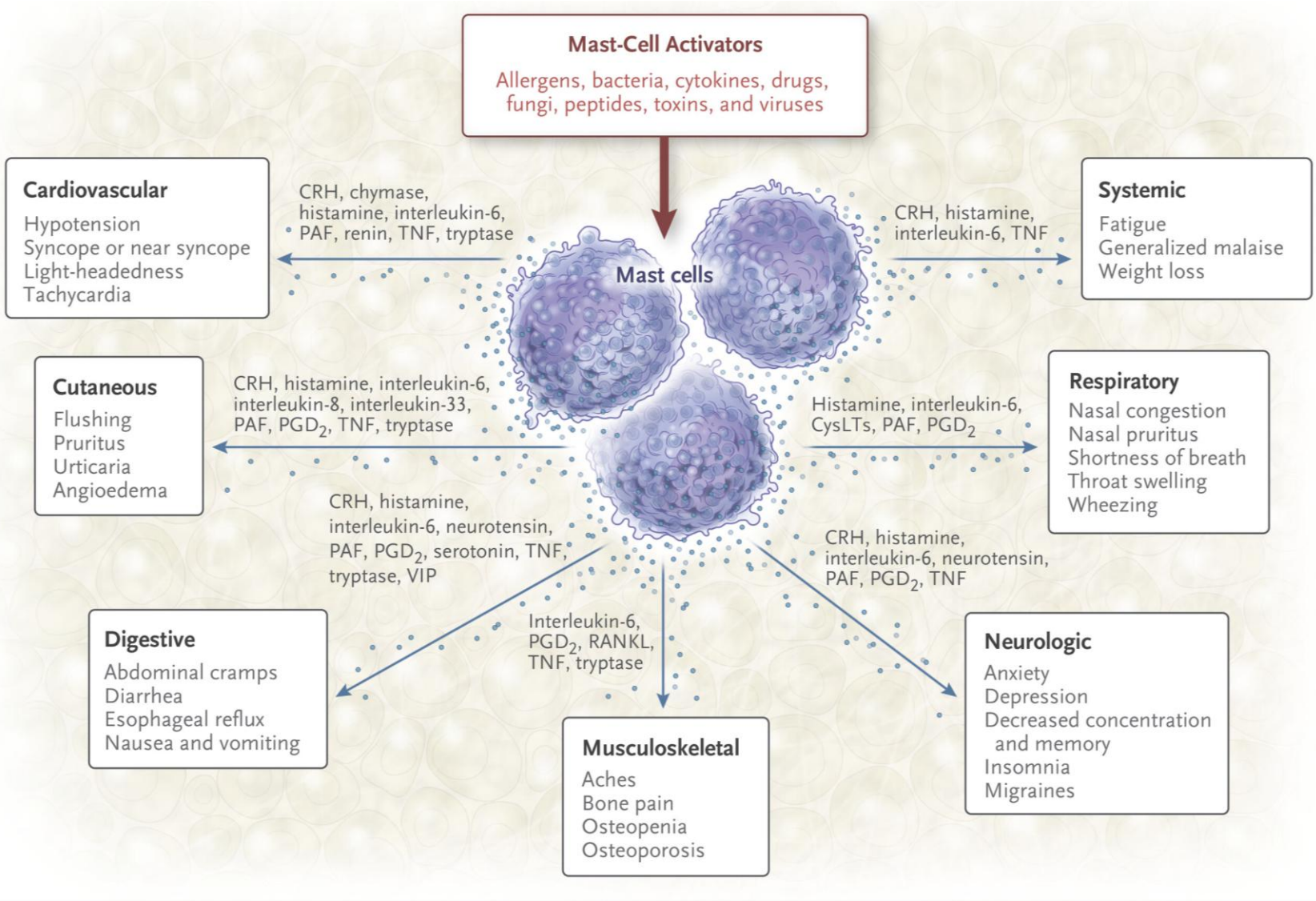
Visible pathologic mastocytes (arrows; Pappenheim stain)

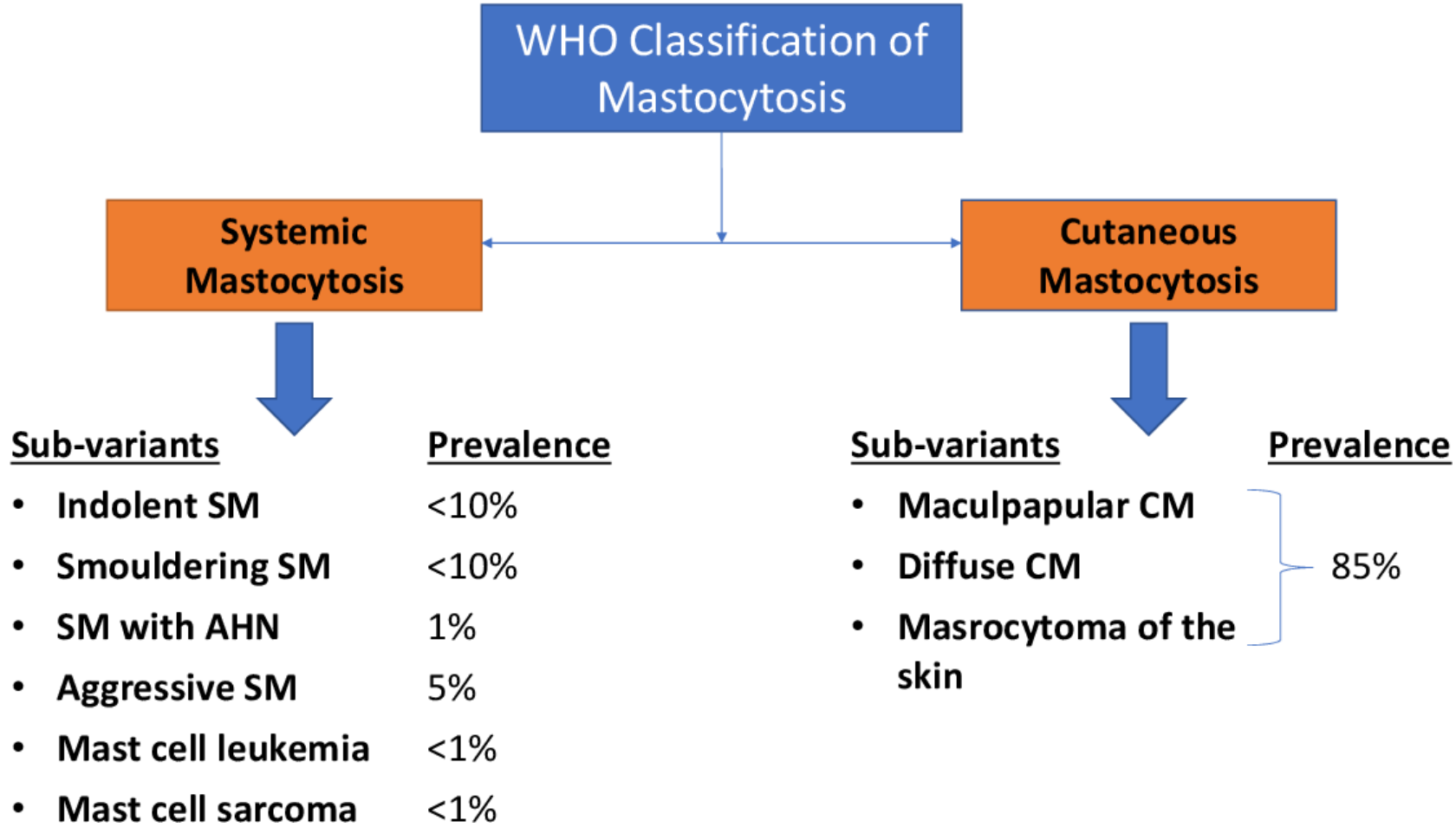
Approach Eosinophilia



Roufosse, Florence et al.
Journal of Allergy and Clinical Immunology, Volume 126, Issue 1, 39 - 44

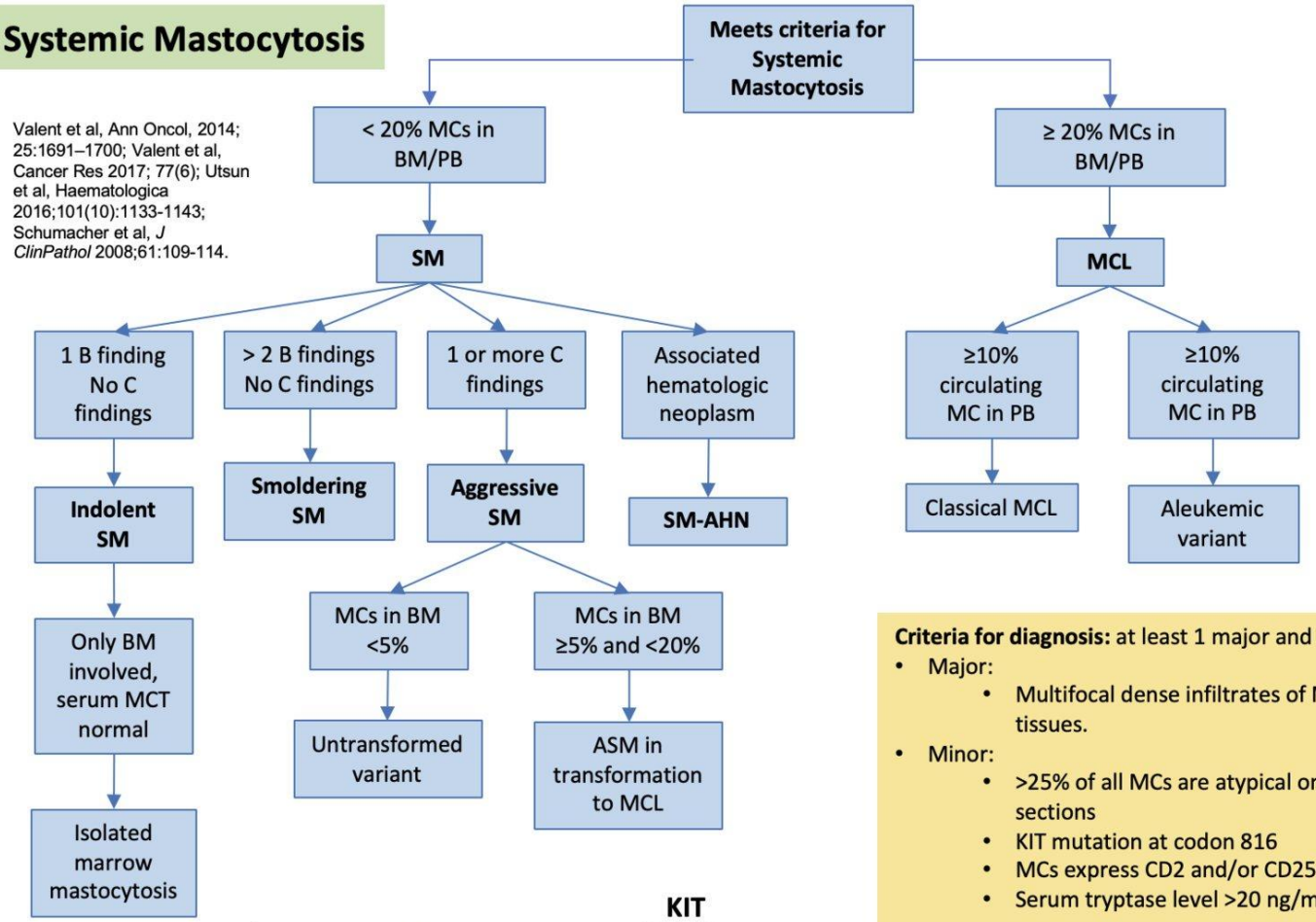
Mast Cells Biology and Pathophysiology

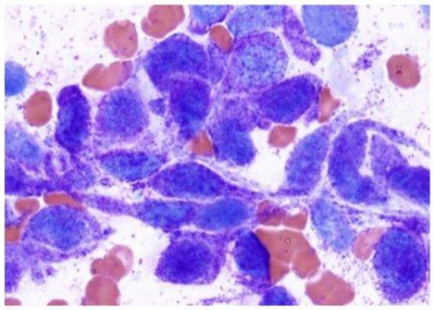


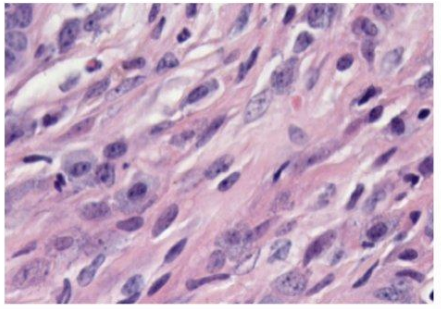

WHO Classification of Mastocytosis
Systemic Mastocytosis
Cutaneous Mastocytosis
Sub-variants
Prevalence
• Indolent SM <10%
• Smouldering SM <10%
• SM with AHN 1%
• Aggressive SM 5%
• Mast cell leukemia <1%
• Mast cell sarcoma <1%
Sub-variants
Prevalence
• Maculpapular CM
• Diffuse CM
• Masrocytoma of the skin
85%

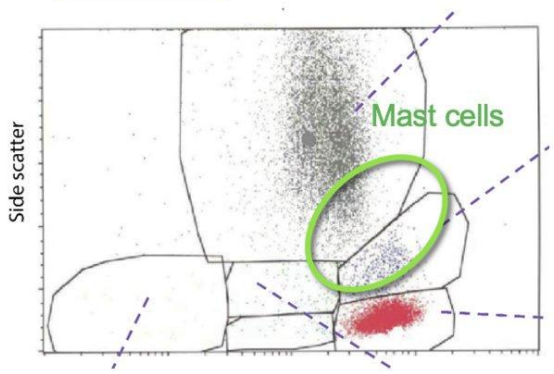
Systemic Mastocytosis

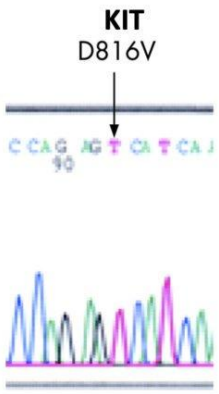
Valent et al, Ann Oncol, 2014; 25:1691–1700; Valent et al, Cancer Res 2017; 77(6); Utsun et al, Haematologica 2016;101(10):1133-1143; Schumacher et al, *J ClinPathol* 2008;61:109-114.









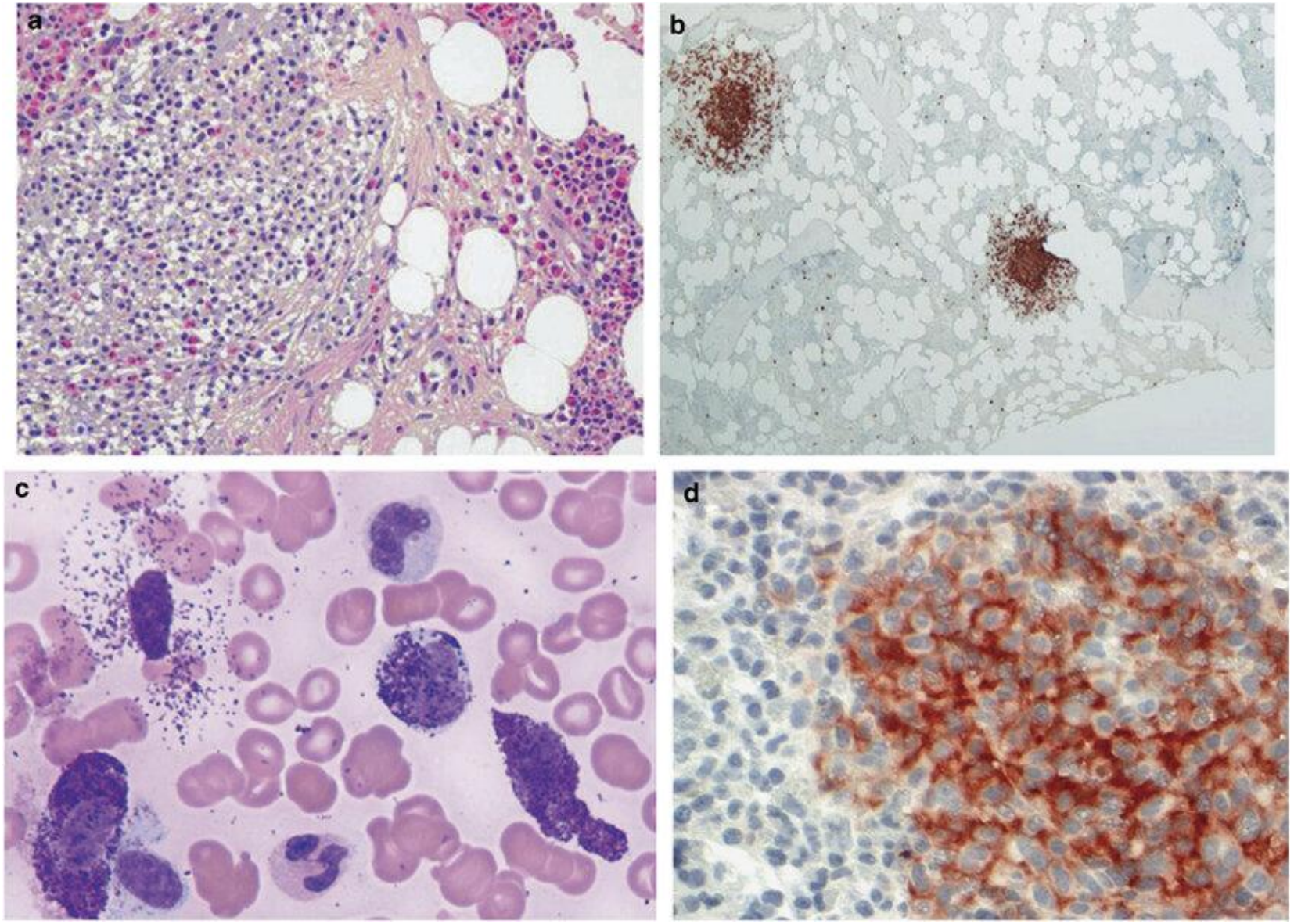


Criteria for diagnosis: at least 1 major and 1 minor or 3 minor criteria present

- Major:
  - Multifocal dense infiltrates of MC (≥ 15 MCs in aggregates) in BM or other tissues.
- Minor:
  - >25% of all MCs are atypical on BM aspirate or spindle shaped on tissue sections
  - KIT mutation at codon 816
  - MCs express CD2 and/or CD25
  - Serum tryptase level >20 ng/mL (unless an AHN is present)

B- and C-Findings:

- B-findings: mediator release
  - MCs in BM >30% and serum tryptase > 200 ng/ml
  - Hypercellular BM + dysmyelopoiesis, w/o cytopenias or meeting criteria for MDS or MPN
  - Organomegaly without organ dysfunction
- C-Findings: possible tissue damage
  - Cytopenia (ANC<1000, Hb <10, Plt < 100k)
  - Hepatomegaly with ascites/impaired liver function
  - Palpable splenomegaly with hypersplenism
  - Malabsorption with hypoalbuminemia
  - Skeletal lesions



WHO morphologic criteria for systemic mastocytosis. (a) Bone marrow biopsy, H&E, 200: large aggregate of mast cells (>15) with intermixed lymphocytes and eosinophils. (b) Bone marrow biopsy, tryptase immunostain, 40: multifocal aggregates of mast cells, positive for tryptase. (c) Aspirate smear, Wright–Giemsa, 1000: atypical morphology of mast cells including spindled, degranulated, and hypogranulated forms. (d) Bone marrow biopsy, CD25 immunostain, 400: aggregate of mast cells with positive membranous staining with CD25.

Management of Systemic Mastocytosis

INDOLENT/SMOLDERING ⟷ **ADVANCED**

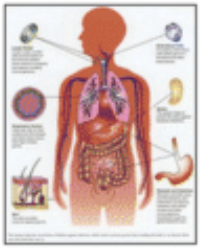
- Avoid trigger of mediator release
- Control mediator-release syndrome
  - Anti-H1/H2 blockers
  - MC stabilizers
  - Leukotriene inhibitors
  - Epinephrine self-injectors
- Osteoporosis
  - Vitamin D supplementation
  - Bisphosphonates
  - Low-dose Interferon
- Monitor organ damage

ADVANCED

- **Cytoreductive treatment**

- *Challenging subsets:*

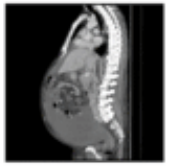
Indolent (ISM) according to WHO but **with severe mediator-related syndrome**



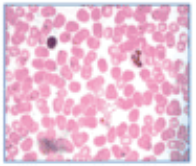
- ✓ Recurrent anaphylaxis
- ✓ Diffuse bone pain
- ✓ GI symptoms

Aggressive variant (ASM)

Ascitic effusion

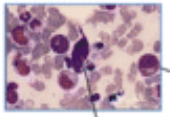


BM failure

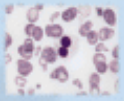


- ✓ Wide heterogeneity of clinical picture and time to clinical progression
- ✓ Distinction between mediator-related signs/symptoms and "true" organ damage

With an associated haematological neoplasm (AHN)



AHN



SM

- Cytopenias
- BM fibrosis
- Dysplasia
- Organomegaly
- Molecular profile

✓ Challenging assessment of dominating picture

Case 4: Systemic Mastocytosis

- ✓ Approach eosinophilia
- ✓ Diagnosis and management of systemic mastocytosis

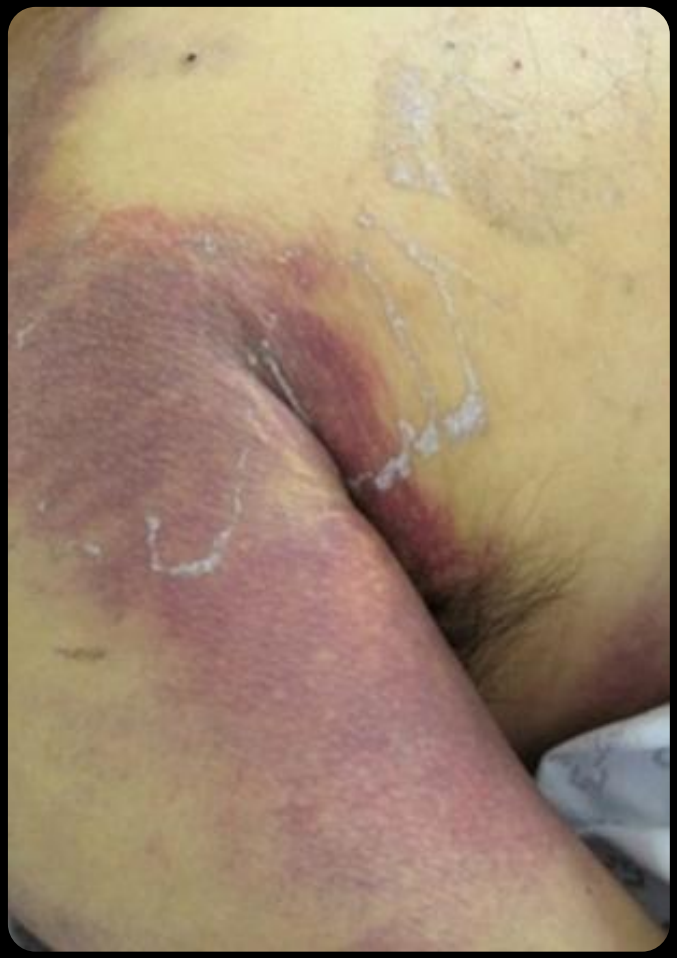
Case 5

Q5

A 72-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.

