

Paroxysmal Nocturnal Hemoglobinuria

Clonal stem-cell disease • complement-mediated hemolysis • thrombosis

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Learning outcomes

Trace an acquired PIGA mutation to loss of GPI-linked complement regulators.

Explain why PNH produces intravascular hemolysis, urinary iron loss, and thrombosis.

Interpret mixed normal and PNH cell populations in flow cytometry.

Relate PNH to aplastic anemia, myeloid neoplasms, and complement inhibition.

Three interacting facets of PNH

Clonal hematopoiesis

Acquired PIGA mutation in a hematopoietic stem cell

Intravascular hemolysis

Complement attacks red cells lacking surface protection

Marrow / vascular disease

Aplasia, thrombosis, and occasional myeloid evolution

PNH is an acquired genetic hemolytic anemia

The initiating defect is somatic, not a conventional inherited red-cell mutation.

PIGA is required to construct GPI anchors for selected cell-surface proteins.

Cells from the mutant stem-cell clone have reduced GPI-anchored proteins.

A genetic disorder can be acquired after conception.

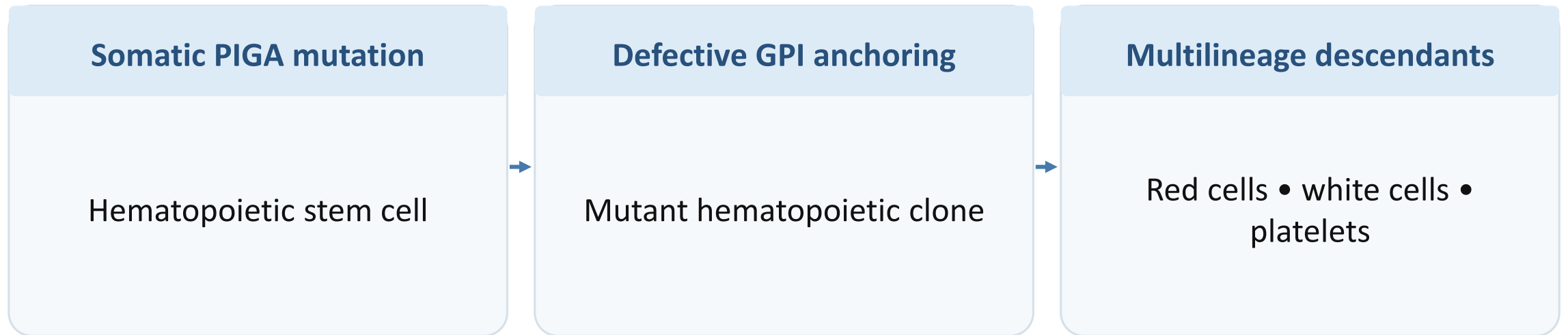
PNH is rare but potentially high risk

A US incidence of 2–5 per million; The excerpt does not specify the time denominator.

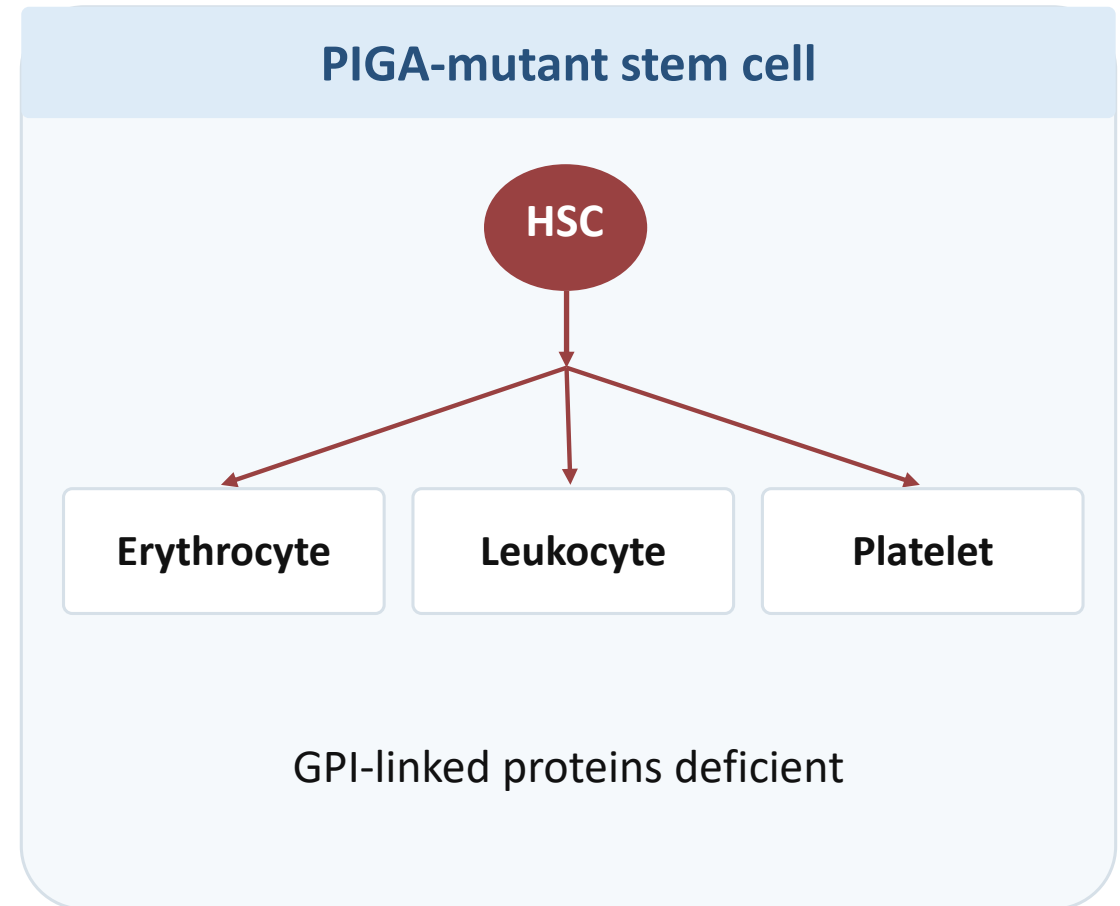
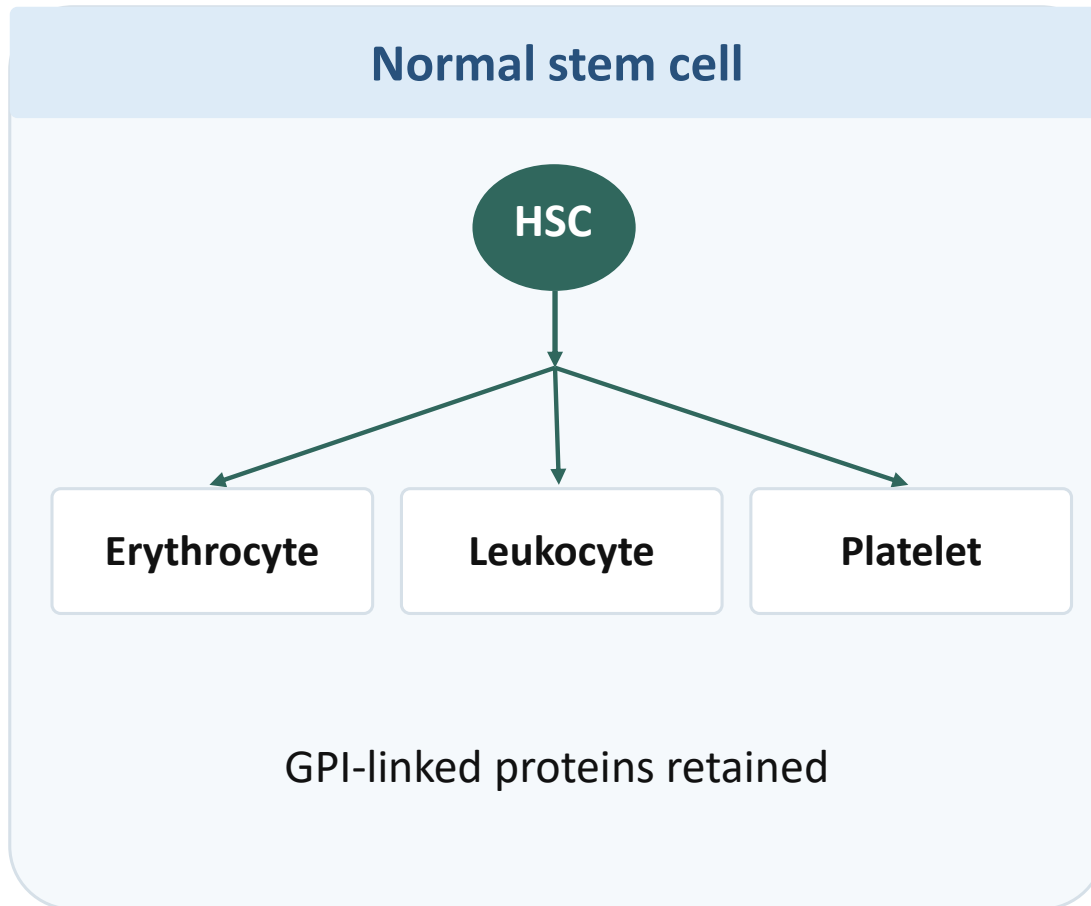
Its significance extends beyond anemia because thrombosis is a major cause of morbidity and death.