CBC reveals 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 level is 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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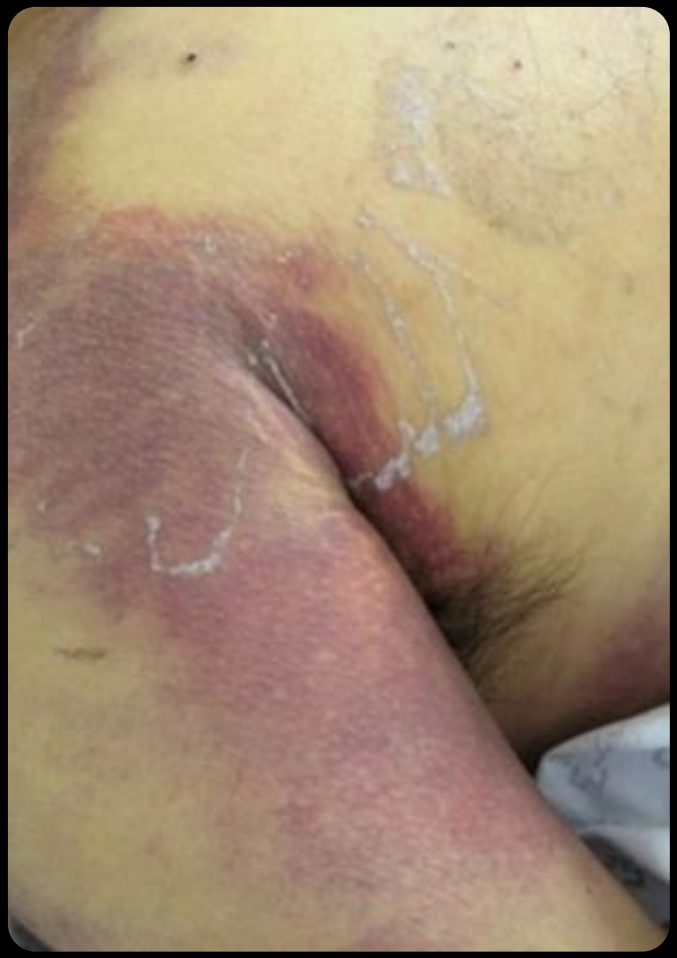


A. Acquired factor VIII inhibitor
B. Acquired factor X deficiency
C. Acute disseminated intravascular coagulation (DIC)
D. Chronic DIC
E. Lupus anticoagulant positivity

Approach Bleeding Tendency

History taking

History of presenting complaint (HPC)

Bleeding pattern
(Bruising?, Onset, Course, Duration, Distribution
Bleeding sites, Frequency, Aggravating factors, Trauma)
Other sites of bleeding (GI, GU, GYN, CNS)

Red flags (Dizziness, Shock, Coma, Postural hypotension, Oliguria, Symptoms of CNS bleeding)

Other associations
Recent blood loss
Blood donation
Blood transfusion

Past medical history

Underlying conditions
SLE?, CTD?, Bleeding disorders?

Drug history

Antiplatelet?, NSAIDS?
Anticoagulant?, Heparin?
Herbals?, Steroid?

Family history

Pedigree
Same condition?, Cancer?
Bleeding disorder?

Social history

Impact

Concern

Physical examination

Rash

Morphology
Distribution
Petechiae?, Purpura?
Ecchymosis?

Signs of anemia

Face & Mouth (for HHT)

Abdomen for organomegaly

Red flags

Pulse & JVP for shock and hypovolemia
CNS; mental score & neurological examination

Investigation

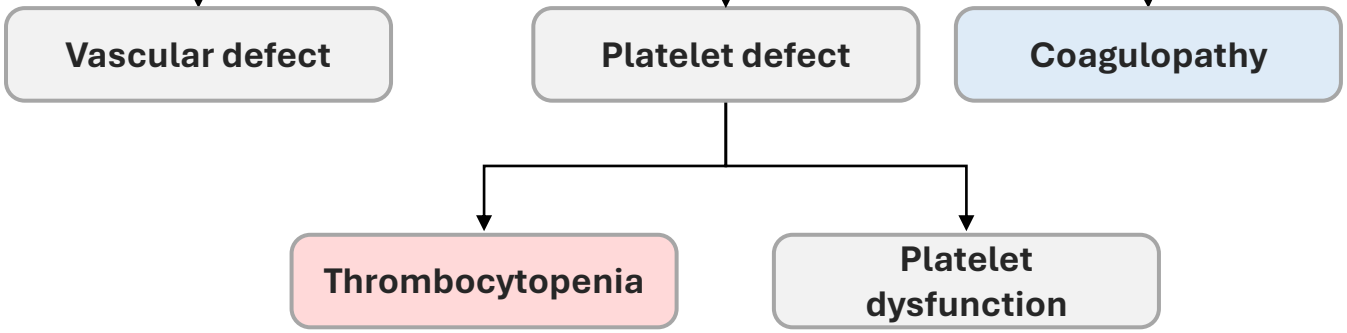
Basic lab

CBC
Blood film
PT
APTT
TT, Fibrinogen & FDPs
LFTs
Viral hepatitis serology
Autoimmune profile
HIV serology

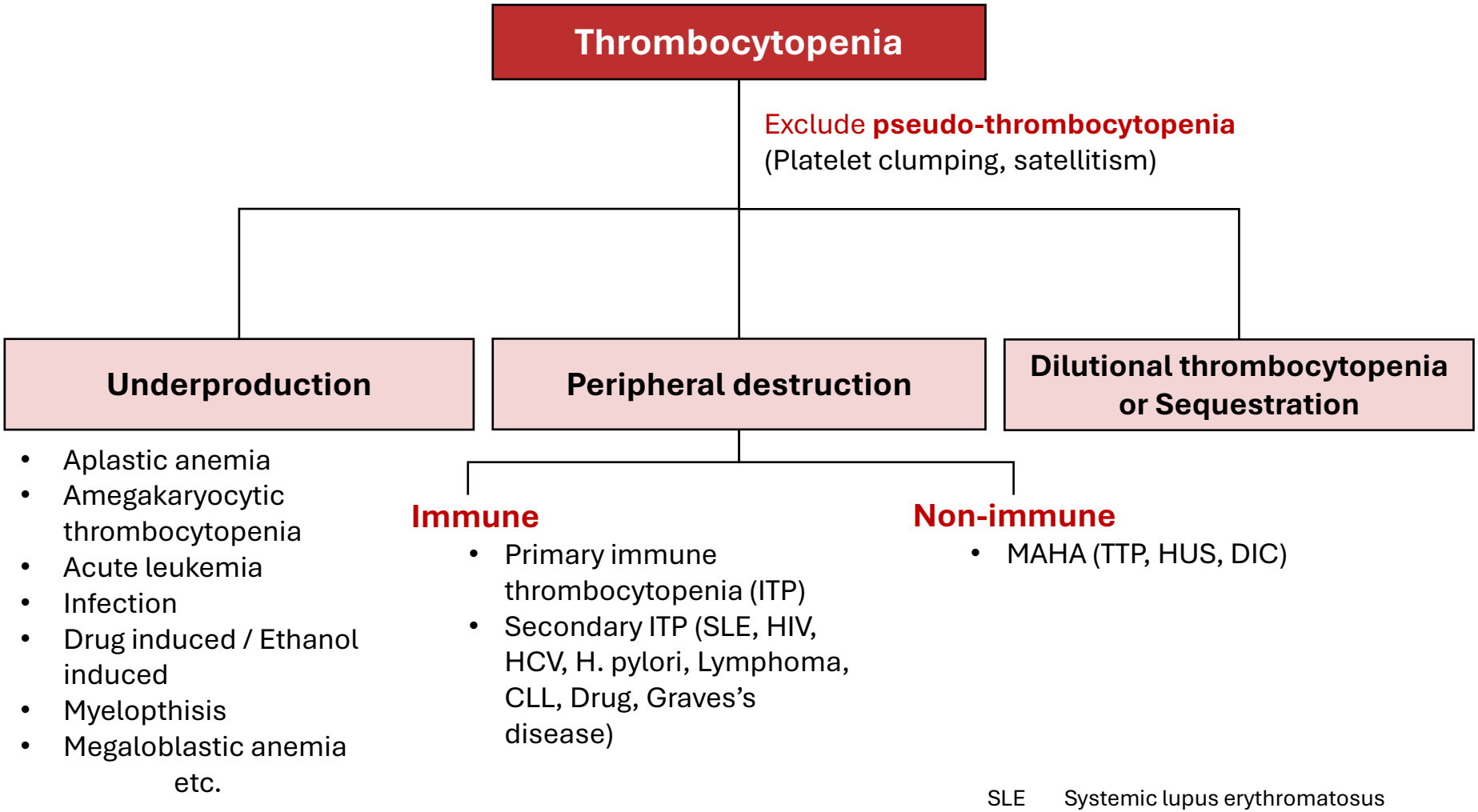
Sophisticate lab

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

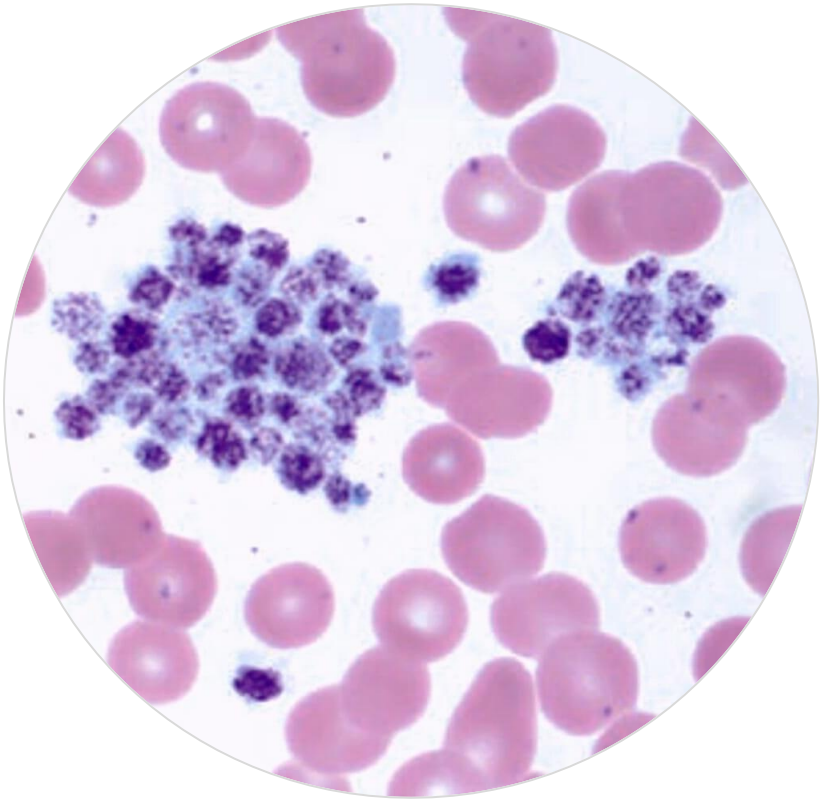


Approach Thrombocytopenia

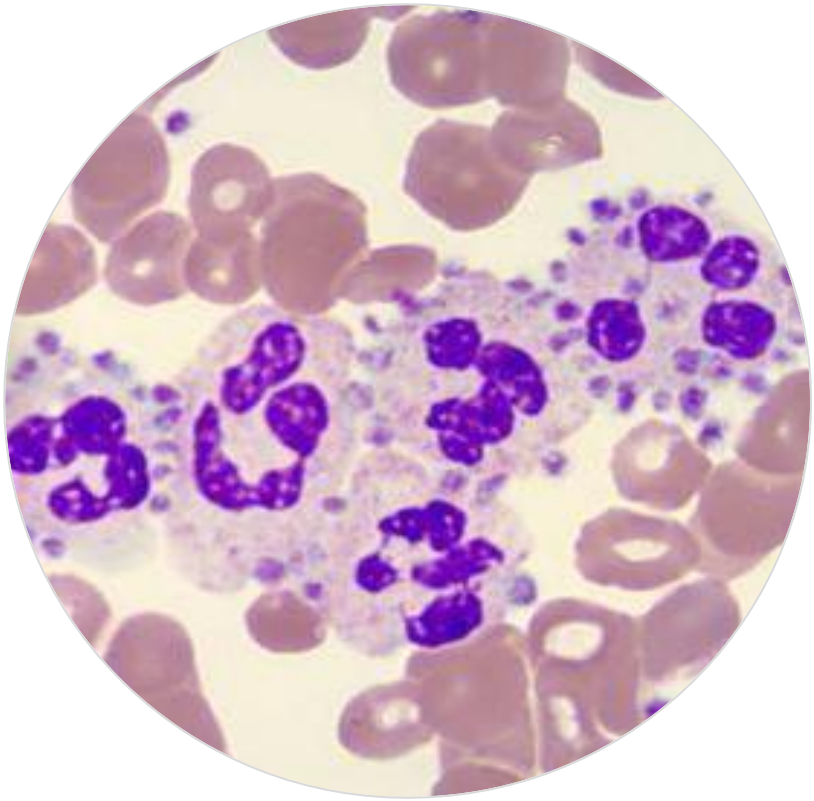


SLE	Systemic lupus erythromatosus
HCV	Hepatitis C virus
CLL	Chronic lymphocytic leukemia
TTP	Thrombotic thrombocytopenic purpura
HUS	Hemolytic uremic syndrome
DIC	Disseminated intravascular coagulation

Pseudo-thrombocytopenia

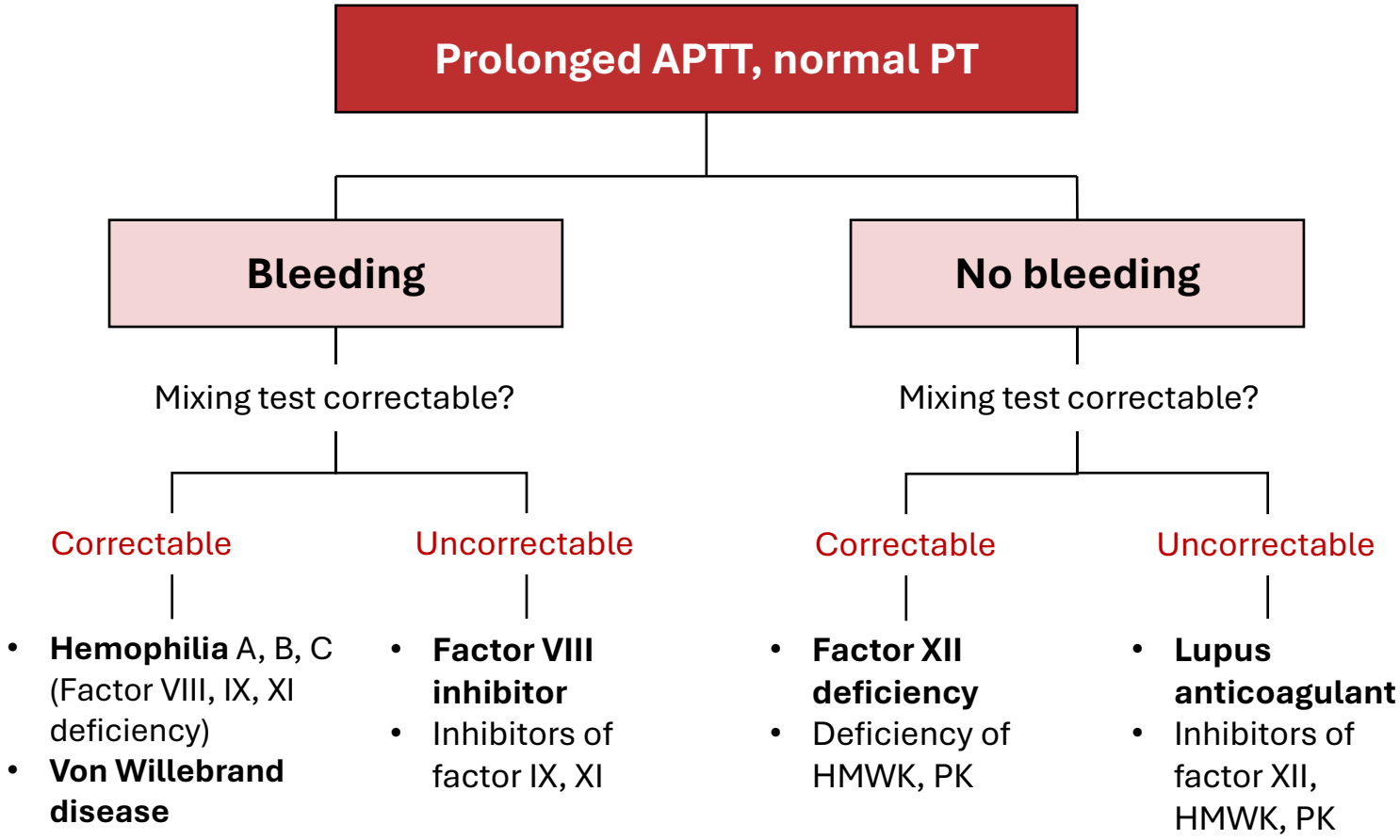


Platelet clumping



Platelet satellitism

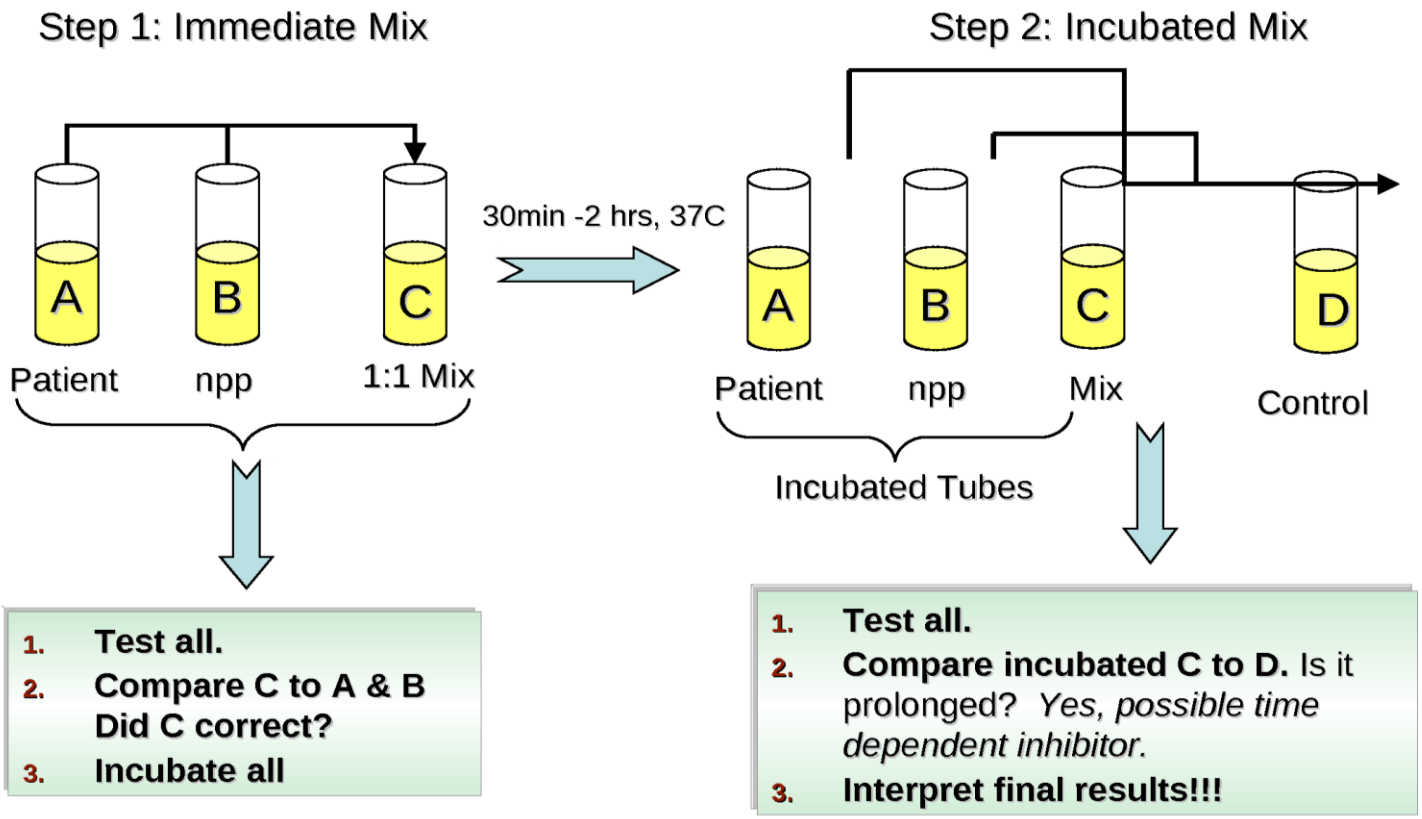
Approach Coagulopathy 1



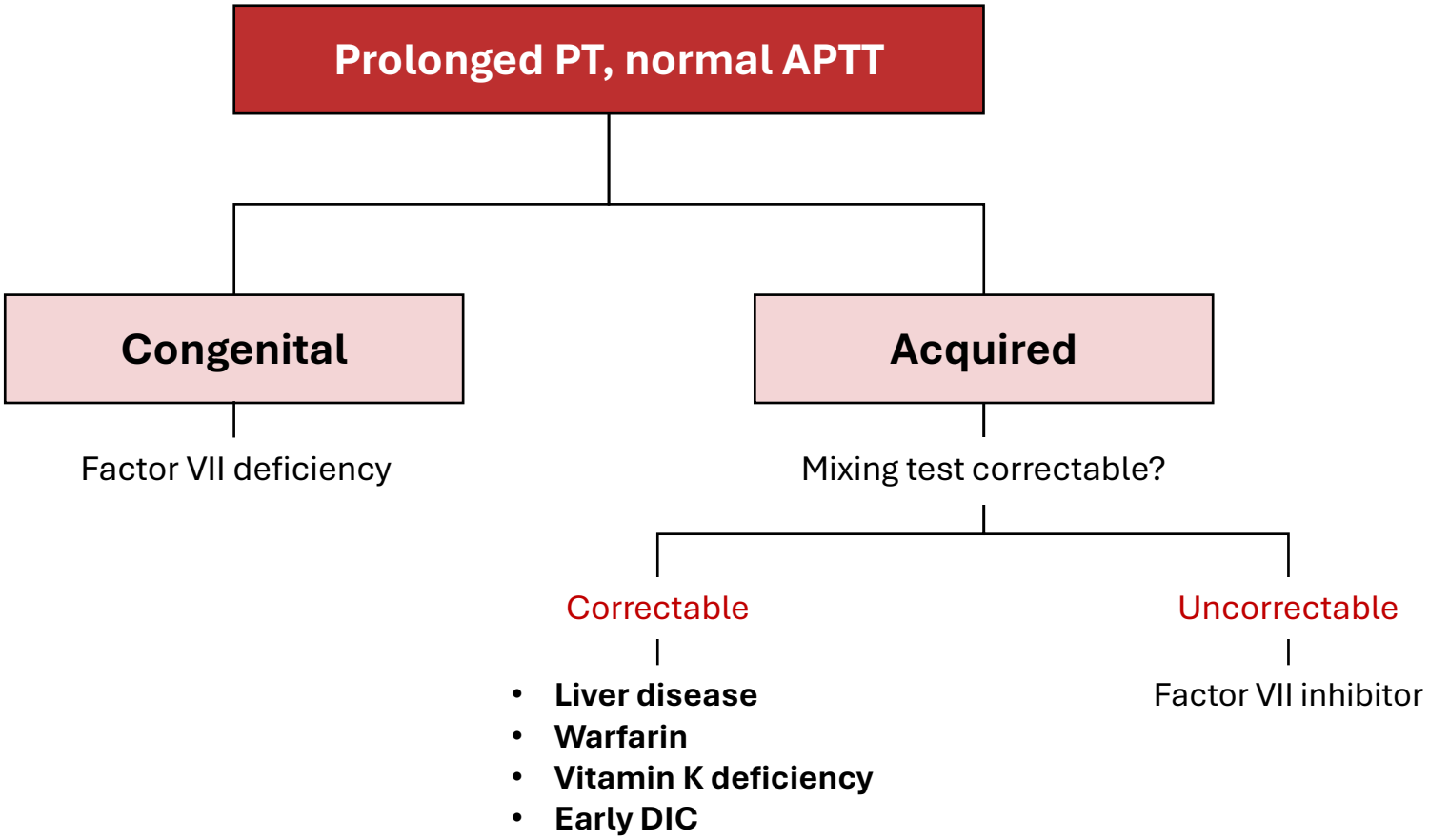
****Mixing study does not correct or prolongs with 1 to 4-hour incubation**