Clinical presentation varies: The stereotypical nocturnal attacks are not required.

The initiating lesion occurs in a stem cell

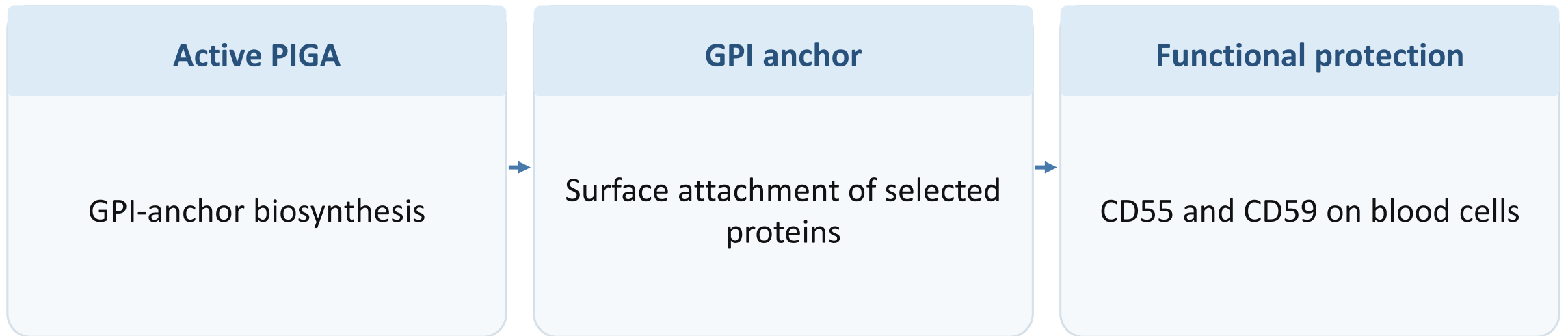


The abnormal phenotype spans blood lineages



The initiating PIGA lesion is carried across hematopoietic lineages.

PIGA acts upstream of membrane-protein loss



The mutation disrupts the anchor, rather than independently mutating CD55 and CD59.

Why a single PIGA mutation can suffice

PIGA is located on the X chromosome.

In cells with two X chromosomes, lyonization leaves one transcriptionally active copy.

An acquired pathogenic mutation in the active PIGA allele can remove functional GPI anchoring.

Mutant and normal stem cells coexist



Mixed populations are expected; This is clonal mosaicism, not a uniform change in every blood cell.

A mutation alone may not explain clone expansion

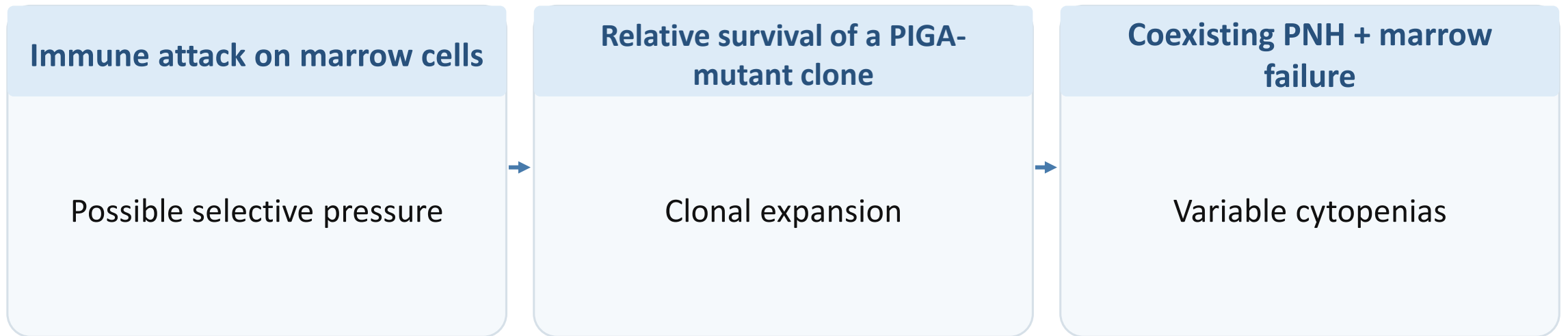
Small PIGA-mutant populations have been described in otherwise healthy individuals.

Clinical disease generally requires expansion of the mutant population.

Immune-mediated selection as a hypothesis, not a proven universal mechanism.

Separate established PIGA causation from proposed selection pressure.

Aplastic anemia provides an evolutionary context



Hypothesized selection model: Not every PNH clone develops this way.

The PNH–aplasia association is bidirectional

In a patient with PNH

Anemia may reflect red-cell destruction

Marrow failure can coexist and limit compensation

Other cytopenias call for marrow evaluation

In a patient with aplastic anemia

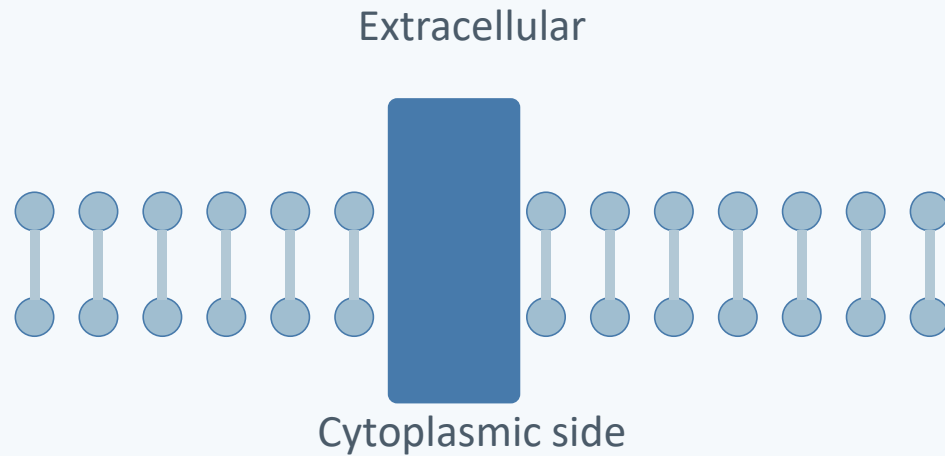
A PNH clone may coexist

Immune selection is one proposed explanation

Clinical significance depends on phenotype and clone behavior

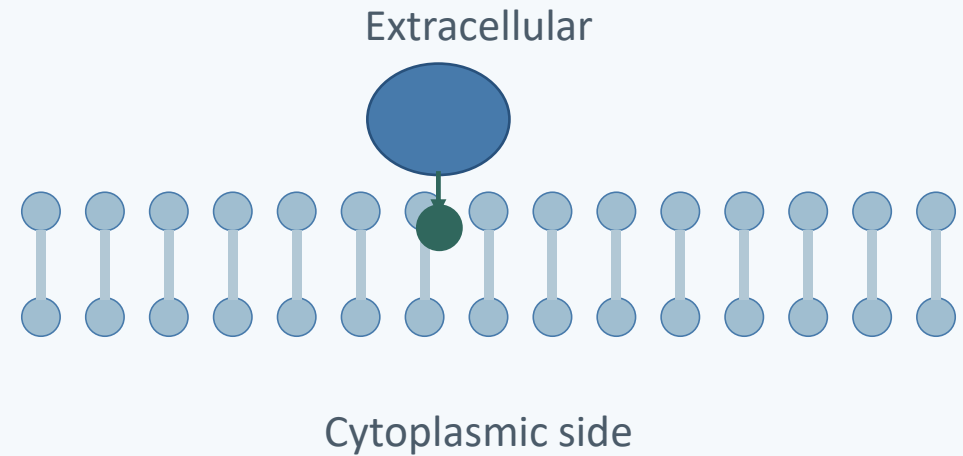
GPI anchors differ from transmembrane segments

Integral transmembrane protein



Protein spans membrane

GPI-anchored protein



Protein linked to outer-leaflet GPI

GPI deficiency removes several proteins at once

The primary lesion is loss of a common anchoring mechanism.

Multiple distinct membrane proteins can therefore be absent together.

The key hemolysis-relevant losses are CD55 and CD59; Robbins also names C8-binding protein.

Membrane complement control: Two levels

CD55 / DAF

Destabilizes C3/C5 convertases



Limits complement amplification

CD59 / MIRL

Prevents terminal C5b–9 assembly



Blocks membrane pore formation

Verified correction to the supplied Robbins wording: CD59 does not principally inhibit C3 convertase.

CD55: Decay-accelerating factor

CD55 is a GPI-anchored regulator at the convertase stage.

It accelerates dissociation of C3 convertases and also regulates C5 convertases.

Its loss permits increased complement activation on the cell surface.