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

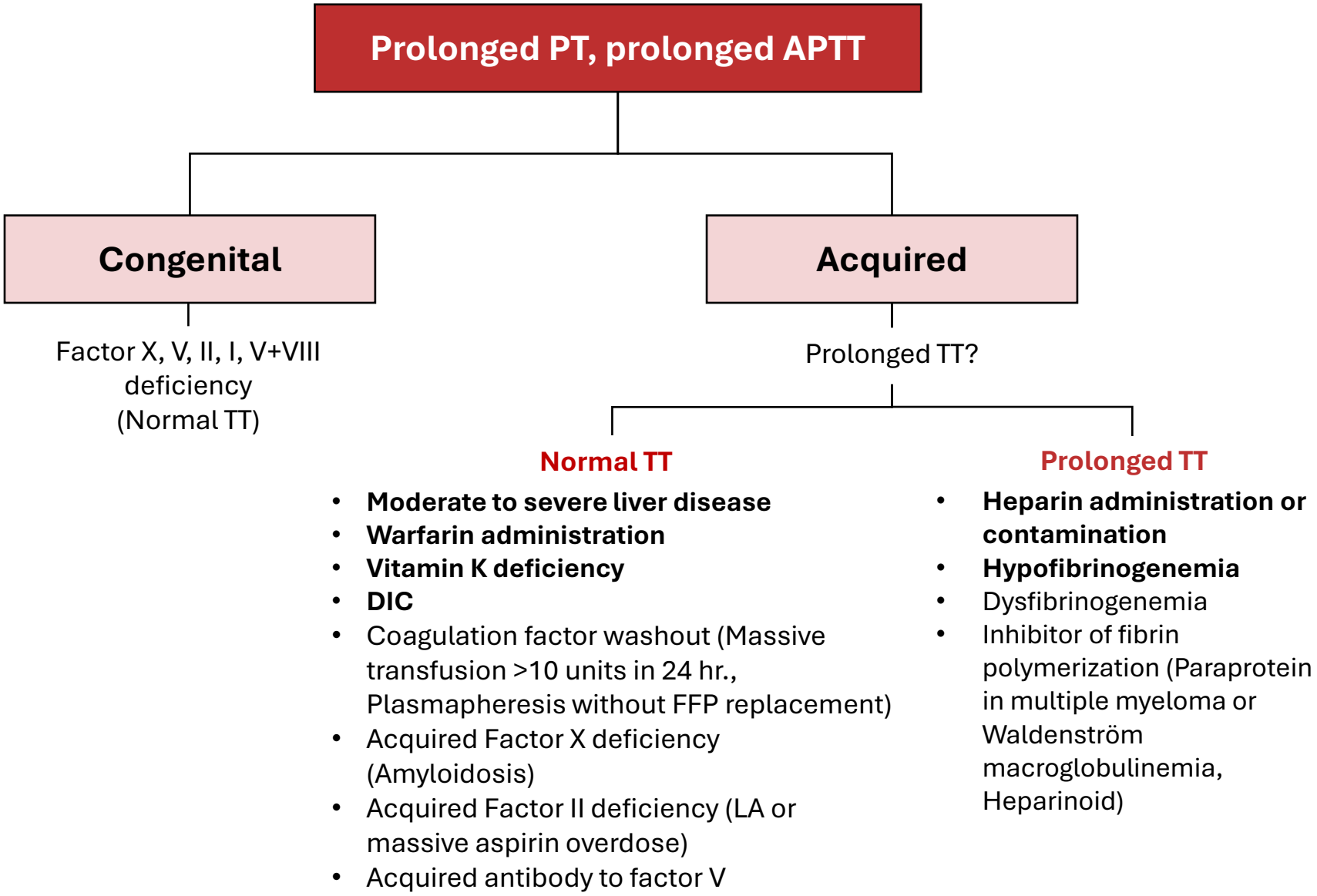
Classical 1:1 Mixing Test



Approach Coagulopathy 2



Approach Coagulopathy 3



Causes of Abnormal Bleeding not Detected
by TT, PT, PTT, bleeding time, and platelet count

Poor fibrin polymer cross-linking

- Factor XIII deficiency / Inhibitor of Factor XIII
- Abnormal fibrinogen

Abnormal or excessive fibrinolysis

- a_2-antiplasmin deficiency
- Increased TPA, TPA inhibitor deficiency
- Urokinase
- Primary fibrinolysis

Mild bleeding disorders

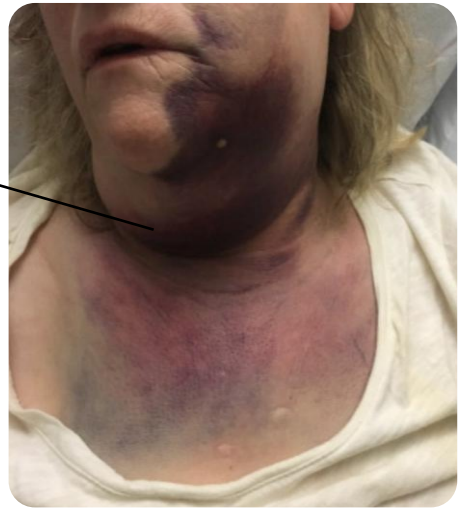
- Platelet dysfunction
- von Willebrand disease

Vascular purpura

- Scurvy
- Amyloid
- Senile purpura
- Vasculitis
- Henoch-Schoenlein purpura
- Connective tissue disorders (Marfan's syndrome, Ehlers-Danlos syndrome)
- Cryoglobulins
- Autoerythrocyte purpura
- Hereditary hemorrhagic telangiectasia

Acquired Factor VIII Inhibitor

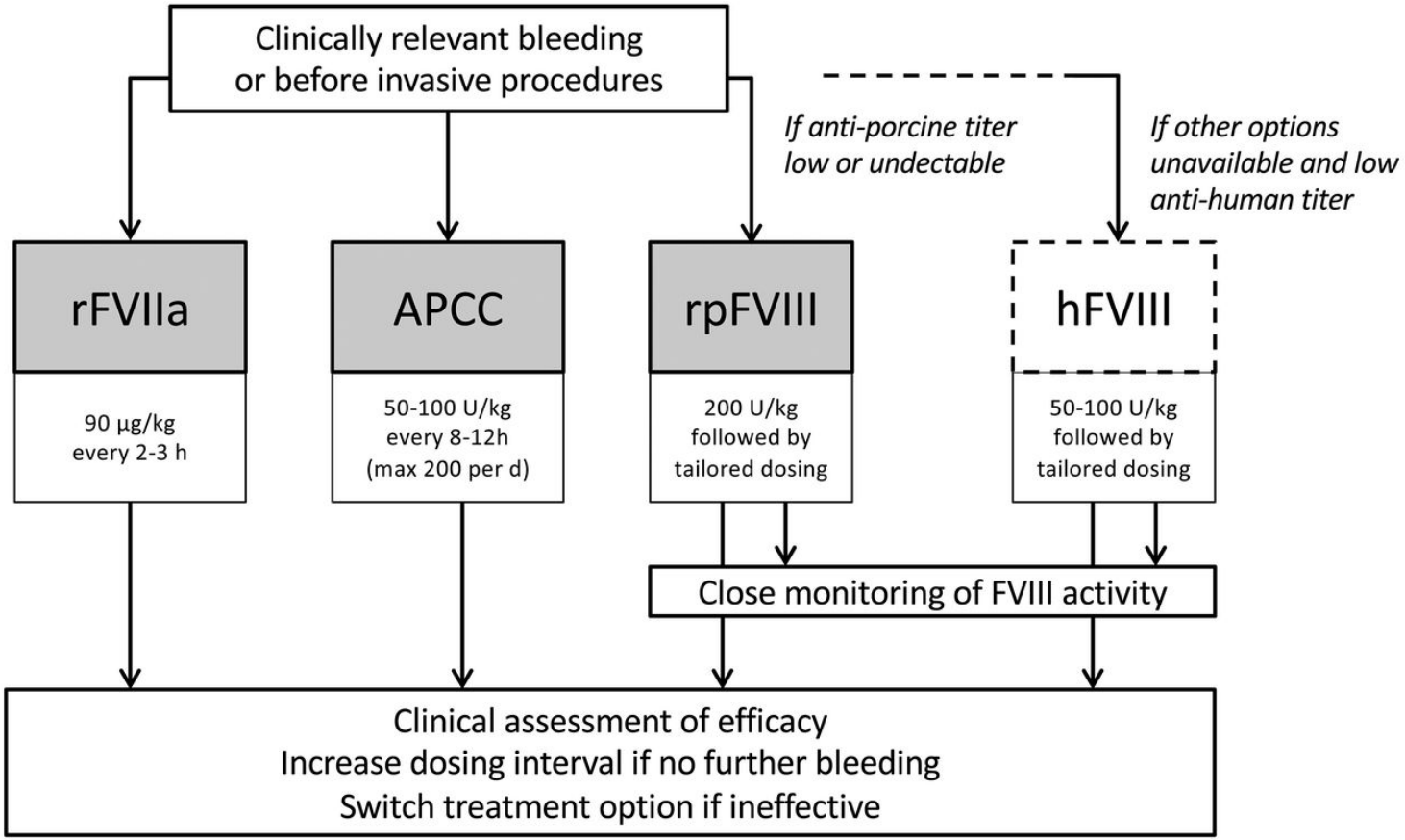
Extensive purpura after a routine tooth extraction



- **Age:** 60-67 years
- **Sex:** M:F = 1:1
- **Pathogenesis:** Autoantibody to factor VIII
- **Clinical Presentations**
  - Purpura, soft tissue or muscle bleeding, hematuria, epistaxis, GI bleeding, Intracerebral hemorrhage
  - Hemarthrosis (Rare)
  - Isolated aPTT prolongation and
  - Uncorrected aPTT after mixing test

- **Causes**
  - Autoimmune diseases (17–18%)
  - Solid tumors
  - Lymphoproliferative malignancies.
  - Skin disorders
    - Pemphigus
    - Epidermolysis bullosa
  - Drugs: Penicillin and interferon
  - Infections
  - Chronic graft-versus-host disease (cGVHD)

Management of Acquired Factor VIII Inhibitor



Case 5: Acquired Factor VIII Inhibitor

- ✓ Approach bleeding tendency
- ✓ Approach thrombocytopenia
- ✓ Approach coagulopathy
- ✓ Diagnosis and management of acquired factor VIII inhibitor

Case 6

Q6

An 18-year-old student presents with a lifelong history of easy bruising and menorrhagia. She has no family history of bleeding disorders. Physical exam is unremarkable.

CBC shows Hb 11.5 g/dL, Hct 35%, MCV 75 fL, platelet count 250,000/μL. PT and aPTT are 12 sec, and 42 sec. vWF antigen is 25% (↓). Factor VIII activity is 30% (↓).

Additional testing shows:

- Ristocetin cofactor activity (vWF:RCo): 15% (↓↓)
- vWF:Collagen Binding (vWF:CB): 50% (relatively preserved)
- vWF:RCo/vWF:Ag ratio: 0.6 (↓)
- Ristocetin-induced platelet aggregation (RIPA) is markedly increased at low ristocetin concentrations, and the abnormal aggregation is corrected by mixing studies with normal plasma.

What is the most likely diagnosis?

A. Acquired von Willebrand syndrome from autoantibodies
B. Hemophilia A
C. Pseudo-von Willebrand disease
D. Von Willebrand disease type I
E. Von Willebrand disease type IIN

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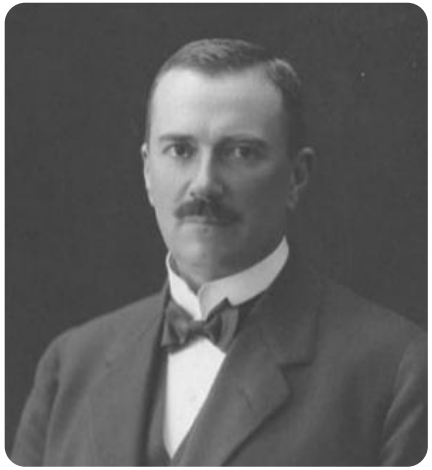
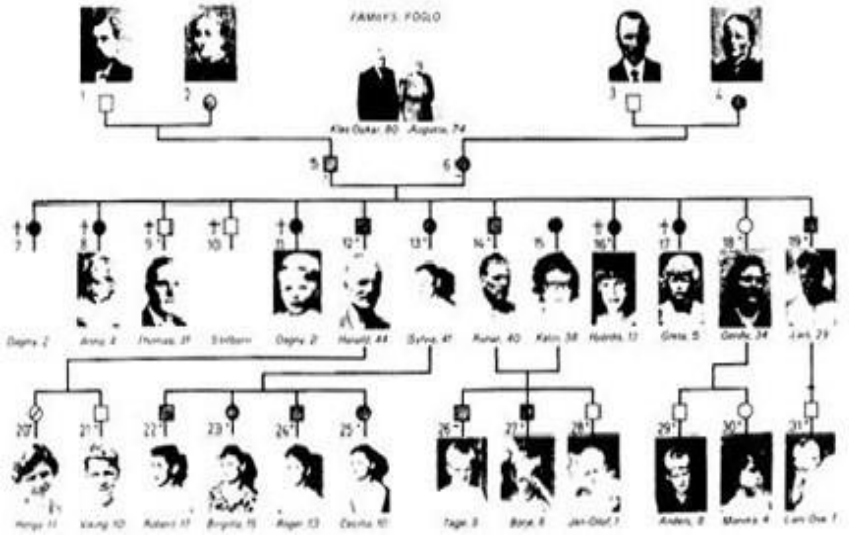
Von Willebrand Disease (vWD)



Erik Adolf von Willebrand
(1870-1949)

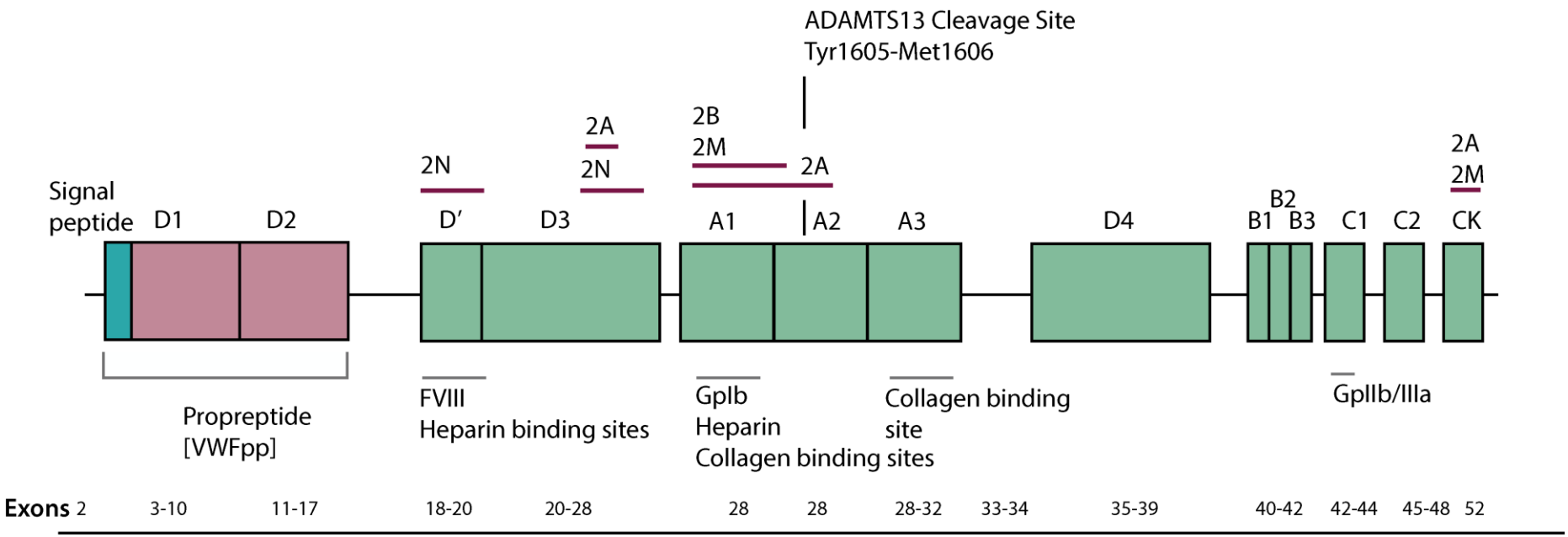


History

- First investigated 1924
- Erik Adolf von Willebrand described a large family with a severe bleeding disorder from the Aland Islands in 1926.
- Differences in bleeding from classic hemophilia:
  - ✓ Lack of joint bleeding
  - ✓ Presence of mucosal bleeding
- Proband died of bleeding during 4th menstrual period

- Most common of the genetically transmitted bleeding disorders
- **Genetics:**
  - Usually inherited, though spontaneous mutations do occur
  - Autosomal dominant, although subtypes may have varying inheritance patterns
  - Equally passed to males and females
  - Inheritance may occur from either parent
  - Gene defect on chromosome 12
- **Prevalence:** 1-2%

The Gene of vWF and Mutations



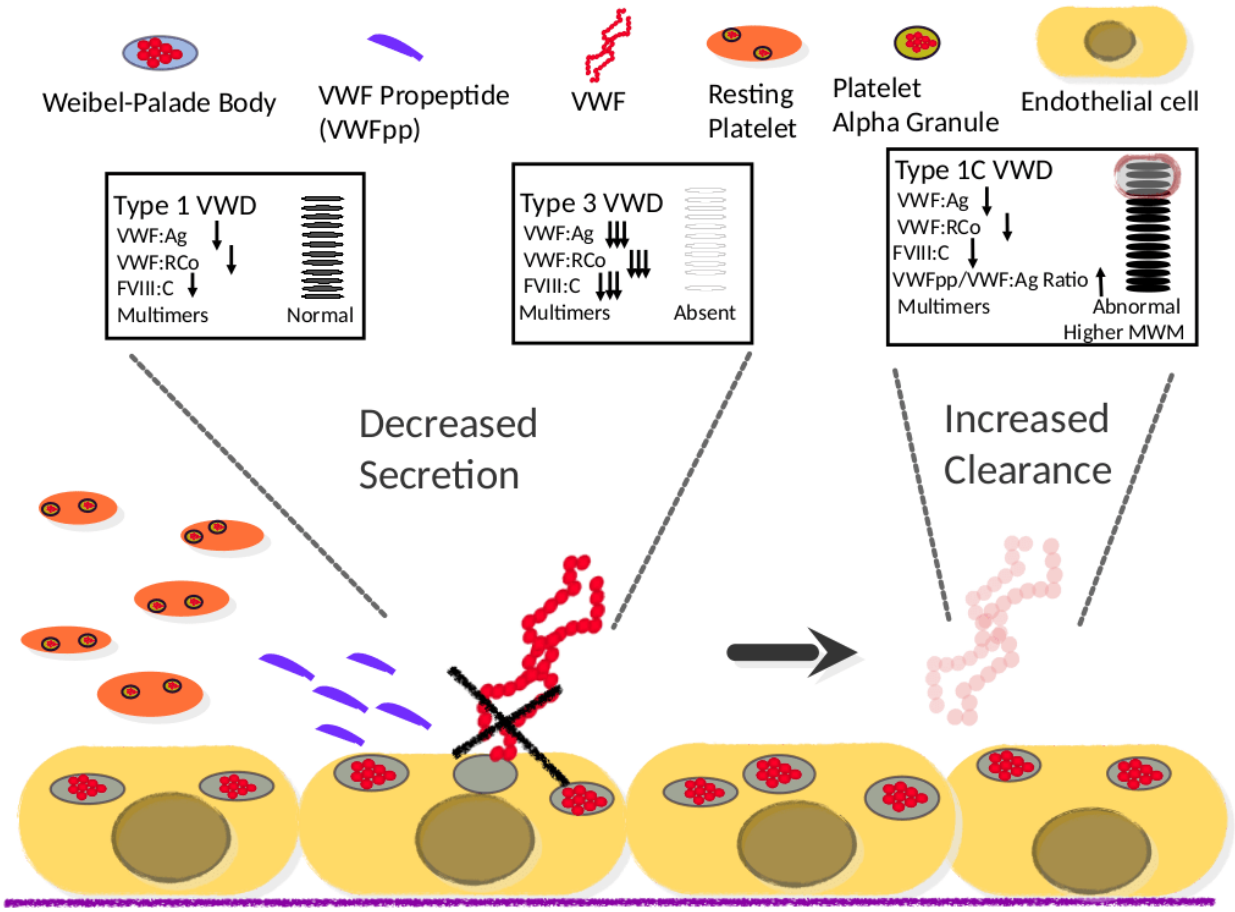
The gene for VWF spans approximately 172kb of genomic sequence, consists of 52 exons, maps to chromosome 12 [12p13.3], and encodes a protein of 2813 amino acids that includes a signal peptide of 22 amino acids, a pre-propeptide of 741 amino acids [residues 23-763] and a mature protein of 2050 amino acids [residues 764-2800]. The mature protein is divided into the domains containing various functional domains.

The mature VWF protein in the plasma has a half-life of approximately 12 (9-15) hours.

Laboratory Tests for vWD

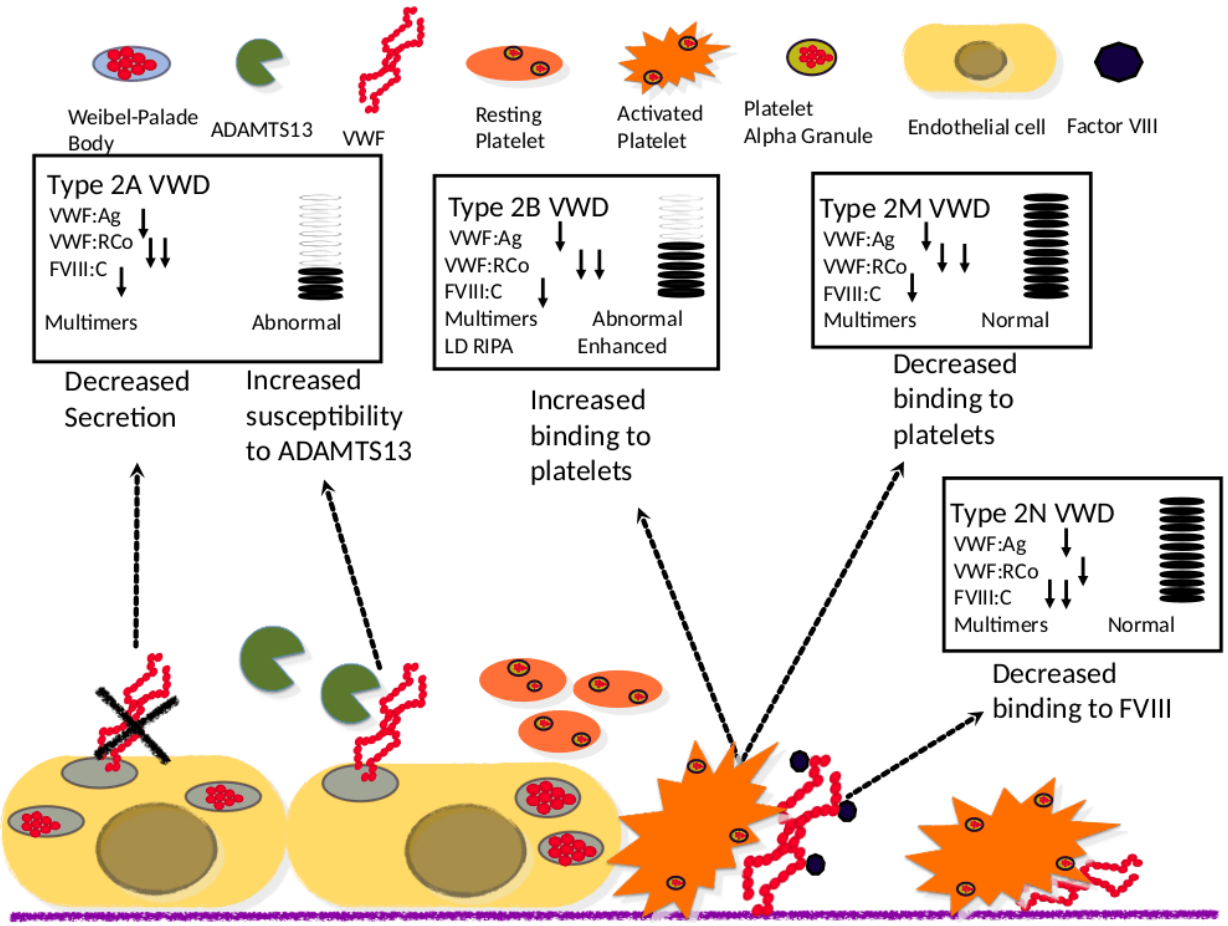
Test	Purpose
Factor VIII coagulant activity (FVIII:C)	Measures the functional activity of factor VIII
von Willebrand factor antigen (VWF:Ag)	Measures the amount of VWF
Ristocetin co-factor and/or collagen binding activity (VWF:RCo and/or VWF:CB)	Measures the functional activity of VWF
von Willebrand factor multimers	Provides a visualization of how well the VWF monomer is multimerized (joined into chains)
Ristocetin induced platelet aggregation (RIPA)	Measures how sensitive VWF is to ristocetin (useful in diagnosing Type 2B VWD)

Quantitative Defects in vWD



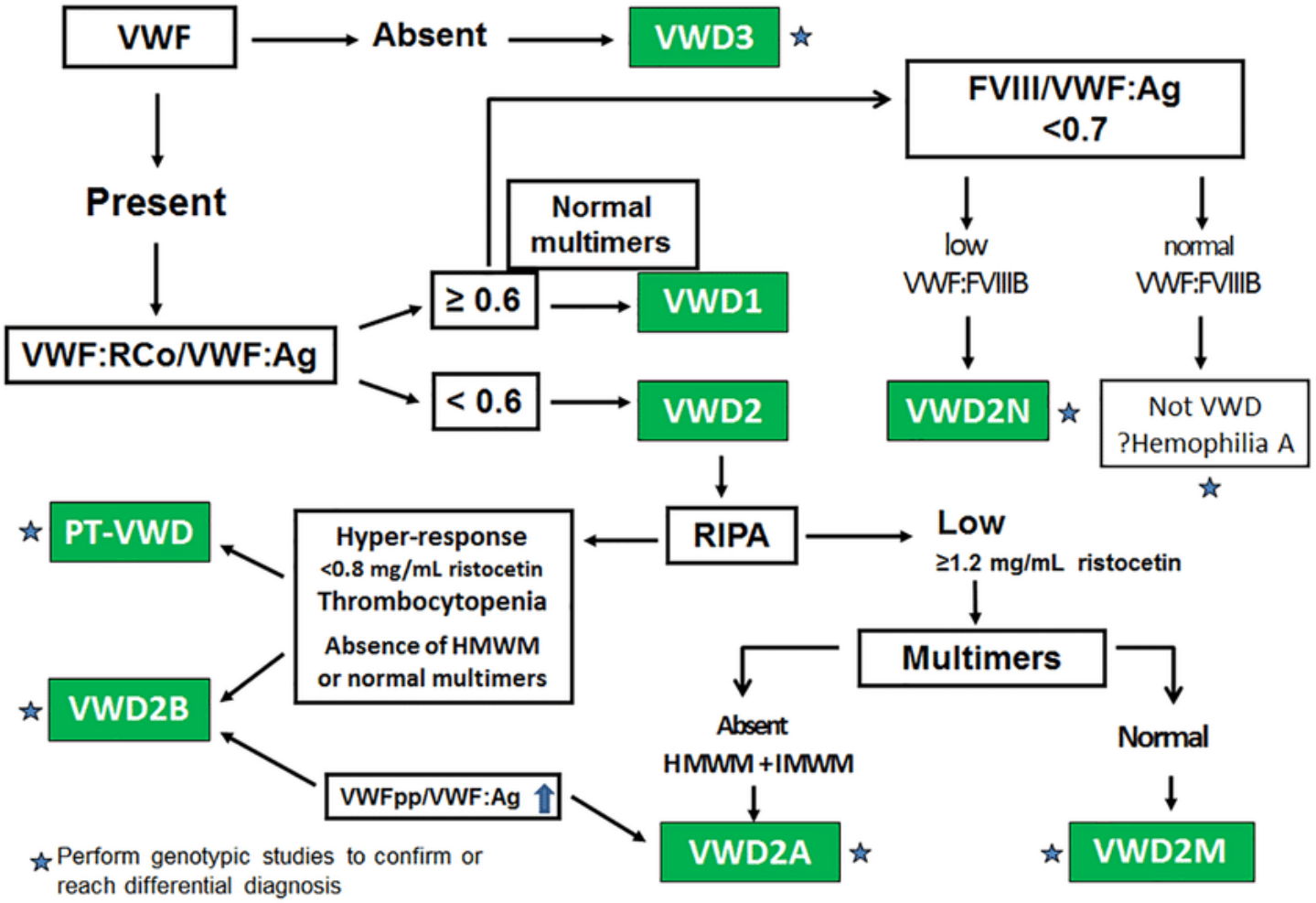
Quantitative defects of von Willebrand factor, as seen in von Willebrand disease types 1 & 3. In the classic presentation, type 1 VWD sees a decrease in VWF:Ag, VWF:RCo, and FVIII:C, and multimer levels are normal. Type 3 VWD presents with the same decreases, but to a much greater degree, and multimers are absent. Types 1 & 3 both show decreased secretion. Type 1C presents similar decreases to type 1, but shows an increase in the ratio of VWFpp to VWF:Ag and an abnormally high quantity of multimers, as well as increased clearance.

Qualitative Defects in vWD



Qualitative defects of von Willebrand factor, as seen in von Willebrand disease type 2. Like types 1 & 3, all forms of type 2 VWD present with a decrease in VWF:Ag, VWF:RCo, and FVIII:C. In type 2A, there is decreased secretion of VWF and an increased susceptibility to ADAMTS13 and abnormal multimers. Type 2B presents with increased binding to platelets, abnormal multimer count, and enhanced LD RIPA. Type 2M shows decreased binding to platelets and multimer levels are normal, while type 2N presents with decreased binding to FVIII and normal multimers as well.

Algorithm of vWD Diagnostic Strategy



VWF, von Willebrand factor; VWD, von Willebrand disease; RIPA, ristocetin-induced platelet aggregation; HMWM, high molecular weight multimers; IMWM, intermediate molecular weight multimers.

Treatment of vWD

Disease Type	Treatment	Alternative or Additional Treatment
Low VWF†	Desmopressin, administered intravenously (0.3 μg per kilogram of body weight), intranasally (total dose, 300 μg [150 μg per nostril]; in patients with body weight <50 kg, only one dose of 150 μg), or subcutaneously (0.3 μg per kilogram)	Alternative or additional treatment: tranexamic acid (1 g, 3 or 4 times daily)
Type 1	Desmopressin, at same doses as above	Additional treatment: tranexamic acid, at same dose as above
Type 2	Desmopressin, at same doses as above, or VWF–factor VIII or VWF concentrate‡	Additional treatment: tranexamic acid, at same dose as above
Type 3	VWF–factor VIII or VWF concentrate	Additional treatment: tranexamic acid, at same dose as above

VWF denotes von Willebrand factor.
Patients presenting with bleeding symptoms and VWF levels between 30 and 50 IU per deciliter (the lower limit of the normal range) are classified as having low VWF but not von Willebrand's disease.
Desmopressin is contraindicated in patients with type 2B disease.

Treatment of vWD

Indication for VWF–Factor VIII or VWF Concentrate*	Dose†	Target Levels for VWF–Ristocetin Cofactor Activity and Factor VIII Activity‡	Duration of Treatment
	IU/kg	*IU/dl*	*days*
Bleeding			
Mild to moderate	20–40	Peak, >50–80 on day 1; trough, >30 after day 1	1–3
Severe	50	Peak, >100 on day 1; trough, >50 after day 1	7–10
Intervention			
Dental extraction	25	Peak, >50 on day 1	1
Minor surgery	30–60	Peak, >50–80 on day 1; trough, >30 after day 1	1–5
Major surgery	50–60	Peak, >100 on day 1; trough >50 after day 1	7–10
Delivery	40–50	Peak >100 on day 1; trough, >50 after day 1	3–4

* VWF–factor VIII or VWF concentrate is administered in patients with type 3 disease and in patients with type 1 or 2 disease who do not have a response to desmopressin or in whom it is contraindicated.

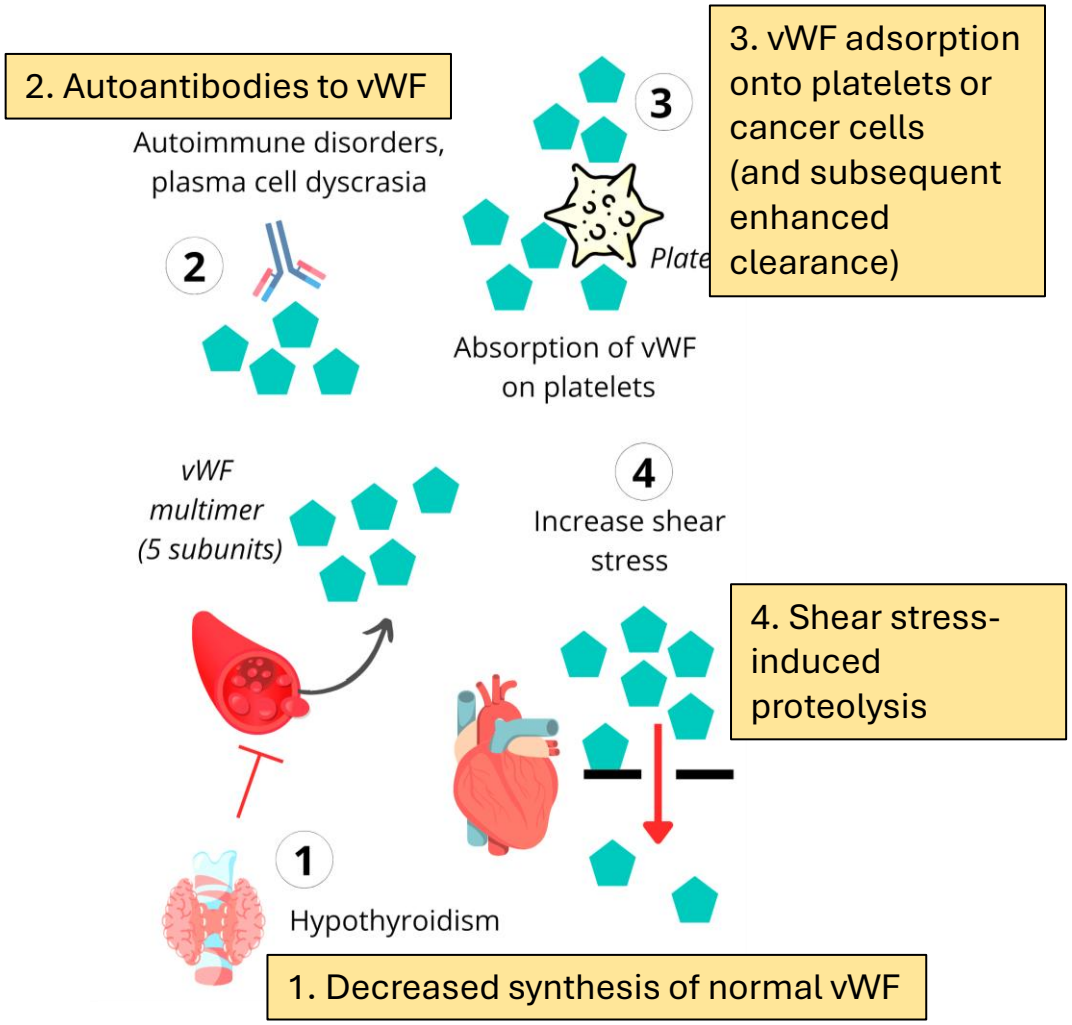
† The dose of factor concentrate depends on the type of concentrate used. If VWF–factor VIII concentrate is used, the dose of factor concentrate also depends on the brand of concentrate. The dose is based on an anticipated in vivo recovery (2 IU per deciliter for every unit of factor VIII activity infused per kilogram of body weight and 1.5 IU per deciliter for every unit of VWF–ristocetin cofactor activity infused per kilogram) and the target levels of both VWF–ristocetin cofactor activity and factor VIII activity. If high-purity or recombinant VWF concentrate is administered, a single dose of factor VIII concentrate should also be administered in order to achieve the target level of factor VIII immediately.

‡ Factor VIII activity, and preferably also VWF–ristocetin cofactor activity, should be monitored regularly in all patients undergoing surgical procedures and all patients with severe bleeding episodes. If measurement of VWF–ristocetin cofactor activity is not immediately available at a local laboratory, dosing should be based on factor VIII activity levels.

Leebeek F. *NEJM*. 2016.

Acquired von Willebrand Syndrome

- **Mechanism and etiologies**



- A diagnosis of AvWS should be suspected when new onset of mucosal bleeding occurs in patient with a known predisposing condition, and whom the platelet count and PT are both normal.
- APTT may be normal or high.
- Diagnosis can be confirmed by measuring vWF activity, vWF antibodies, and FVIII activity.
- **Treatment options for acute bleeding** in AvWS include:
  - vWF concentrate
  - Desmopressin
  - IVIG (in the presence of anti-vWF antibodies)
- **Long term treatment** of AvWS is treatment of underlying condition.

Case 6: Platelet-type von Willebrand disease

- ✓ Diagnosis and management of von Willebrand disease
- ✓ Mechanism of acquired von Willebrand syndrome

Case 7

Q7

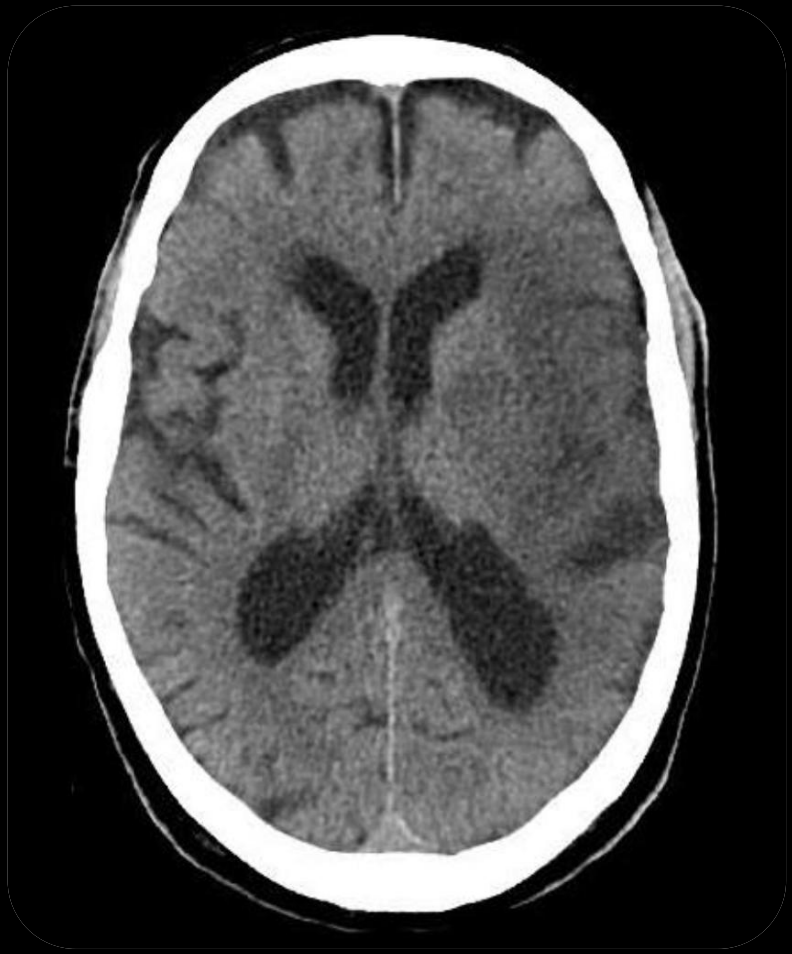
A 30-year-old male banker presents with sudden right hemiparesis and aphasia. She has no underlying disease. Physical examination shows left facial palsy, and right motor weakness grade 3 with hyperreflexia.

CBC shows Hb 12.0 g/dL, Hct 36%, MCV 85, WBC count 15,000/μL (N 70, L 25, M 3), Platelet count 400,000/μL. Coagulation profile shows APTT of 42 sec, PT of 12 sec, and TT of 15 sec. D-dimer is 3000 ng/ml. Creatinine is 0.8 mg/dL.

EKG reveals normal sinus rhythm.
Echocardiogram demonstrates good ejection fraction without regional wall abnormalities.
There is no detectable oscillating mass at cardiac valves.

What is the most likely cause of thrombosis?

A. Acquired antithrombin deficiency
B. Antiphospholipid syndrome
C. Homozygous protein S deficiency
D. Patent foramen ovale
E. Systemic AL amyloidosis



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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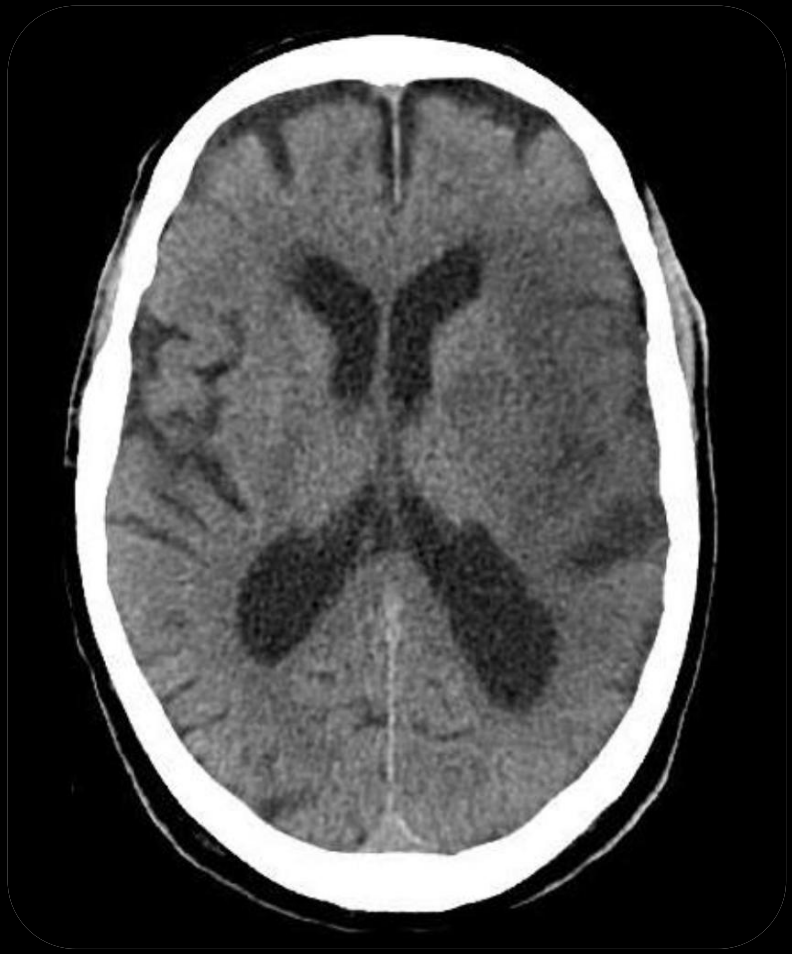

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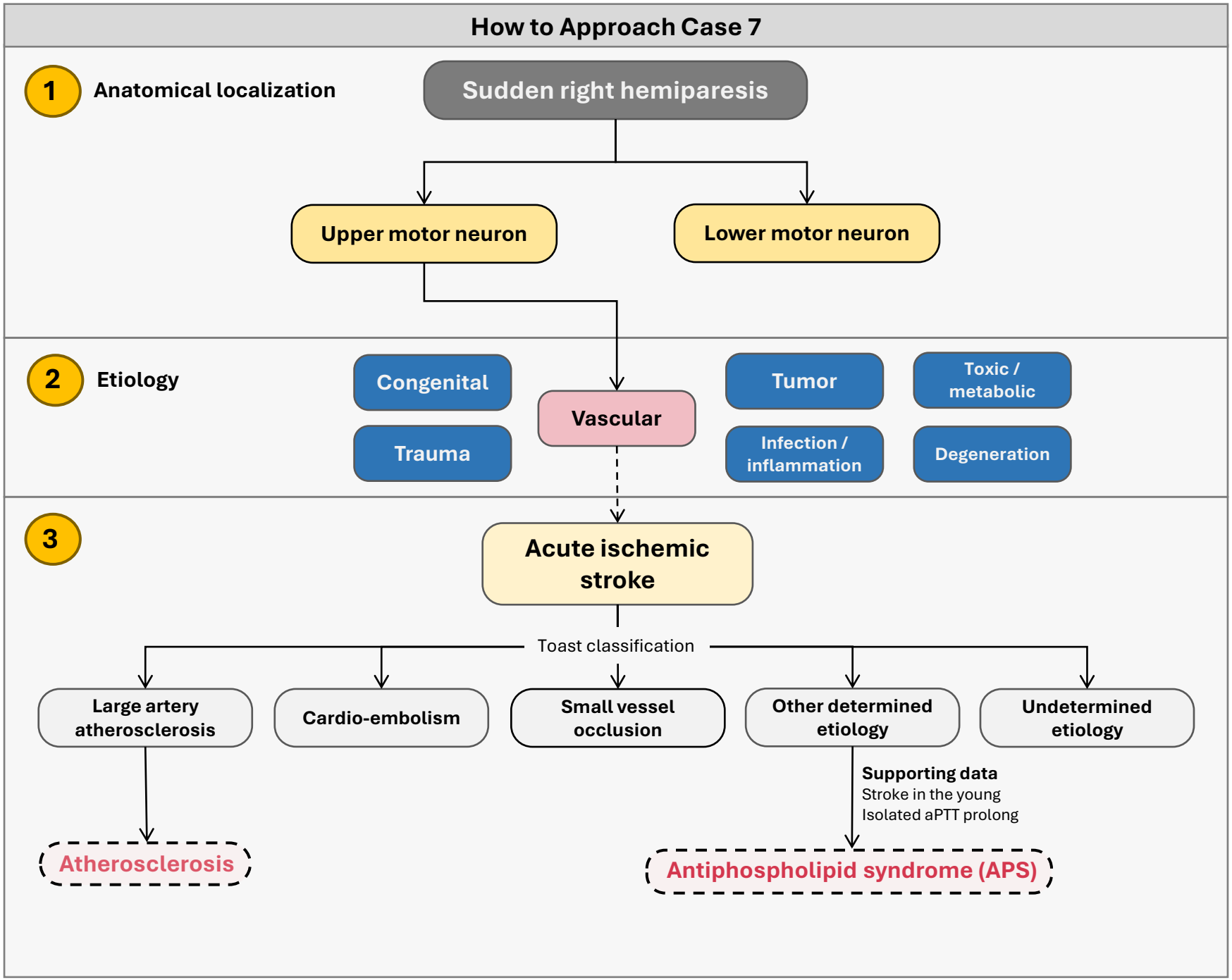
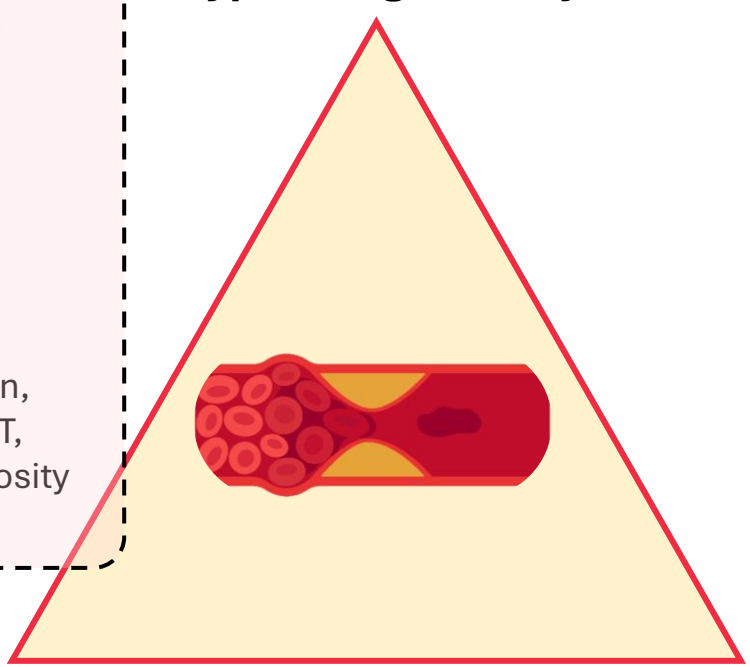

How to Approach Case 7
1
Anatomical localization
Sudden right hemiparesis
Upper motor neuron
Lower motor neuron
2
Etiology
Congenital
Trauma
Vascular
Tumor
Infection / inflammation
Toxic / metabolic
Degeneration
3
Acute ischemic stroke
Toast classification
Large artery atherosclerosis
Cardio-embolism
Small vessel occlusion
Other determined etiology
Undetermined etiology
Supporting data
Stroke in the young
Isolated aPTT prolong
Atherosclerosis
Antiphospholipid syndrome (APS)