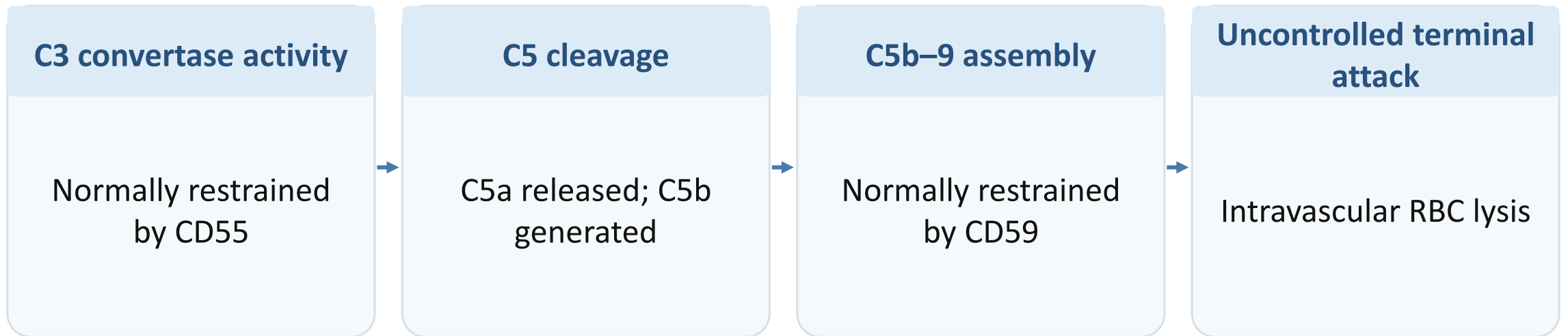
CD59: The terminal protective barrier

CD59 is a GPI-anchored membrane inhibitor of reactive lysis.

It prevents incorporation/polymerization of C9 in the developing membrane attack complex.

Loss of CD59 leaves a red cell susceptible to terminal complement-mediated lysis.

CD55 and CD59 protect distinct checkpoints



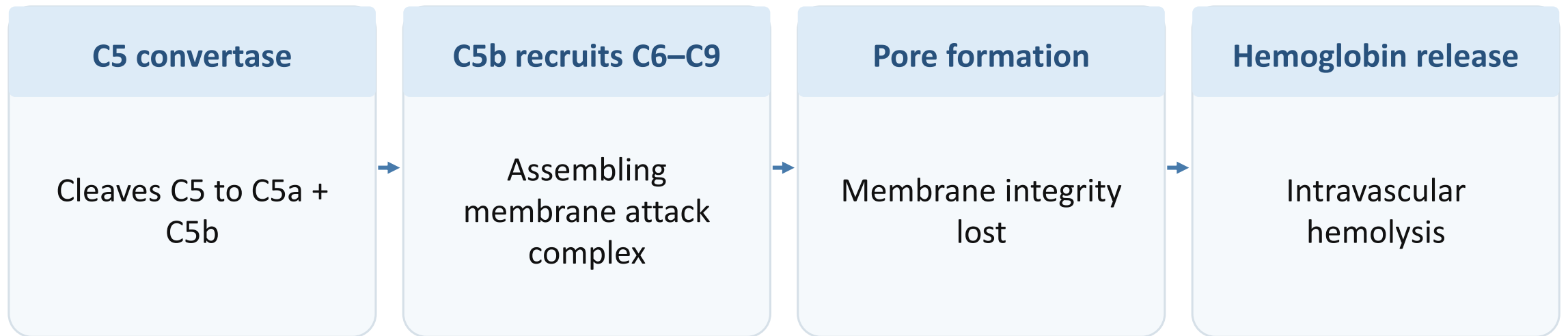
Complement can operate without a new antibody

The alternative complement pathway has ongoing low-level activity.

Normal blood cells require surface regulatory proteins to avoid bystander injury.

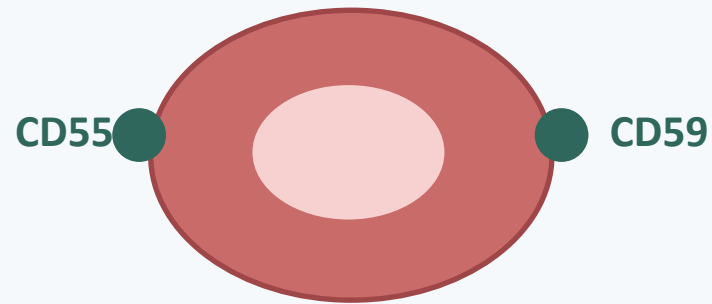
Deficiency of the protective GPI-linked regulators makes PNH cells unusually vulnerable.

Terminal complement creates membrane pores



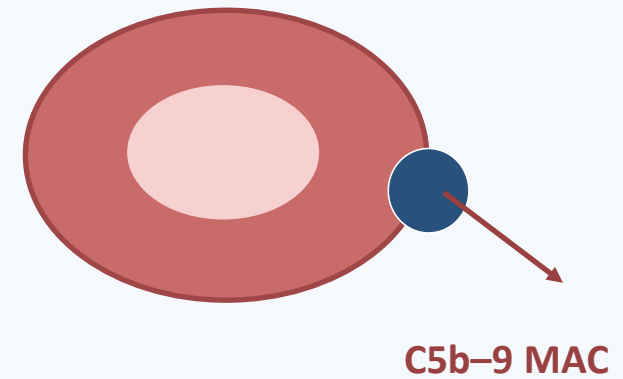
Normal and PNH erythrocytes face the same complement

Protected red cell



Complement attack is restrained

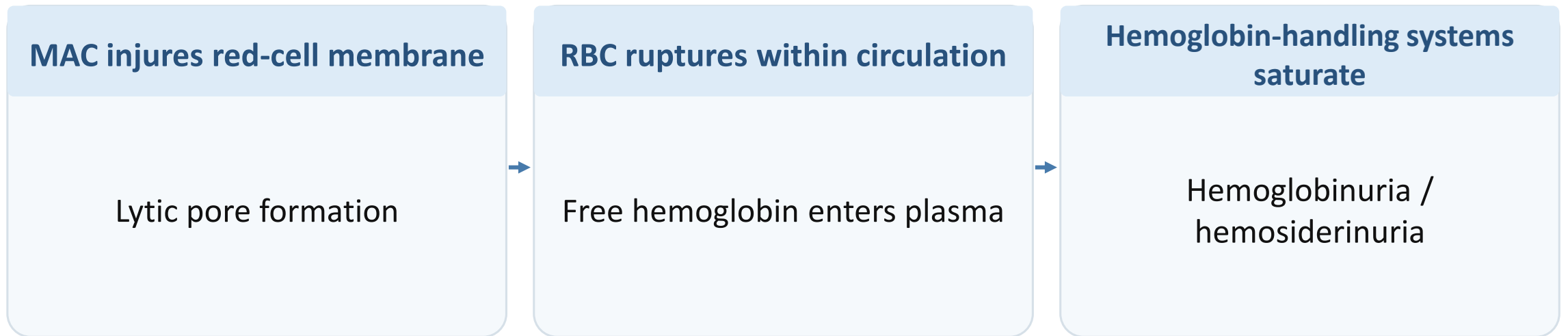
PNH red cell



Loss of CD55/CD59 permits lysis

Original RBC-complement schematic; Not a photomicrograph.

Intravascular hemolysis is the central red-cell lesion



Biochemical effects of red-cell lysis

Premature red-cell destruction shortens circulating erythrocyte survival.

Anemia induces erythropoietin release and compensatory erythropoiesis.

The parent hemolytic-anemia section describes increased bilirubin products and reduced haptoglobin.

Intravascular and extravascular hemolysis differ

Feature	Intravascular	Extravascular
Primary destruction	In bloodstream	Within phagocytes
Free plasma hemoglobin	Prominent	Usually less prominent
Hemoglobinuria	May occur	Not characteristic
Splenic sequestration	Not primary	Central mechanism

The clinical label does not describe most cases

Only a minority have strictly paroxysmal, nocturnal hemoglobinuria.

That a chronic hemolytic pattern is more typical.

An absence of dramatic dark urine does not exclude PNH.

Do not require night-time attacks to suspect PNH.

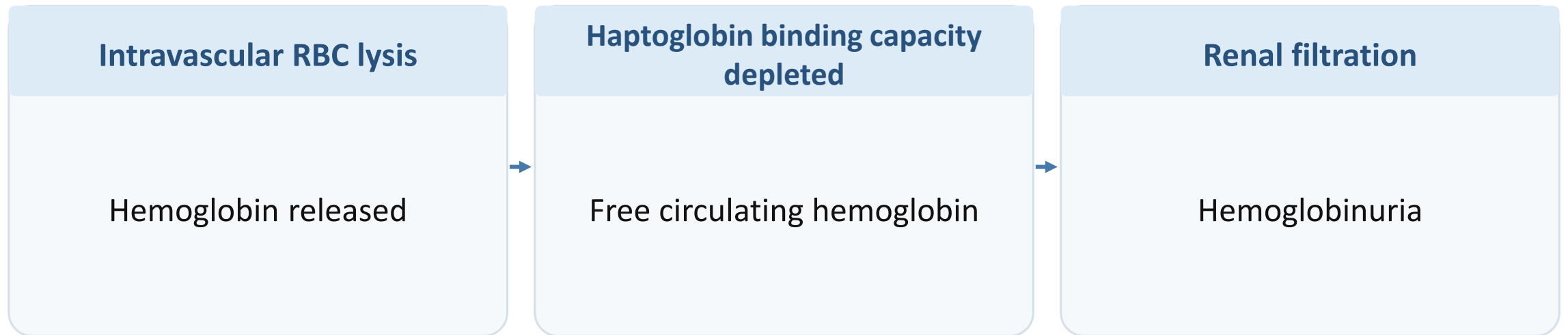
The nocturnal pattern has a proposed mechanism

A modest fall in blood pH during sleep may favor complement activity.

This can amplify hemolysis in susceptible red cells.

The finding explains the historical name without making it a diagnostic requirement.