Virchow's Triad

Arterial
Inherited: Homocysteinemia
Acquired: Leukostatic syndrome
Venous
Inherited: Protein C, Protein S, Antithrombin deficiency, Factor V Leiden, Prothrombin G20210
Acquired: Nephrotic syndrome
Both
Malignancy, APS, Drugs (Estrogen, Thalidomide), DIC, TTP, PNH, HIT, MPNs, Splenectomy, Hyperviscosity syndrome

Hypercoagulability



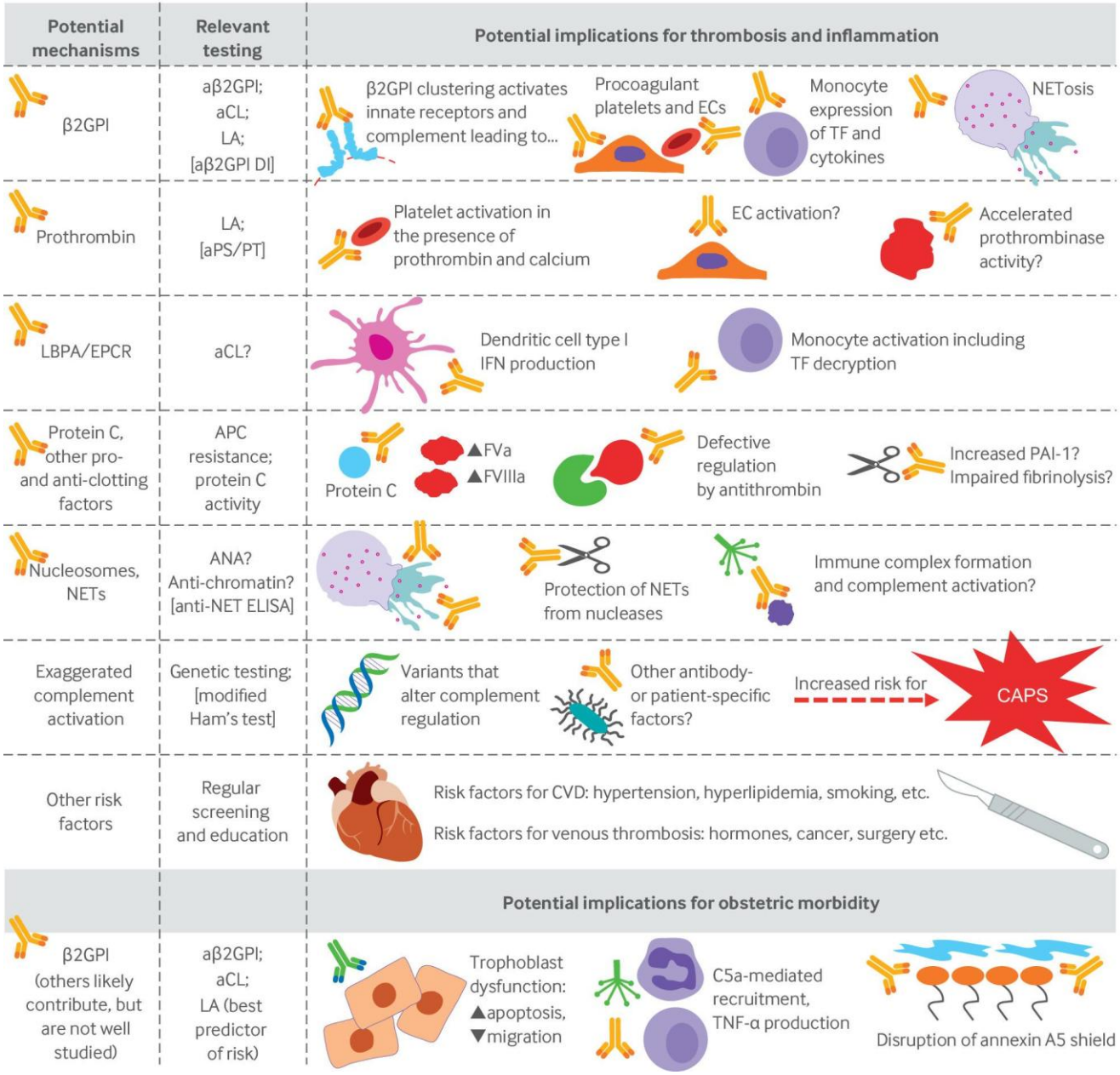
Endothelial Injury

Arterial
Atherosclerosis
Venous
Catheter
Local injury (Trauma, Surgery, Inflammation)

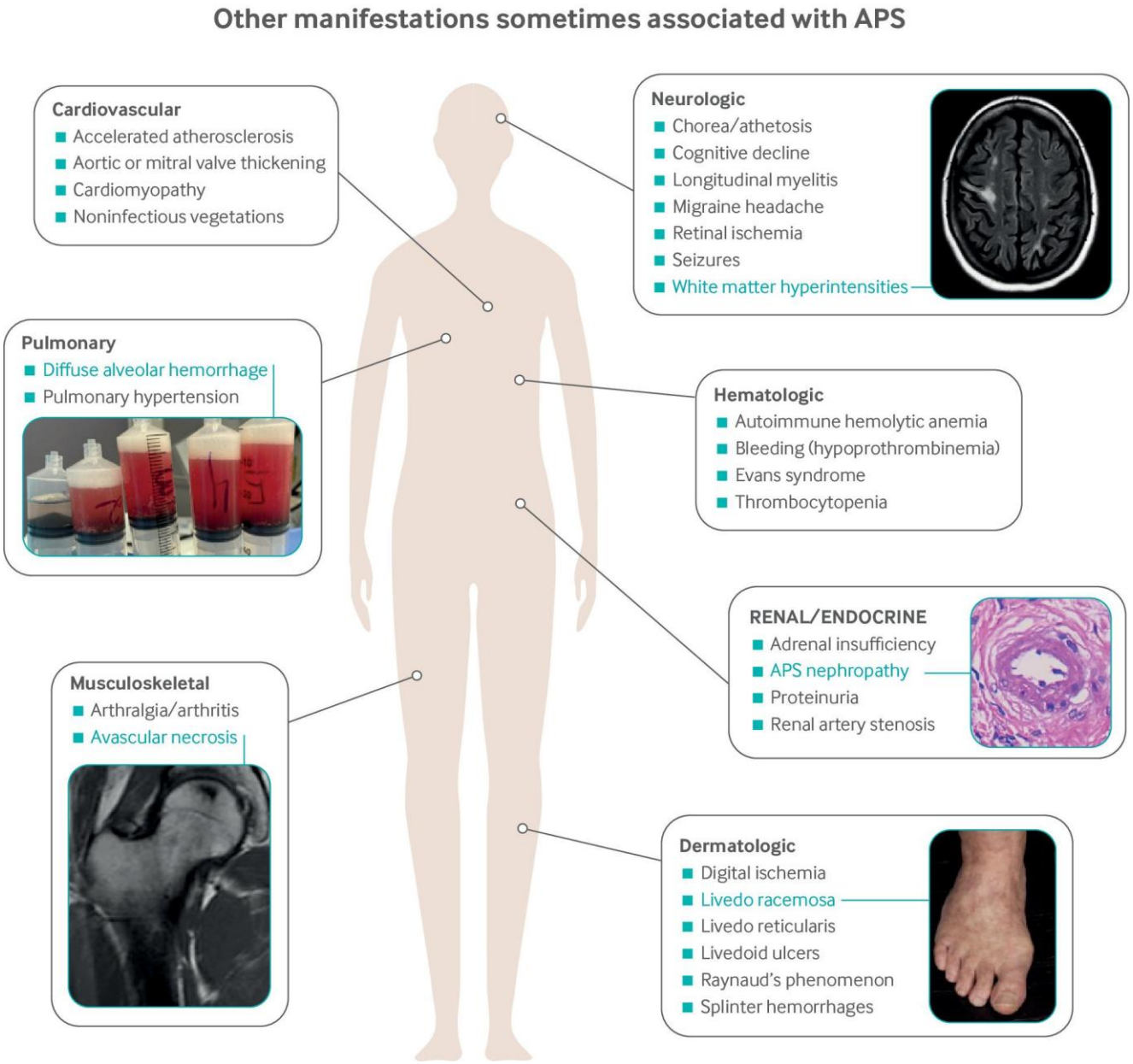
Venous Stasis

Arterial
Atrial fibrillation
Aneurysm
Venous
Immobilization
Cast
Venous compression
Chronic venous insufficiency

Potential Mechanisms of APS



Clinical Manifestations Associated with APS



2023 ACR/EuLAR Classification Criteria of APS

Entry criteria

At least 1 documented clinical criterion listed below (domain 1-6) + +aPL test within 3 years of the clinical criterion

Present

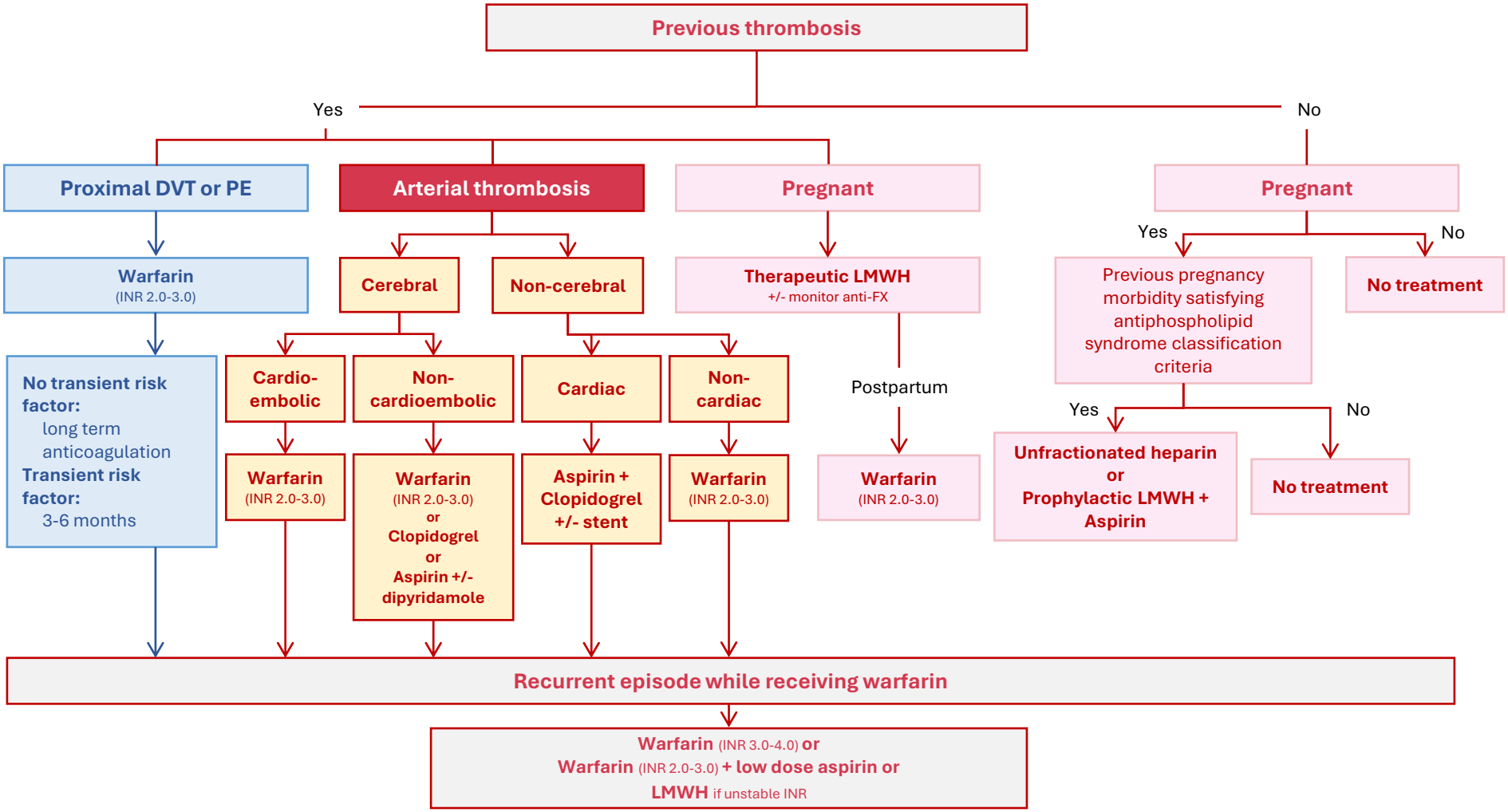
Clinical domains and criteria	Weight		Weight
D1. Macrovascular (VTE)		**D2. Macrovascular (AT)**	
VTE with a high-risk VTE profile	1	AT with a high-risk CVD profile	2
VTE without high risk VTE profile	3	AT without high risk CVD profile	4
D3. Microvascular		**D4. Obstetric**	
Suspected: 1 or more of the following	2	≥3 consecutive pre-fetal (<10w) and/or early fetal (10-15w6d) deaths	1
Livedo racemose, livedoid vasculopathy lesion, aPL nephropathy, Pulmonary hemorrhage (PH)	5	Fetal death (16-33w6d) without preeclampsia (PEC) or placental insufficiency (PI)	1
Established by pathology: 1 or more of the following		PEC or PI with/without fetal death	3
Livedoid vasculopathy, aPL nephropathy, PH, Myocardial disease, adrenal hemorrhage		PEC and PI with/without fetal death	4
D5. Cardiac valve		**D6. Hematology**	
Thickening	2	↓platelet count (20-130x10^9/L)	2
Vegetation	4		
Laboratory (aPL) domains and criteria	**Weight**		**Weight**
D7. Lupus anticoagulant (LAC)		**D8. aPL test by solid phase assay**	
+LAC (1 time)	1	Moderate or high +(IgM) (aCL and/or aβ2-GPI)	1
+LAC (Persistent)	5	Moderate +(IgG) (aCL and/or aβ2-GPI)	4
		High +(IgG) (aCL or aβ2-GPI)	5
		High +(IgG) (aCL and aβ2-GPI)	7

Total score

Classify as APS for **research** purposes;
≥3 pts. From clinical domains AND ≥3 pts. From laboratory domains

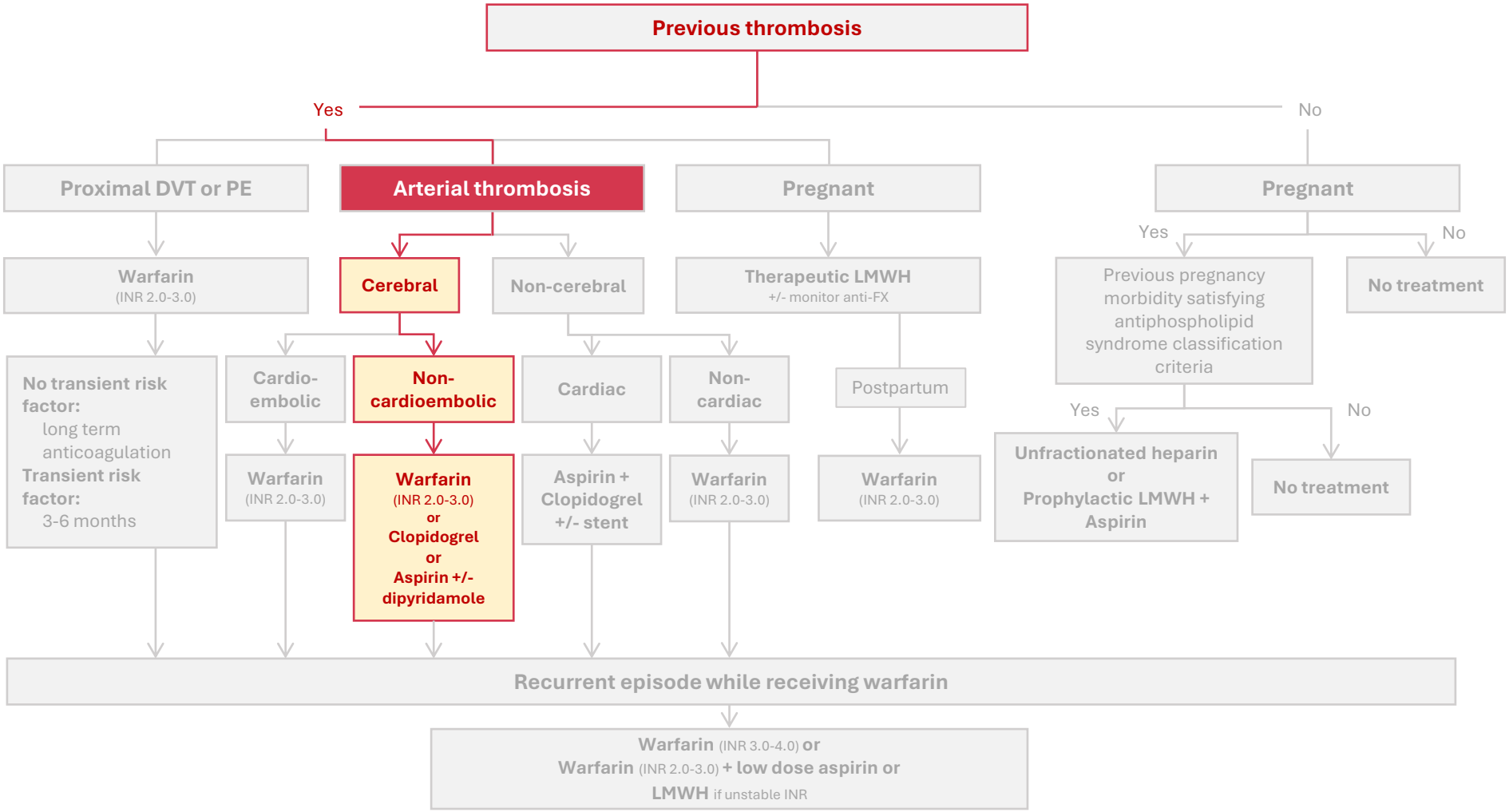
Barbhaiya M, Zuily S, Naden R, et al. *Ann Rheum Dis*. 2023;82:1258–1270.

Treatment Algorithm of APS



Giannakopoulos B, Krilis SA. *Blood*. 2009;114:2020–2030.

Treatment Algorithm of APS



Giannakopoulos B, Krilis SA. *Blood*. 2009;114:2020–2030.

Case 7: Acute ischemic stroke with Antiphospholipid syndrome

- ✓ Approach thrombosis
- ✓ New diagnostic criteria of antiphospholipid syndrome
- ✓ Management of thrombosis in antiphospholipid syndrome

Case 8

Q8

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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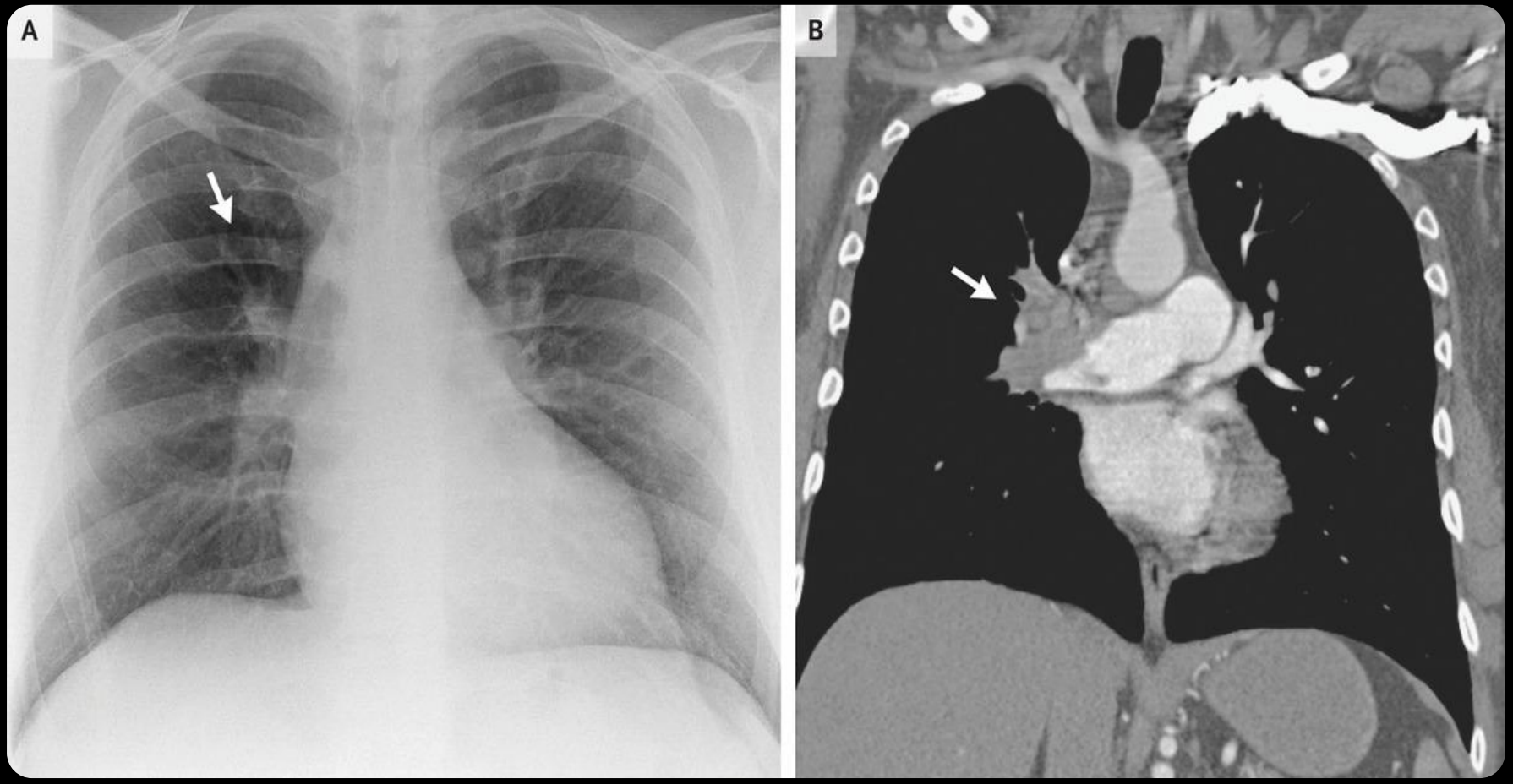
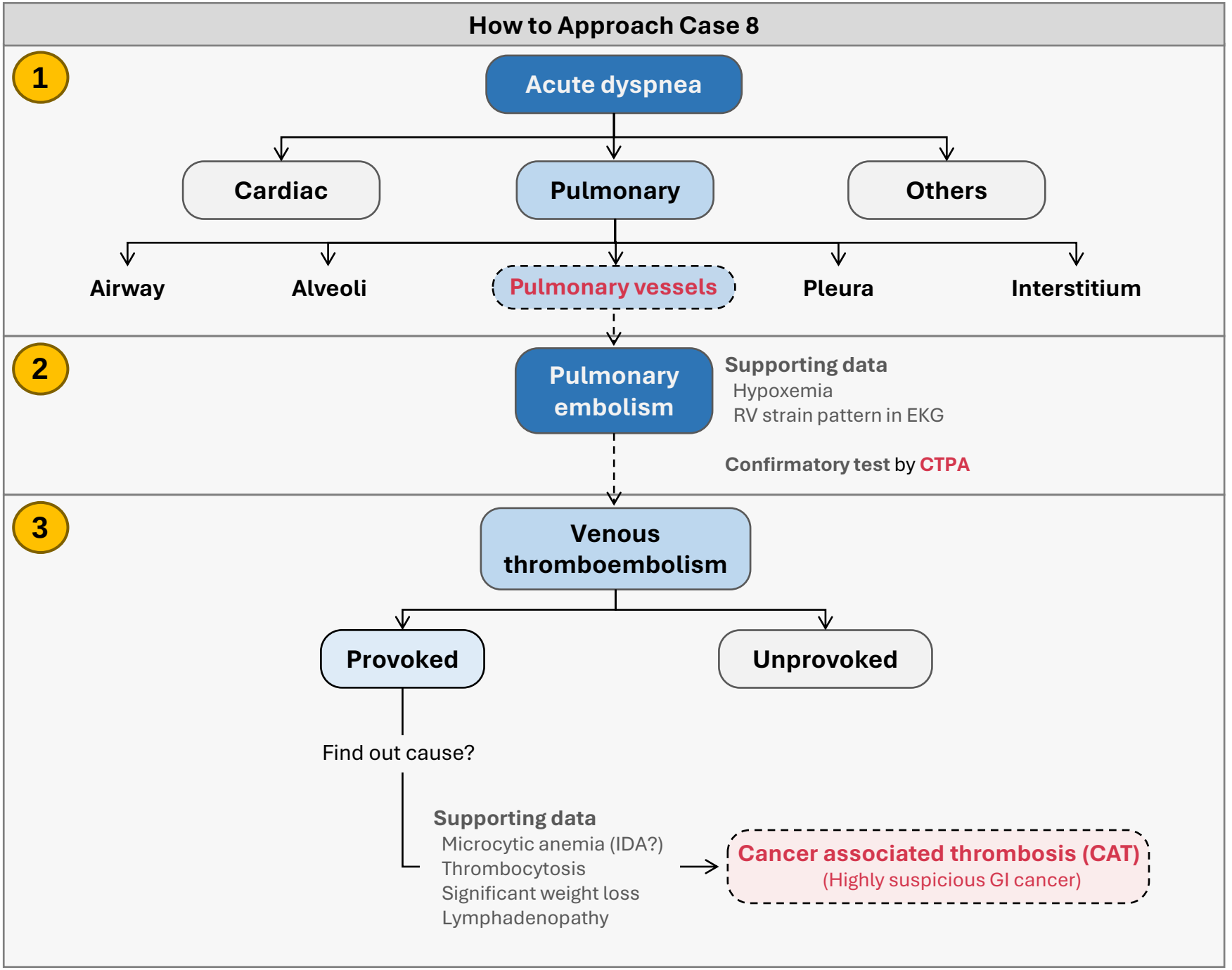


A: CXR shows ‘Westermark sign’ in the right lung.

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


How to Approach Case 8
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)

Diagnosis and Management of Pulmonary Embolism

2-level PE Wells score

Clinical features	Points
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpitation of deep veins)	3
An alternative diagnosis is less likely than PE	3
Heart rate more than 100 bpm	1.5
Immobilization for more than 3 days or surgery in previous 4 weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1
Malignancy (on treatment, treated in the last 6 months, or palliative)	1
PE likely: More than 4 points PE unlikely: 4 points or less	

Well score 4.5 points

Adapted from Wells et al. (2000)

Suspected PE

Determined 2-level PE Wells score

Well score >4 points
PE likely

Well score ≤4 points
PE unlikely

Quantitative D-dimer test and result in 4 hours
or
Interim therapeutic anticoagulation while awaiting result

D-dimer +ve

D-dimer -ve

Immediate CTPA
or
Interim therapeutic anticoagulation while awaiting CTPA

CTPA +ve

CTPA -ve

Diagnose PE and offer or continue treatment

DVT suspected

DVT not suspected

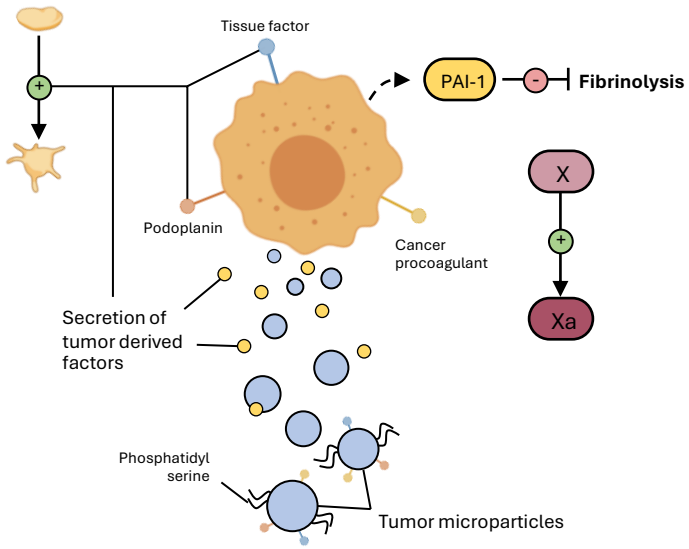
Stop anticoagulation and consider other diagnosis

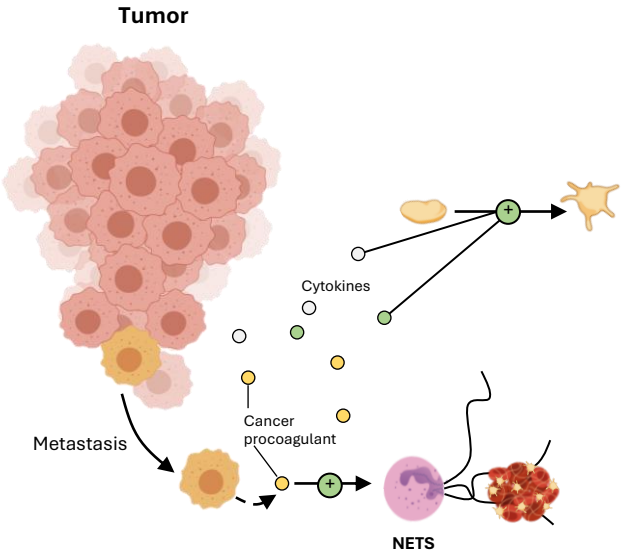
Consider proximal leg vein ultrasound scan

Cancer Associated Thrombosis (CAT)

- 4-20% of cancer patients will have VTE during the course of their disease. (15% symptomatic, 50% Asymptomatic, 50% autopsy)
- Highest incidence of VTE in cancer occurs within first 3 months.
- VTE is the second most common cause of death in cancer patients

Mechanism of CAT





Direct mechanisms

- Direct activation of coagulation and platelets through several factors expressed on or released from cancer cells.

Indirect mechanisms

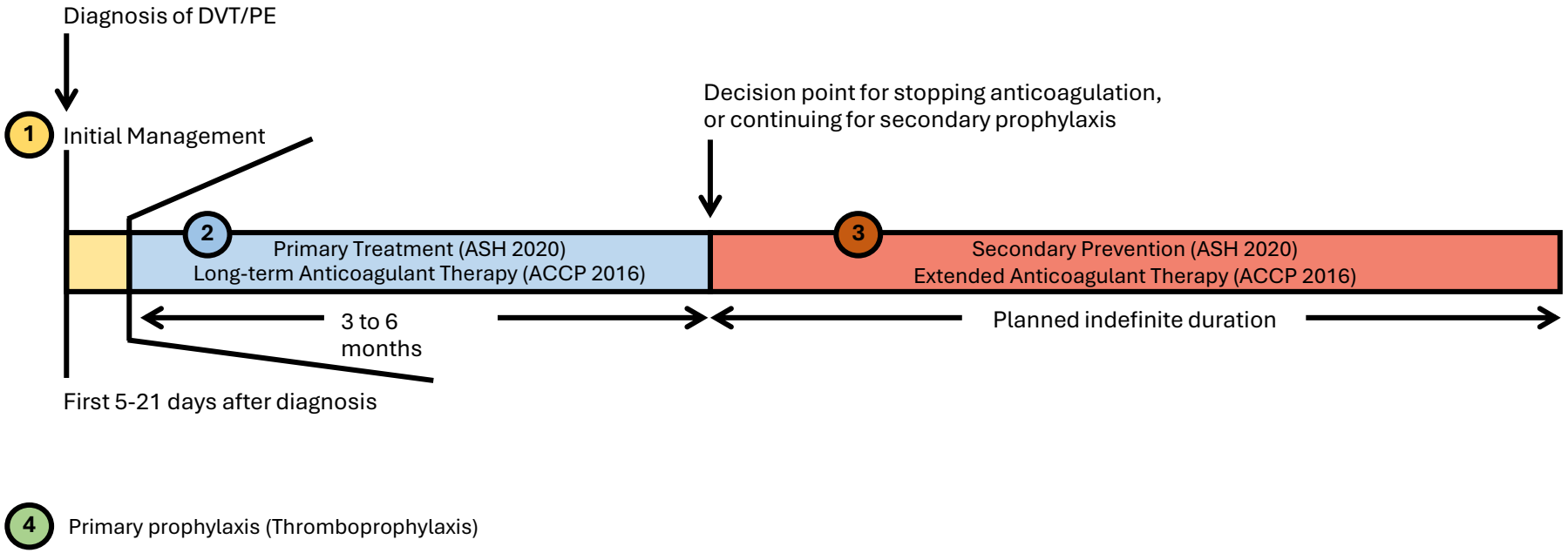
- Metastatic cancer cells disseminate and intravasate into nearby blood vessels.
- Inflammatory cytokine secretion from tumor cells cause activation of platelets and promote a procoagulant phenotype in endothelial cells.
- Cancer-derived factors stimulate neutrophils to release neutrophil extracellular traps (NETs) that act as scaffold to entrap platelets and RBC.

Razak NBA. *Cancers*. 2018.

Cancer and Risks of Venous Thromboembolism (VTE)

Cancer-related factor	Treatment-related factor	Patient-related factor	Biomarkers
• Tumor type: - Pancreas - Stomach - Gynecology - Lung - Renal - Primary brain - Lymphoma • Advanced stage • Initial period after diagnosis (3-6 months) • Histology (Adeno-carcinoma)	• Major surgery • Hospitalization • Cancer therapy - Chemotherapy - Hormonal therapy - Anti-angiogenesis drugs • Erythropoiesis stimulating agents • Central vein catheters	• Older age • Female sex • Race (Black) • Comorbidities: - Infection - Renal - Pulmonary artery thrombosis, - Anemia, - Obesity • Prothrombotic mutations • Prior VTE • Immobility	• Hb <10 g/L • Pre-chemotherapy platelet count >350,000/μL • Pre-chemotherapy WBC count >11,000/μL • ↑Tissue factor • ↑D-dimer • ↑P-selectin • ↑CRP

Schematic Management of VTE



Ortel TL. ASH 2020.
Guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism.

Clinical Guideline Recommendations for Anticoagulants and Length of Therapy in the Treatment of CAT

	ACCP 2021	ASCO 2020	ASH 2021	ITAC 2019	NCCN 2021
Initiation (up to 10 days)	**DOACs** (apixaban, edoxaban, rivaroxaban) over LMWH • **Apixaban** may be preferred in patients with luminal GI malignancy	**LMWH**, UFH, fondaparinux or rivaroxaban	**DOACs** (apixaban, rivaroxaban) or **LMWH**	**LMWH** • Can use edoxaban/ rivaroxaban in patients without a high risk of GI/GU bleeding • UFH or fondaparinux can be used if LMWH or DOACs are contraindicated	**LMWH** or **DOACs** (edoxaban, rivaroxaban)
Maintenance (up to 6 months)		**LMWH** or **DOACs** (edoxaban or rivaroxaban)	**DOACs** (apixaban, edoxaban, rivaroxaban) over LMWH • Up to 6 months	**LMWH** or **DOACs** (edoxaban or rivaroxaban) • Use caution with DOACs and GI tract malignancy	**LMWH** or **DOACs** (edoxaban or rivaroxaban) • For minimum of 3 months
Long-term (beyond 6 months)	**DOACs** • No scheduled stop date with periodic assessment • Can use VKA if DOACs are contraindicated	**LMWH, DOACs or VKAs** • Patients with active cancer, metastatic disease or receiving chemotherapy • Intermittent assessment of risk-benefit ratio	**DOACs or LMWH** • Indefinite therapy, and periodic re-evaluation for those with active cancer	**LMWH or DOACs** • Should be used for minimum of 6 months based on individual evaluation	**LMWH or DOACs** • Patient with active cancer, undergoing treatment or with a persistent risk factor • Based on clinical judgement

Ramcharitar RK. *Heart International*. 2022.

Case 8: Advance Gastric Adenocarcinoma with Cancer-Associated Thrombosis

- ✓ Diagnosis and management of pulmonary embolism
- ✓ Clinical guideline recommendation for anticoagulation therapy of cancer-associated thrombosis

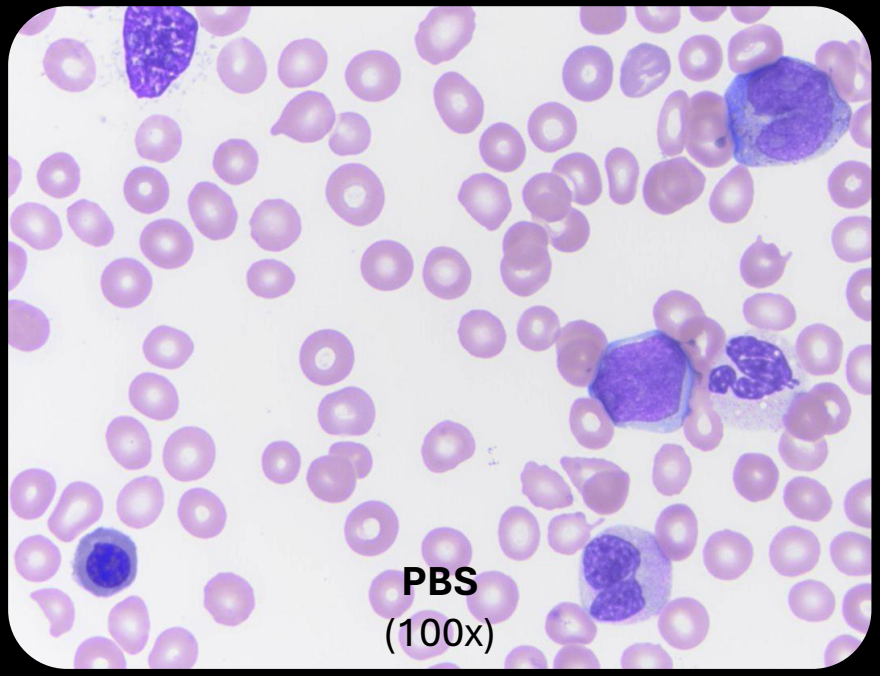
Case 9

Q9

A 50-year-old lawyer presents with significant weight loss for 3 months. Physical examination shows pallor and splenomegaly. He has no sign of chronic liver disease. CBC reveals Hb 9.1 g/dL, Hct 28%, MCV 80 fL, WBC count 10,000/μL (N 50, L 30, M 10), platelet count 130,000/μL.

What is the most likely diagnosis?

A. Chronic myeloid leukemia (CML), chronic phase
B. Essential thrombocythemia (ET)
C. Metastatic adenocarcinoma
D. Primary myelofibrosis (PMF), overt phase
E. Visceral leishmaniasis



PBS
(100x)

Q9

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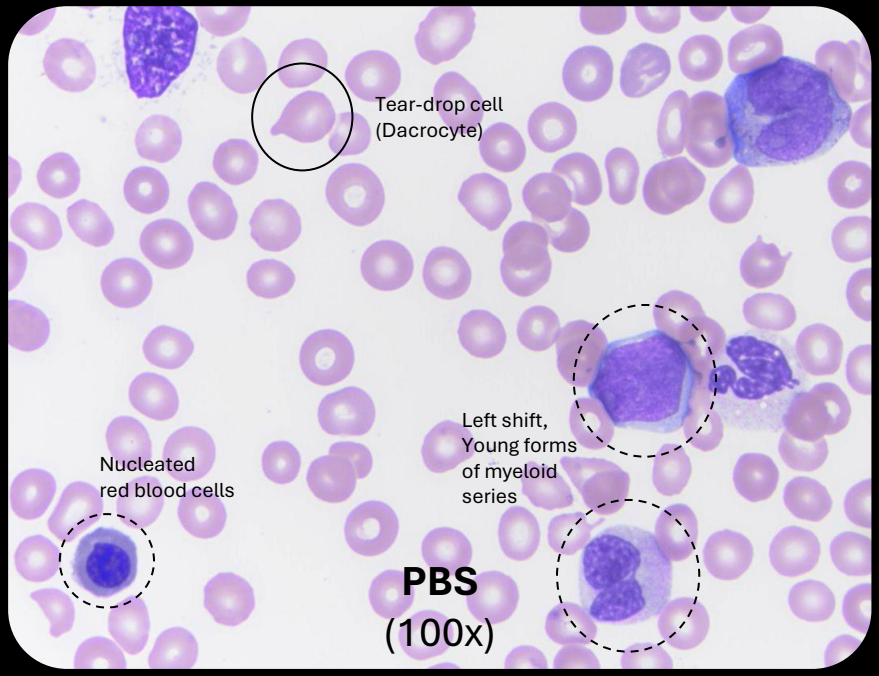
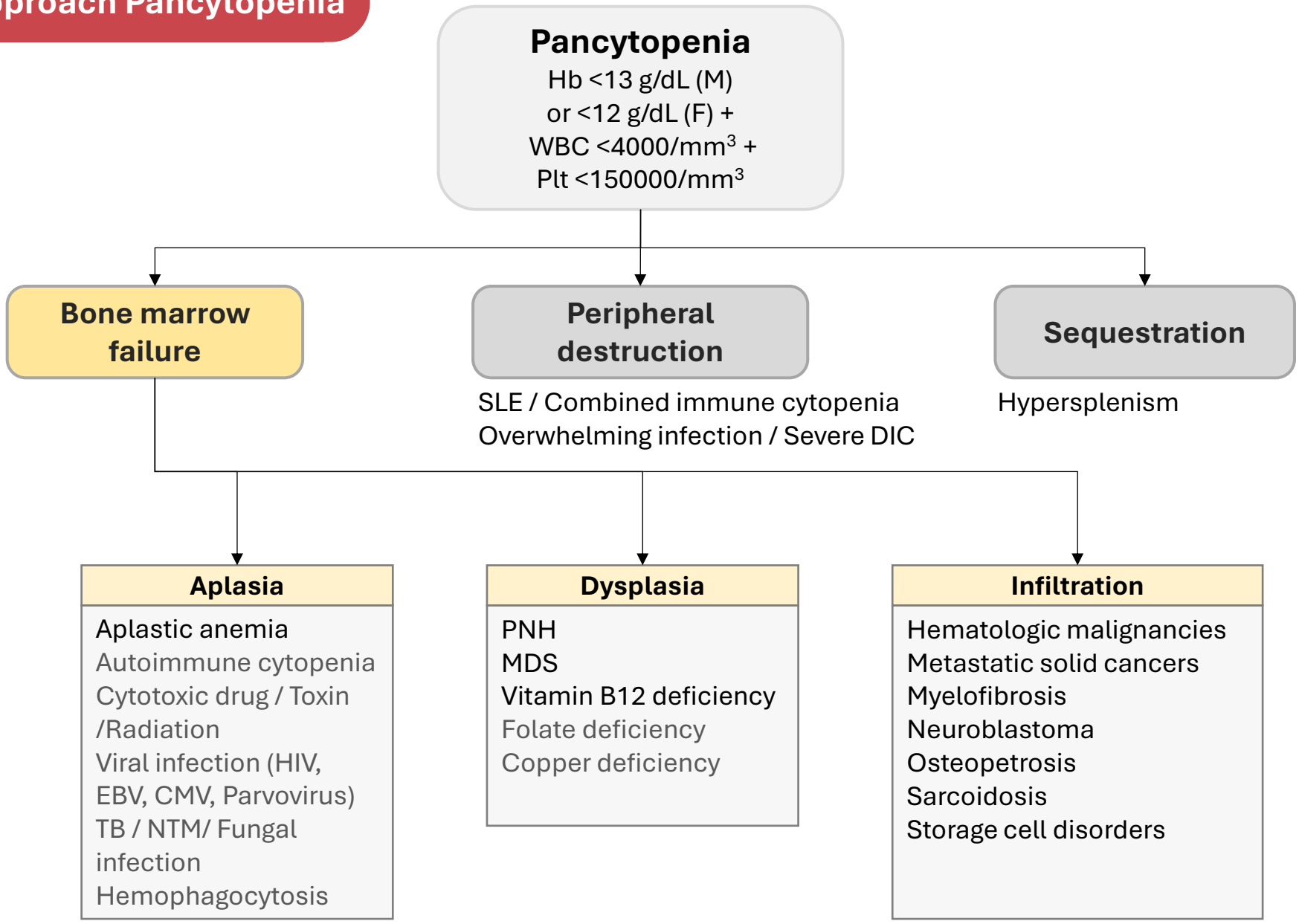


Myelophthisis (Leukoerythroblastosis)
PBS findings:

- Tear drop red blood cell (esp. myelofi brosis)
- Immature myeloid cell
- Nucleated red blood cell
- Giant platelet

Approach Pancytopenia



Approach Splenomegaly

Splenomegaly

Congestive

Evidences of portal hypertension or coagulopathy

- Cirrhosis
- Hepatic vein thrombosis
- Portal vein thrombosis
- Splenic vein thrombosis

Non-portal related

Infectious

- Bacterial
- Parasite
- Viral
- Fungal

Inflammatory

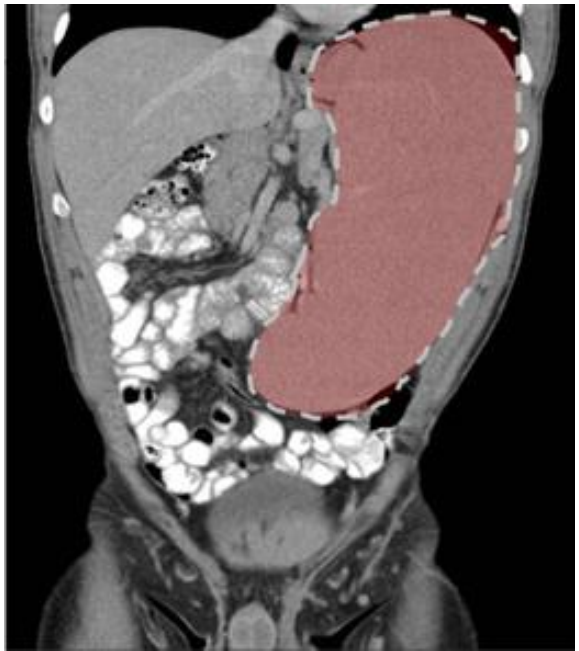
- SLE
- Sarcoidosis
- Serum sickness

Infiltrative

Malignant
- Lymphoma
- Leukemia
- MPNs (CML, PMF, PV, ET)

Non-malignant
- Gaucher's disease
- Glycogen storage disease
- Amyloidosis

Hemolytic disease
(Extravascular hemolysis)

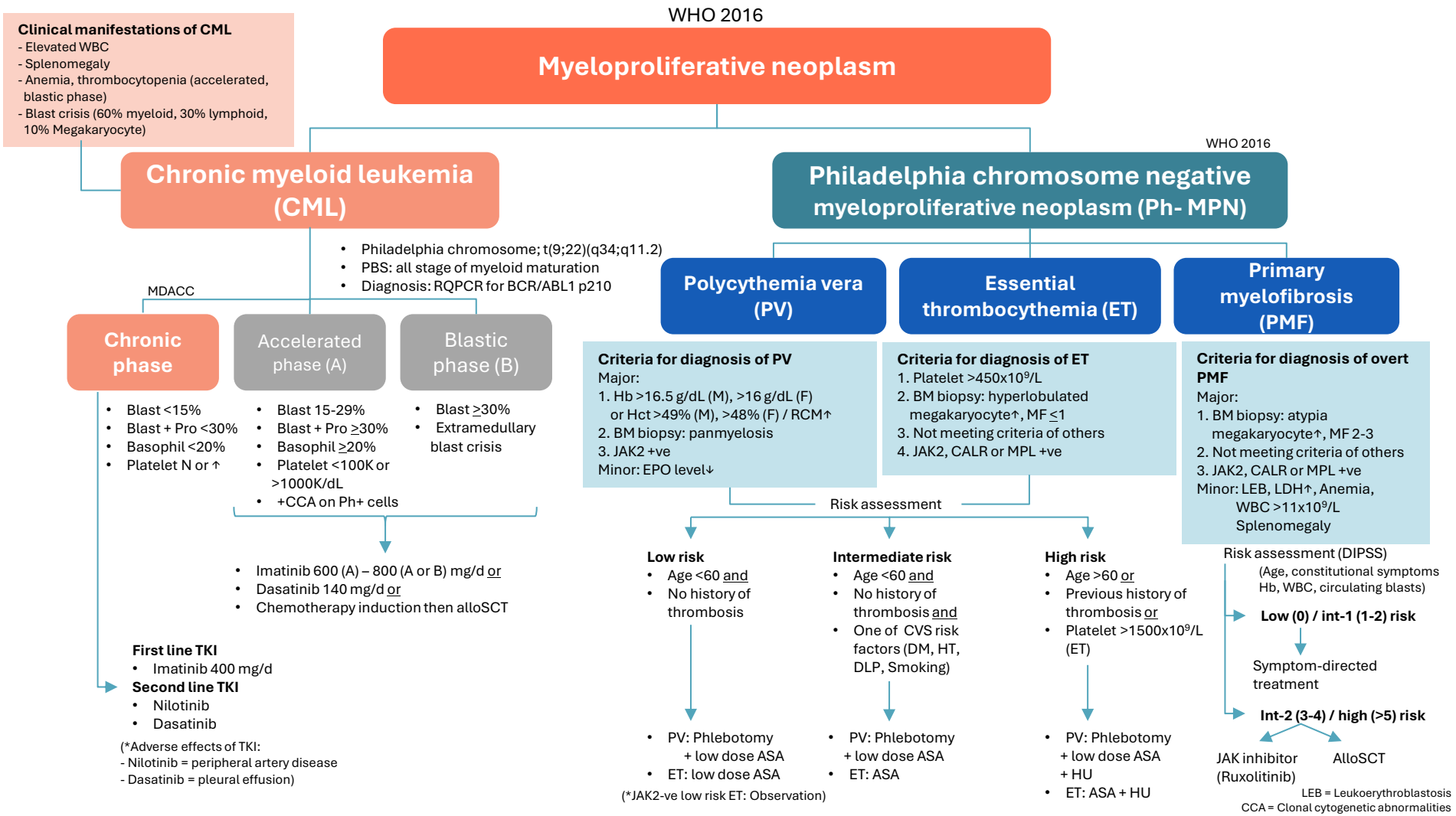


Secondary Myelofibrosis

(Leukoerythroblastic blood picture with marrow fibrosis)