Hemoglobinuria follows overwhelming free hemoglobin



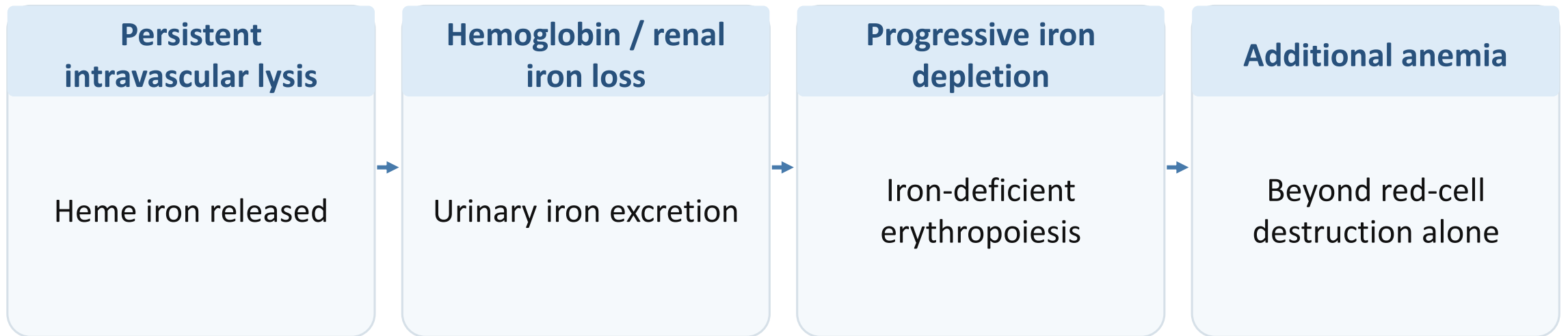
Hemosiderinuria records chronic urinary iron loss

Renal tubular cells take up and catabolize filtered hemoglobin.

Iron can accumulate in tubular cells as hemosiderin.

Urinary shedding of iron-containing material can progressively deplete body iron.

PNH can become iron deficient despite hemolysis



The anemia reflects several simultaneous processes

Destruction

Complement-mediated lysis
of circulating erythrocytes

Nutrient loss

Urinary iron loss can impair
hemoglobin synthesis

Production failure

Coexisting aplasia may
blunt marrow
compensation

The three major adverse trajectories

Hemolytic disease

Chronic complement injury
and iron loss

Thrombotic disease

Venous clots, often in
atypical sites

Stem-cell disease

Marrow aplasia or
evolution to myeloid
neoplasm

Thrombosis dominates disease-related mortality

Thrombosis as the leading cause of PNH-related death.

Venous events are especially characteristic.

Thrombosis in approximately 40% of patients in its cited disease context.

A clot may be more immediately dangerous than the anemia.

Recognize unusual venous thrombosis sites

Hepatic veins

Outflow obstruction should prompt consideration of PNH

Portal veins

Splanchnic thrombosis is an important clue

Cerebral veins

An unusual-site venous event can reveal PNH

The thrombotic mechanism is incompletely settled

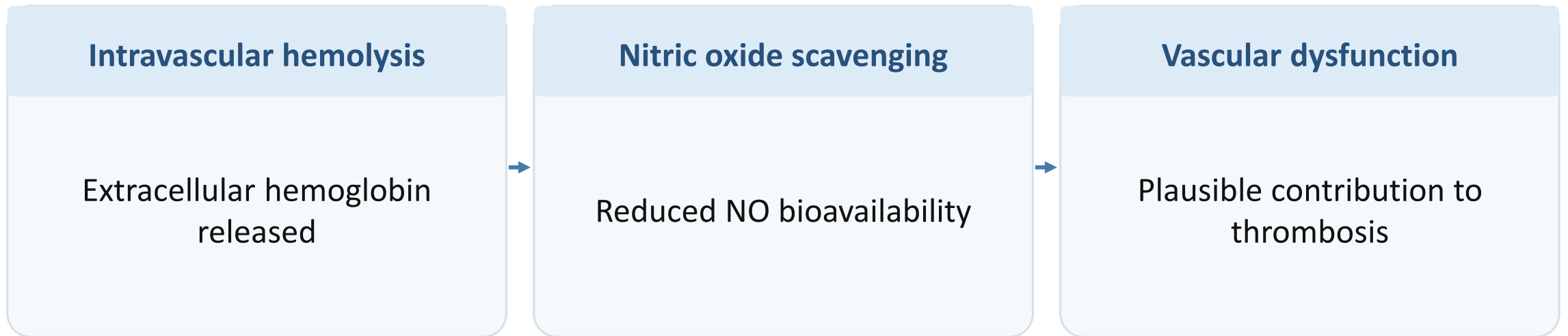
Complement activation and thrombotic risk are linked.