- Bone marrow metastasis
- Hematologic malignancies
  - Hodgkin lymphoma
  - Hairy cell leukemia
- Spent phase of polycythemia vera (PV) and essential thrombocythemia (ET)
- Autoimmune diseases
  - SLE
  - Rheumatoid arthritis
  - Sjogren's syndrome
- Granulomatous diseases
  - TB
  - Histoplasmosis
  - sarcoidosis
- Drug induced myelofibrosis (Chlorambucil, Anagrelide, etc.)
- Hyperparathyroidism

Diagnosis and Management of PMF



Case 9: Primary Myelofibrosis

- ✓ WHO 2016 diagnostic criteria for myeloproliferative neoplasm
- ✓ Management of primary myelofibrosis

Case 10

Q10

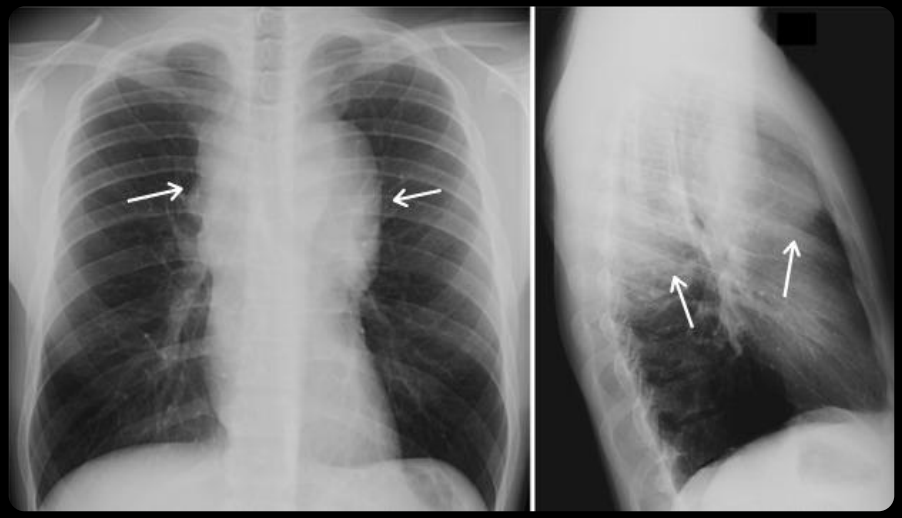
A 35-year-old female TikToker presents to the medicine clinic with persistent dry cough and progressive positional related SOB for 2 mo. She also had alcohol intolerance, and significant weight loss. Physical examination shows enlarged left cervical lymphadenopathies, and no adventitious lung sound.

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.

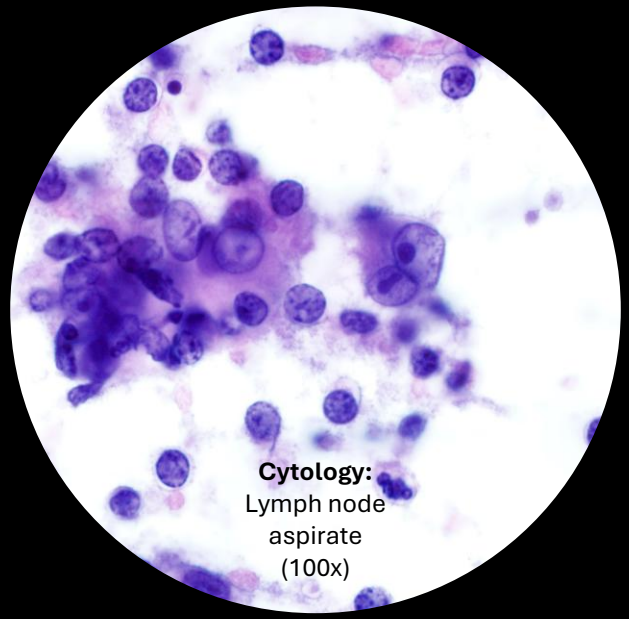
What is the most likely diagnosis?

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

PA and right lateral CXR:



Large, bulky, lobulated soft tissue mass in mediastinum.



Credit cytology image: Emily Mason, M.D., Ph.D.

Q10

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

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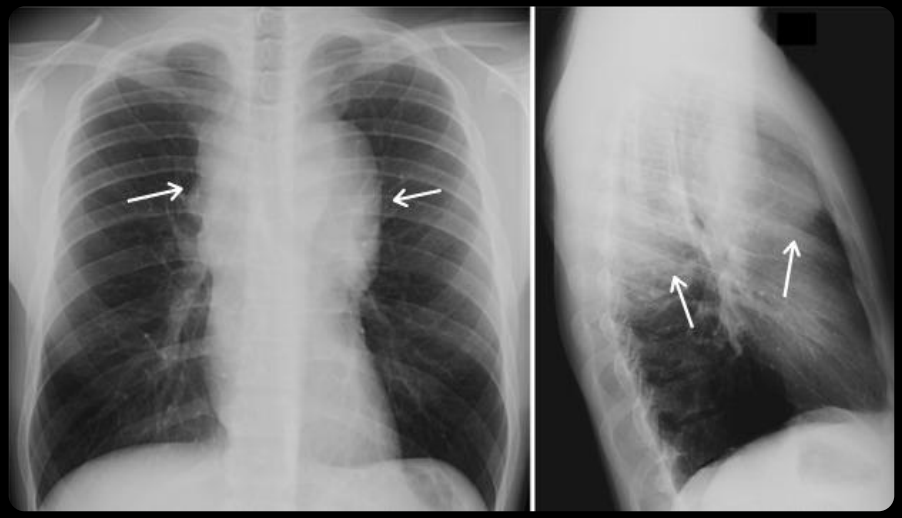

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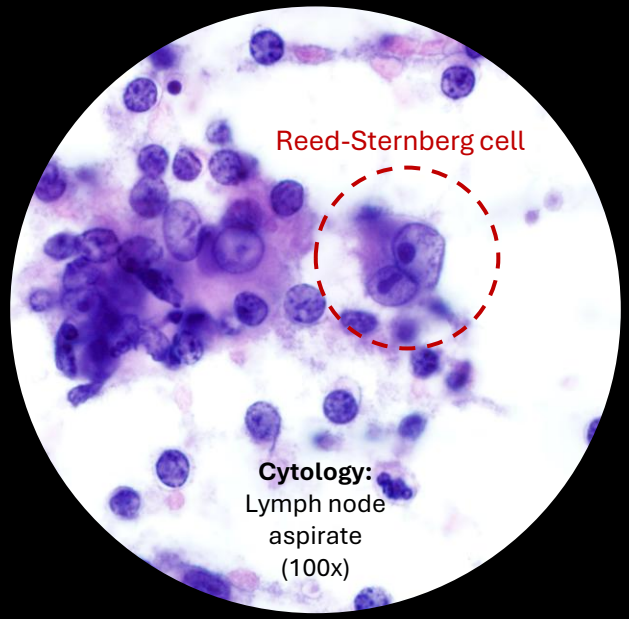
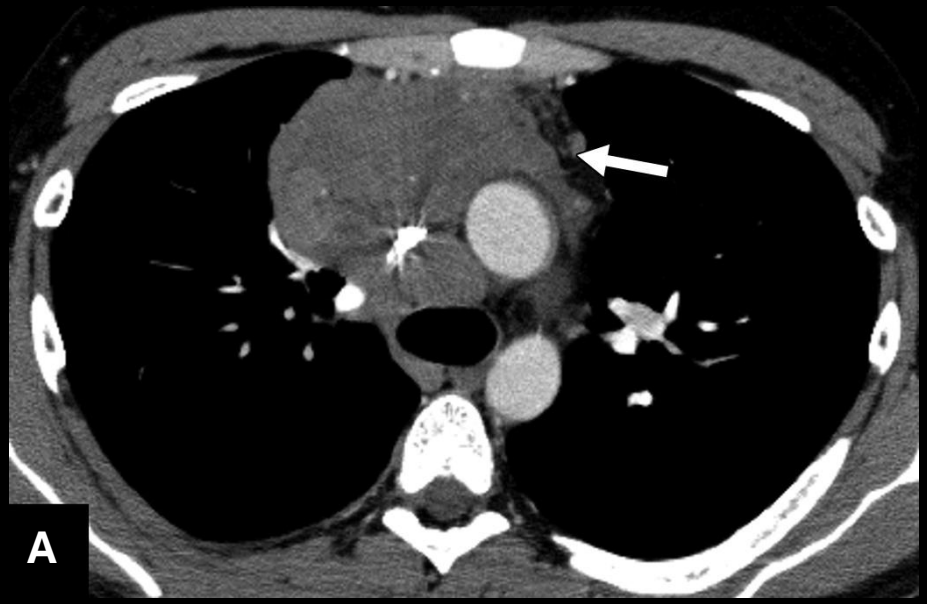
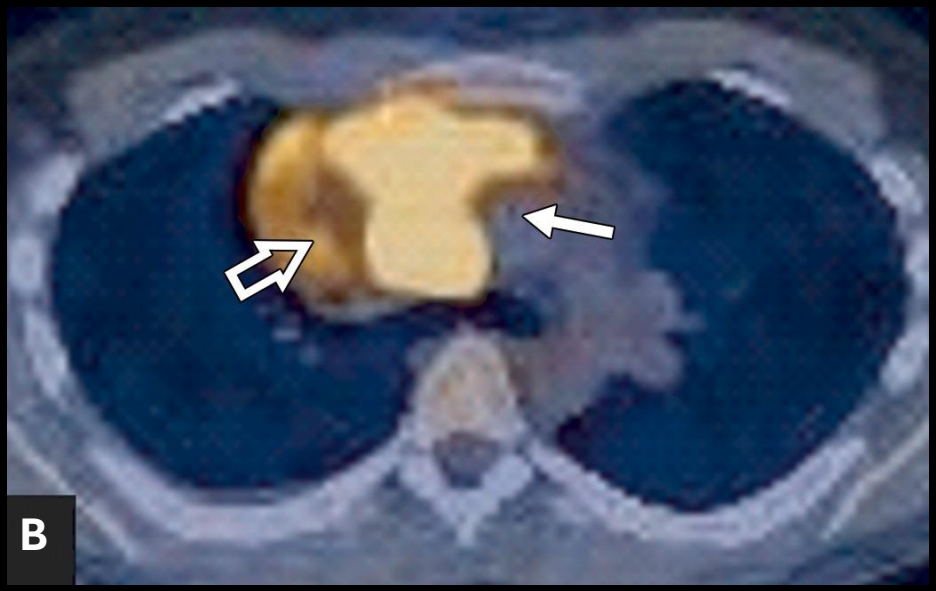


Credit cytology image: Emily Mason, M.D., Ph.D.

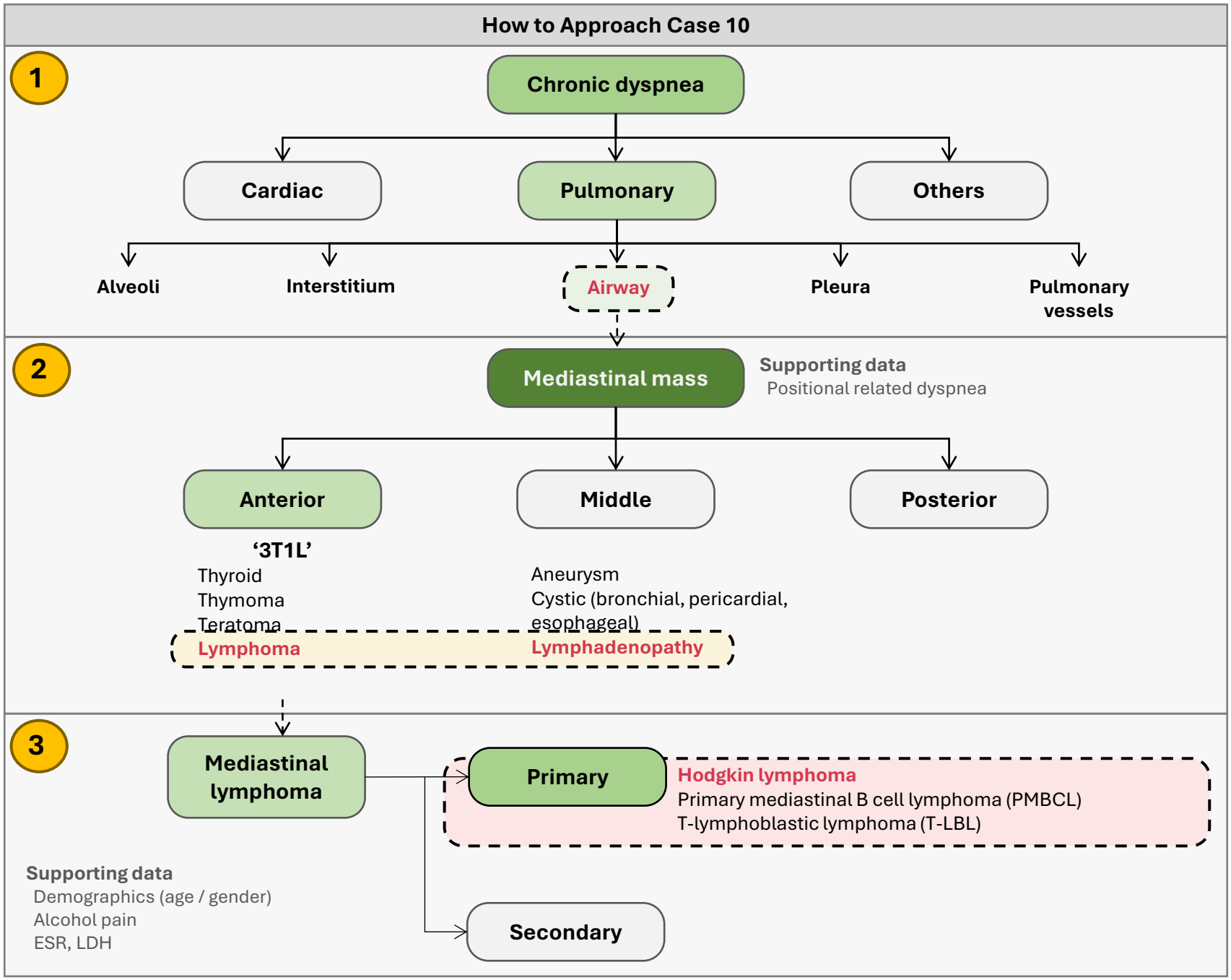
Q10



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.



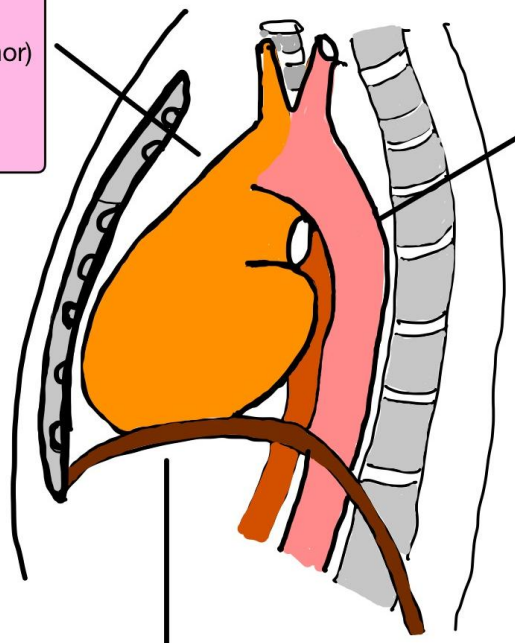
B: Transverse fused FDG PET/CT image of chest shows FDG-avid structure (*solid arrow*) corresponding to lymphoma. Signal heterogeneity reflecting necrosis of lesion is clearly detectable (*open arrow*).


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

Mediastinal Mass – Differential Diagnosis

Anterior Mediastinal Mass:
5T's
-Thymic neoplasm
-Teratoma (or other germ cell tumor)
-Thyroid (goiter/neoplasm
-Terrible Lymphoma
-Thoracic aorta (Aneurysm)

Posterior Mediastium:
-Bronchogenic tumor
-Aneurysm
-Enteric cyst
-Esophageal diverticula/tumor
-Neurogenic tumor



Middle Mediasinum:
-Vascular masses
-Bronchogenic cyst/ Tumor
-Lymph node hyperplasia
-Lymphoma
-Pleuropericardial cyst

Mediastinal tumors:

Anterior (front) mediastinum

- Lymphoma: These malignant tumors include both Hodgkin's disease and non Hodgkin's lymphoma.
- Thymoma and thymic cyst: These are the most common causes of a thymic mass. The majority of thymomas are benign and - surrounded by a fibrous capsule. However, about 30% of these may be more aggressive and grow through the sac into other tissue.
- Germ cell: The majority of germ cell neoplasms (60 to 70%) are benign and are found in both males and females.
- Thyroid mass mediastinal: This is usually a benign growth, such as a goiter.

Middle mediastinum

- Bronchogenic cyst : This is a benign growth with respiratory origins.
- Lymphadenopathy mediastinal: This is an enlargement of the lymph nodes.
- Pericardial cyst: This is a benign growth that results from an "out-pouching" of the pericardium (the heart's lining).
- Tracheal tumors: These can be benign or malignant.
- Esophageal tumors: These can be benign or malignant.
- Esophageal abnormalities: These include achalasia esophageal, diverticulum, and hiatal hernia.
- Vascular abnormalities: These include aortic aneurysm and aortic dissection.

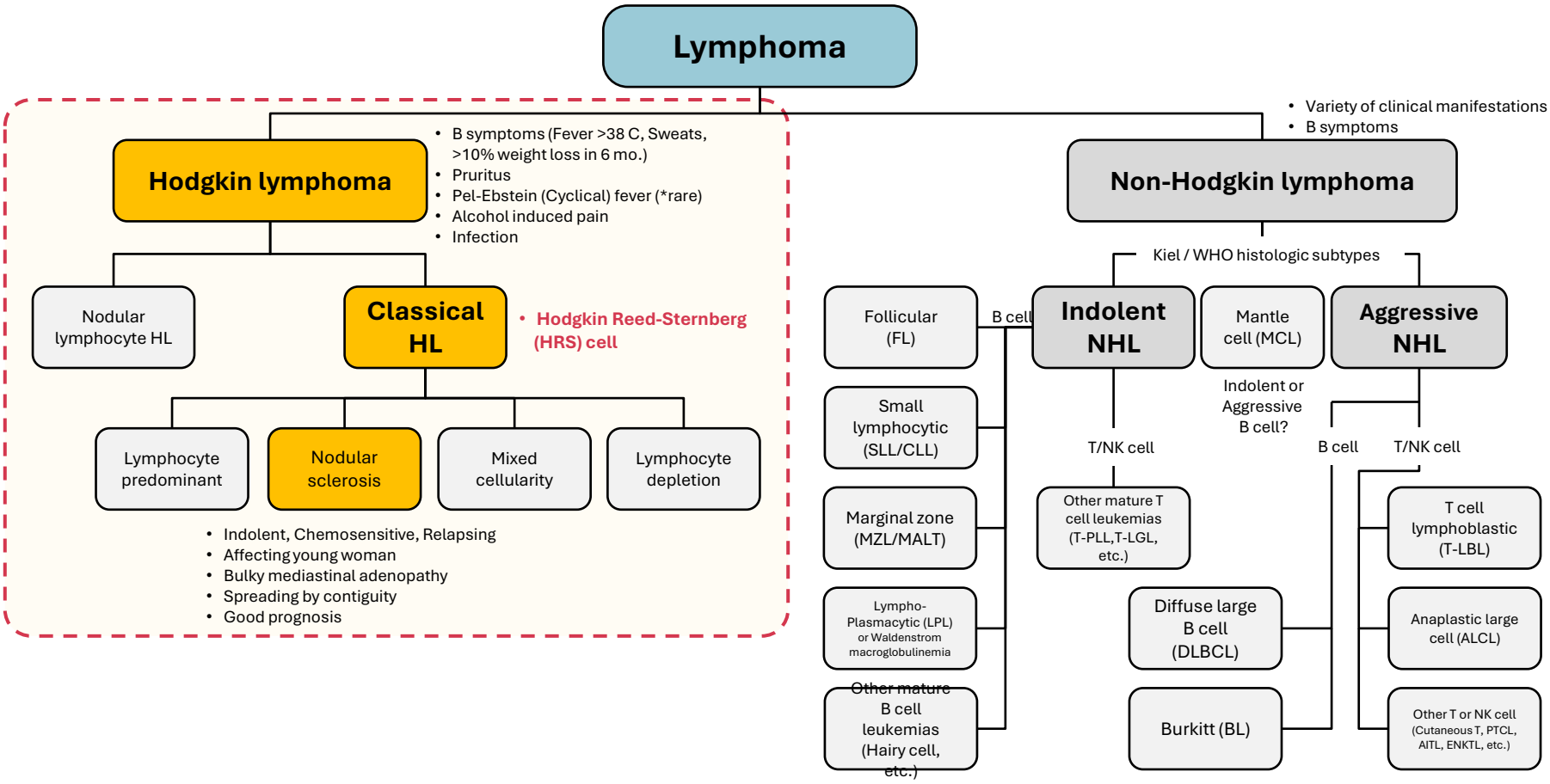
Posterior (back) mediastinum

- Neurogenic tumors: The most common cause of posterior mediastinal tumors, these are classified as nerve sheath neoplasms, ganglion cell neoplasms, and paraganglionic cell neoplasms. Approximately 70% of neurogenic neoplasms are benign.
- Lymphadenopathy: This refers to an enlargement of the lymph nodes.
- Extramedullary haematopoiesis: This is a rare cause of masses that form from bone marrow expansion and are associated with severe anemia.
- Neuroenteric cyst: This is a rare growth, which involves both neural and gastrointestinal elements.
- Paravertebral abnormalities: These include infectious, malignant and traumatic abnormalities of the thoracic spine.
- Vascular abnormalities: These include aortic aneurysms.

Symptoms

- Cough
- Shortness of breath
- Chest pain (somewhat rare)
- Flushing
- Fever
- Chills
- Night sweats
- Coughing up blood
- Hoarseness
- Unexplained weight loss
- Lymphadenopathy (swollen or tender lymph nodes)
- Wheezing
- Stridor (high-pitched and noisy breathing, which could mean a blockage)
- Eye issues (drooping eyelid, small pupil) on one side of the face

Classification of Lymphoma



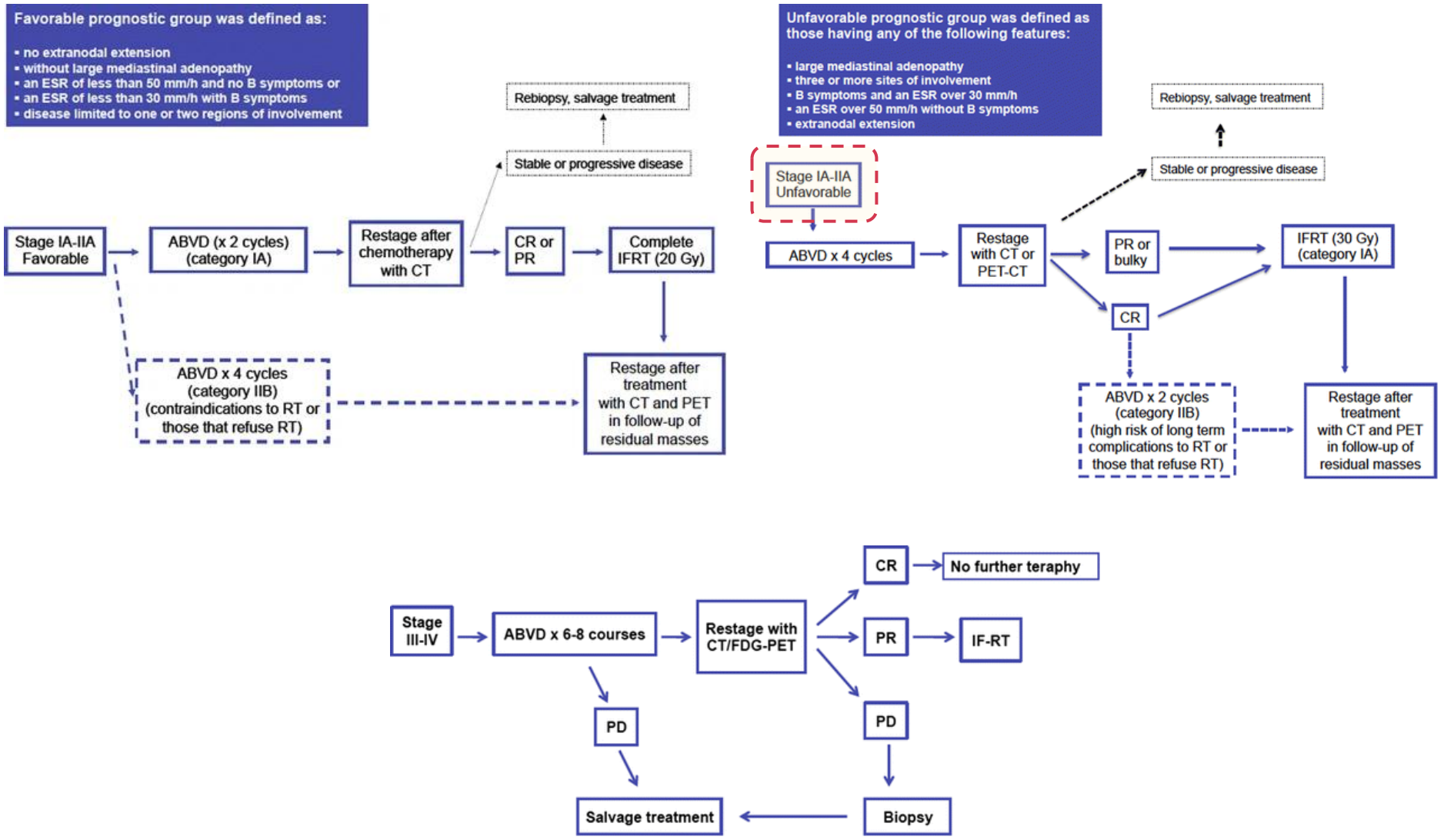
MALT = Mucosa-associated lymphoid tissue lymphoma, PLL = Prolymphocytic leukemia, LGL = Large granular lymphocyte leukemia
PTCL = Peripheral T cell lymphoma, AITL = Angioimmunoblastic T cell lymphoma, ENKTL = Extranodal NK/T cell lymphoma

Differential Diagnosis: Lymphoma in Different Settings

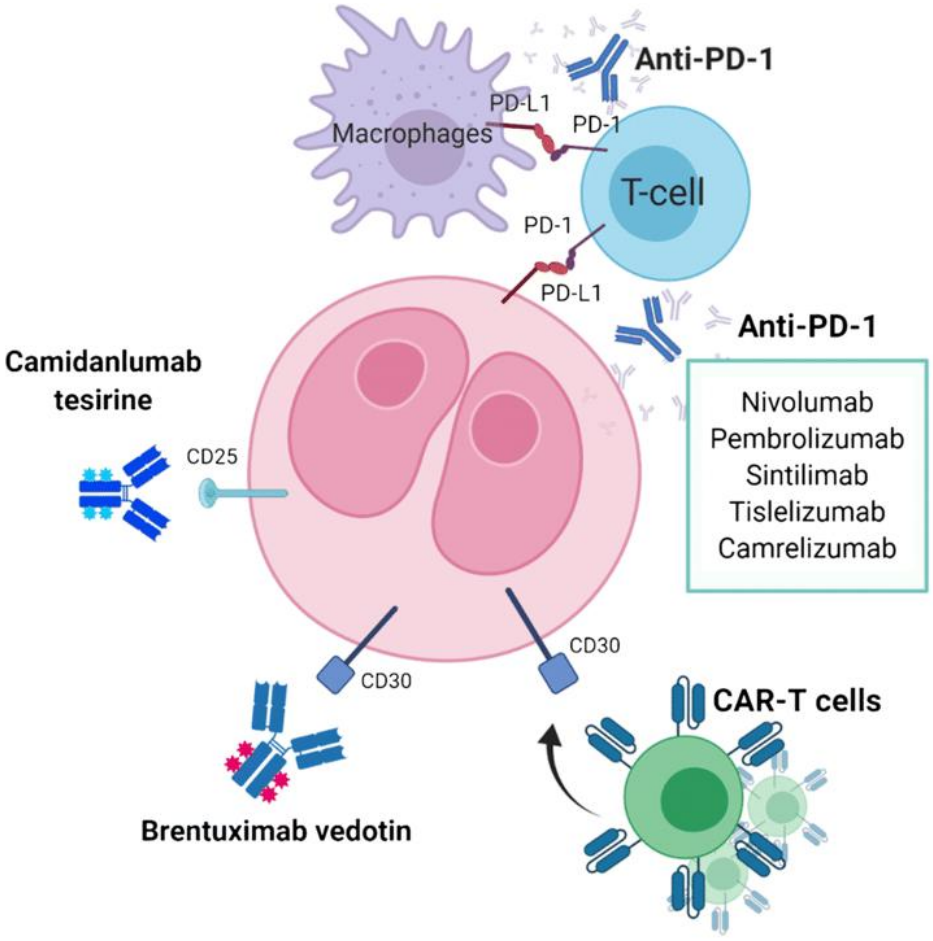
Young adult	Mediastinal mass	HIV related	Primary BM (+/- splenomegaly)	HLH associated	HyperIg
HL	HL (F, Y)	PCNSL	LPL or WM	DLBCL or IVL	LPL or WM (IgM)
DLBCL	PMBCL (F, 35 y/o)	Burkitt	MZL	ALCL	MZL (IgG)
Burkitt	ALCL (M/F, Y)	DLBCL (Imm.)	MCL	SPTCL	AITL (Polyclonal)
ALCL	T-LBL (M,Y)	PBL	SMZL	T-LBL	
T-LBL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

Management of Hodgkin Lymphoma



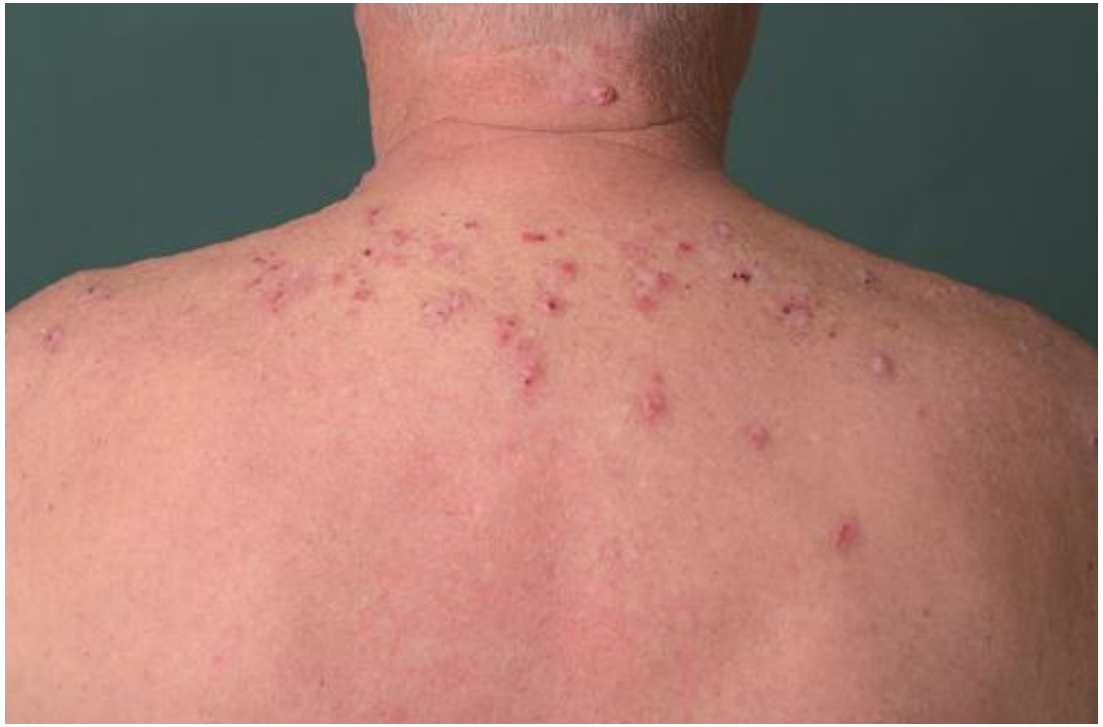
Targeted Therapy in Hodgkin Lymphoma

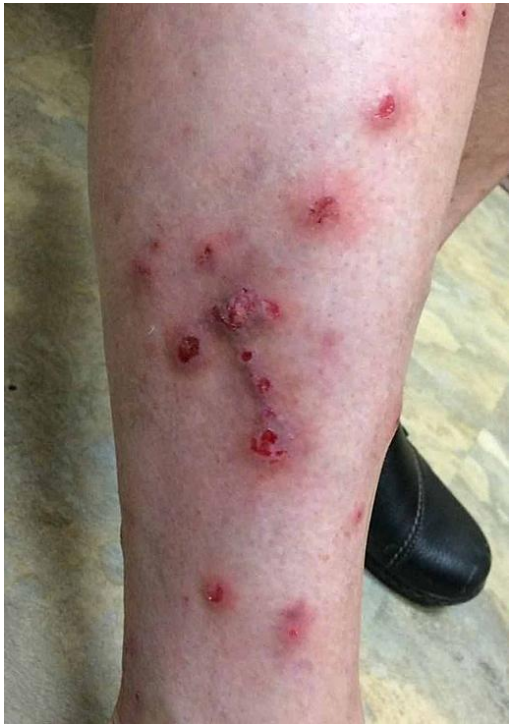


Representation of a Hodgkin Reed-Sternberg cell with surface antigens that are targeted by novel therapeutic agents.

Andrade-Gonzalez, X., Ansell, S.M. *Curr. Treat. Options in Oncol.* **22**, 42 (2021).

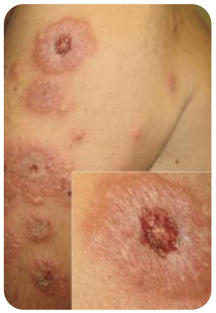
Case 10 (cont.)

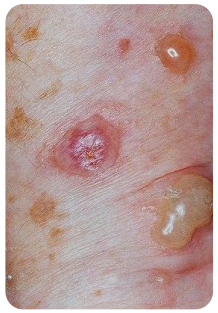


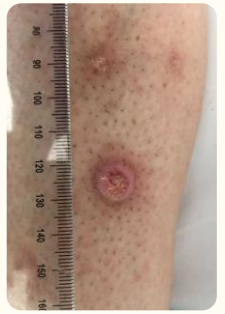


She develops generalized pruritic papulonodular cutaneous lesions with scratch marks and pigmentation on upper back and both legs

Paraneoplastic Mucocutaneous Syndrome in Hematologic Malignancies







	Neutrophilic dermatoses (Sweet's syndrome)	Pyoderma gangrenosum	Erythema elevatum diutinum	Eosinophilic dermatosis	Paraneoplastic pemphigus	Annular granuloma	Dermato-myositis	Prurigo nodularis
Associated with	AML	MDS	IgA MGUS IgA MM	CLL	NHL	NHL	NHL	HL
Treatment	- Steroids (usually required Prednisolone 1 MKD dose for 3-4 weeks)	- Steroids	- Dapsone followed by steroids	- Steroids - Antihistamines - Phototherapy - Doxycycline + nicotinamide - Dapsone - Dupilumab	- Steroids - Rituximab +/- IVIG (r/r case)	- Phototherapy - Isotretinoin - Dapsone - HCQ	- Steroids + azathioprine	- Steroids - Phototherapy

Alvarez-Payares JC. *Cureus*. 2021.

Paraneoplastic Cerebellar Degeneration in Hodgkin lymphoma

Table 1. Paraneoplastic neurological syndromes

Syndrome	Associated antibodies	Predominant lymphoma type	Selected references
LE	mGluR5	HL	16
Granulomatous angiitis	None	HL	40, 41
Cerebellar degeneration	Tr (DNER)	HL	5, 6
Paraneoplastic chorea	CV2/ CRMP5*	<10 cases (NHL in 4)	57, 58
Opsoclonus-myoclonus	None	<10 cases (NHL in 3)	64, 66
Stiff-person syndrome	None	HL	67, 72
Paraneoplastic myelopathy	None	HL and NHL	73, 74
Motor neuronopathy	None	HL	79, 80
Sensory neuronopathy	None†	<10 cases (5 with HL)	81, 82
Autonomic ganglionopathy	nAChR‡	<10 cases (HL, NHL)	87, 88
Sensorimotor neuropathy	None	HL and NHL	94
Vasculitic neuropathy	None	NHL	97
Neuromyotonia	None	<10 cases (HL, NHL)	104
Lambert-Eaton myasthenic syndrome	VGCC‡	<10 cases (NHL)	102
Myasthenia	AChR‡	HL and NHL	105
Dermatomyositis	p155	NHL	99

Classical syndromes are underlined. nAChR, nicotinic acetylcholine receptor; VGCC, voltage-gated calcium channel.

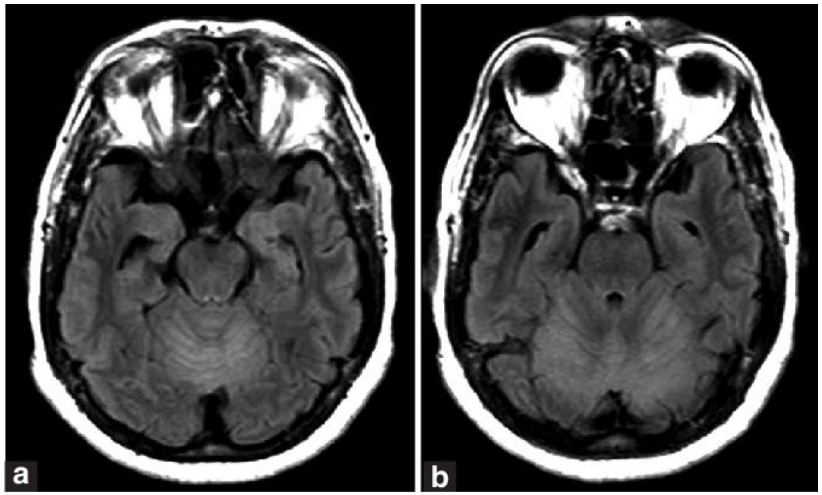
*Not present in all cases.

†One patient with NHL and Ma2 antibodies (not published).

‡Marker of the syndrome, not predictor of cancer.

Use the History and Neurologic Exam to Define the Syndrome and Clinical Phenotype

- Perform targeted antibody testing (in both blood and CSF).
- Evaluate for systemic malignancy. Employ additional adjunctive testing, as needed (e.g., MRI, EEG and EMG/NCS).



FLAIR MRI brain of a patient with Hodgkin lymphoma and paraneoplastic cerebellar degeneration

Chiu D, et al. *Antibodies.* 2023.

Case 10: Hodgkin Lymphoma with Paraneoplastic Dermatosis and Cerebellar Degeneration

- ✓ How to approach anterior mediastinal mass
- ✓ Diagnosis and management of Hodgkin lymphoma
- ✓ Clinical manifestations of paraneoplastic syndrome


Extra Case

Snakebite

- WHO has readded snakebites to the list of neglected tropical diseases in 2017.
- Snakebite affects between 1.8 to 2.7 million people worldwide each year, and it is estimated to cause between 80,000 and 138,000 deaths.[1,2]
- Venom is injected into the body following a bite by a venomous snake.[3]
- Envenoming can be a highly dynamic clinical event. Symptoms can progressively worsen to a life-threatening emergency.
- Snakebites can have long-term physical sequelae such as amputation, paralysis and disability, and psychological health consequences.[4-7]

[1]Chippaux JP. *Bull World Health Organ*. 1998;76:515–24.
[2]Kasturiratne A, et al. *PLoS Med*. 2008;5:e218.
[3]Gutiérrez JM, et al. *Nat Rev Dis Primers*. 2017;3:17063.
[4]Chippaux J-P. *Toxicon*. 2011;57:586–99.
[5]Williams SS, et al. *PLoS Negl Trop Dis*. 2011;5:e1255.
[6]Waiddyanatha S, et al. *Toxins (Basel)*. 2019;11:E193.
[7]Habib ZG, et al. *Int J Psychiatry Med*. 2021;56:97–115.

Common Hemostatic Snake in Thailand

	Malayan pit viper *Calloselasma rhodostoma*	**Green pit viper** *Trimeresurus* sp.	**Russel's viper** *Daboia siamensis*
Key enzymes	• Thrombin-like enzymes • Snake venom metalloproteases (SVMPs)	• Fibrinogenase • SVMPs	• Phospholipase A2 • SVMPs
Local manifestation	• Moderate edema • Multiple hemorrhagic blebs • Ecchymosis	• Marked edema • Ecchymosis • Thrombophlebitis	• Mild local inflammation
Systemic manifestation	• Thrombocytopenia		• DIC • Acute kidney injury • Rhabdomyolysis • Capillary leak syndrome • Facial and conjunctival edema (chemosis), bilateral parotid enlargement, pleural and pericardial effusions, pulmonary oedema, massive albuminuria, hemoconcentration

Most species in Viperidae:
Cardiovascular effects
Visual disturbances, dizziness, faintness, collapse, shock, hypotension, cardiac arrhythmias, myocardial damage (reduced ejection fraction)

South-East Asian snakebites - WHO. Guidelines for the management of snakebites. 2nd ed. 2016.

Management of Hematotoxic Snake Envenomation

Prehospital Management

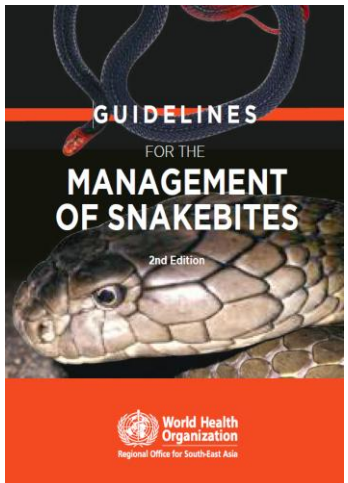
- First-aid treatment
- Transport to the hospital

Diagnosis and Initial Management

- Rapid clinical assessment and resuscitation
- Detailed clinical assessment and species diagnosis
- Investigation and laboratory testing

Treatment

- Antivenom treatment
- Observing the response of Antivenom
- Decide for the further dose(s) of the antivenom are needed
- Supportive/ancillary treatment
- Treatment of the bitten part
- Rehabilitation
- Treatment of chronic complications
- Advice how to avoid future bites



South-East Asian snakebites - WHO. Guidelines for the management of snakebites. 2nd ed. 2016.

Indication for Antivenom Treatment

for patients with proven/suspected snakebite develop one or more of the following signs

Systemic envenoming

- **Hemostatic abnormalities**
  - Spontaneous bleeding
  - +ve non-clotting 20WBCT
  - INR >1,2, or PT >4-5 sec. than control
  - Platelets < 50 x 10^9/L
- **Neurotoxicity** (bilateral ptosis, external ophthalmoplegia, paralysis, etc.)
- **Cardiovascular abnormalities** (hypotension, shock, cardiac arrhythmia, abnormal ECG)
- **Acute kidney injury**
- Hemoglobin- / myoglobinuria (dark urine, +ve urine dipsticks, other evidence of intravascular hemolysis / rhabdomyolysis)

Local envenoming

- Local swelling involving >half bitten limb (in absence of tourniquet) within 48 hr of the bite
- Swelling after bites on digits
- Rapid extension of swelling beyond wrist/ankle within few hours of bites on hand/foot

Risk to Compartment syndrome

- Enlarged tender lymph node draining bitten limb

Courtesy by Ramathibodi Poison Center.

How to Use Antivenom

Preparation

- Dry powder in vials with diluents (sterile water 10 mL)
- Lyophilized antivenoms (shelf life about 5 years) are stored <25ºC, liquid antivenoms (shelf life 2-3 years) at 2-8 ºC.
- Antivenoms retain useful activity for months or even years after these expiry dates.

Dosage

- 1 vial = 10 mL
  - 10 vials for C
  - 10 vials for KC
  - 5 vials for K
  - 3-5 vials for RV, MPV (adjusted for severity)
  - 3 vials for GPV

Administration

- Avoid excessive shaking the solution (Ig aggregate)
- 30 min. IV infusion
- Observation during the early hr. (2 hr.)
- Evaluation at 6 hr.

Adverse reaction

Early AR

Anaphylactoid

- 1-180 minutes
- **Complement activation** by IgG aggregates / residual Fc fragments stimulation of mast cells/basophil by antivenom proteins
- **Incidence:** 81% (43% Severe reaction) (1.2% Fatal)
- **Signs and symptoms:**
  - Urticaria
  - Bronchospasm
  - Angioedema
  - Anaphylactic shock

Pyrogenic

- 1-2 hours
- **Endotoxin reaction**
- **Incidence:** 3.5%
- **Signs and symptoms:**
  - Fever

Late AR

- 1-12, mean 7 days after treatment
- **Serum sickness**

- Administer antivenom only if benefits outweigh risks.
- In patients with severe envenoming, recently expired antivenoms may be considered if there is no alternative.
- Prompt administration remains necessary if coagulation abnormalities persist.

- IgE-mediated Type I hypersensitivity after previous exposure to equine serum – **uncommon**
- Most patients with reactions are **skin test (IgE-mediated) negative.**

Courtesy by Ramathibodi Poison Center.

Extra Case: Hemostatic Snake Envenomation

- ✓ Management of Hemostatic snake envenomation and antivenom therapy

What Did We Learn Today?

How to approach a patient with;

✓ **Case 1:** Chronic anemia	**Dx:** Multiple myeloma
✓ **Case 2:** Hemolysis	**Dx:** Paroxysmal nocturnal hemoglobinuria (PNH)
✓ **Case 3:** Deoxygenation	**Dx:** Dapsone-induced methemoglobinemia
✓ **Case 4:** Eosinophilia	**Dx:** Systemic mastocytosis
✓ **Case 5:** Bleeding 1	**Dx:** Acquired factor VIII inhibitor
✓ **Case 6:** Bleeding 2	**Dx:** Von Willebrand disease (VWD)
✓ **Case 7:** Arterial thrombosis	**Dx:** Antiphospholipid syndrome (APS)
✓ **Case 8:** Venous thrombosis	**Dx:** Cancer-associate venous thromboembolism
✓ **Case 9:** Splenomegaly	**Dx:** Primary myelofibrosis (PMF)
✓ **Case 10:** Mediastinal mass	**Dx:** Classical Hodgkin lymphoma (cHL)
✓ **Case 11:** Snakebite	**Dx:** Viper envenomation

Thank You for Your Attention

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