Robbins does not present a single established pathway explaining every event.

Candidate contributors include nitric oxide depletion and endothelial injury.

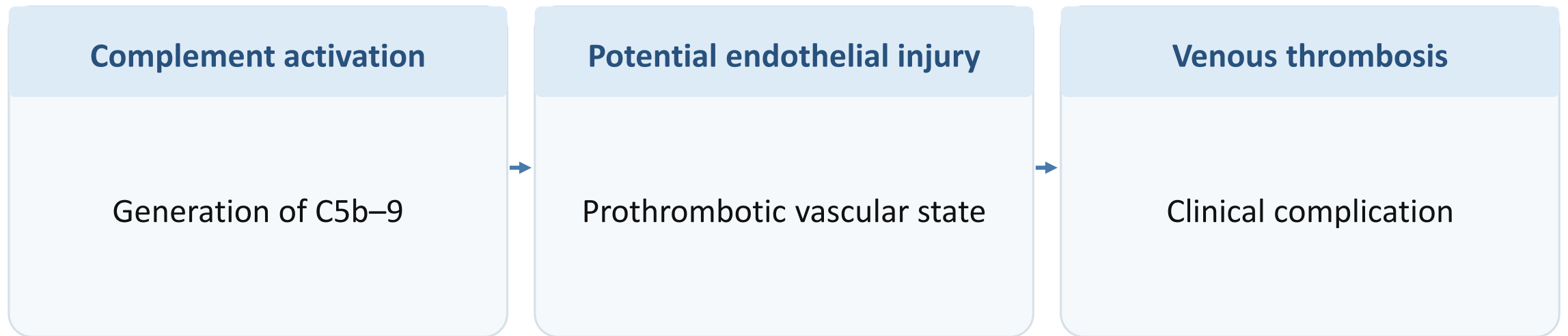
Mechanistic hypotheses are not equivalent to proven single-cause explanations.

Free hemoglobin may reduce nitric oxide availability



Mechanistic hypothesis, not a complete explanation of thrombosis.

Terminal complement may injure endothelium



Proposed contributory pathway; Association does not prove this sequence in every patient.

PNH is a stem-cell disorder, not only an anemia

The clone arises in multipotent hematopoiesis.

Marrow failure and cytopenias may accompany complement-mediated hemolysis.

A fraction of patients later develop a myeloid neoplasm.

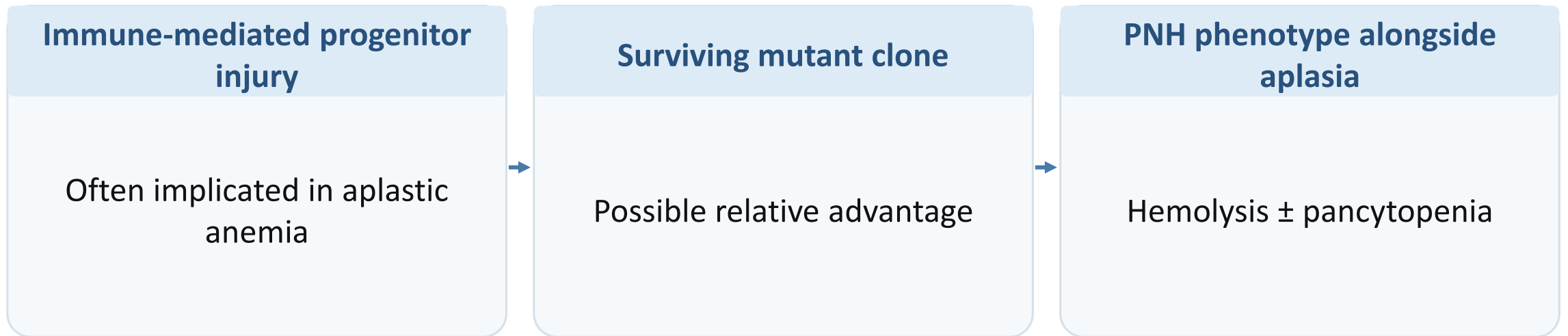
Aplastic anemia impairs blood-cell production

Aplastic anemia is marrow hypocellularity with hematopoietic failure.

Anemia, neutropenia, and thrombocytopenia can occur together.

A patient with PNH may have both peripheral destruction and central production failure.

PNH and immune marrow injury may intersect



Model presented as a mechanistic hypothesis, not a proven inevitable sequence.

Myeloid neoplasms represent clonal progression

Occasional evolution to acute myeloid leukemia or myelodysplastic neoplasm.

This in about 5% of affected patients.

This supports the importance of stem-cell genetic damage beyond the red-cell phenotype.

Three patterns prompt diagnostic consideration

Unexplained hemolysis

Especially intravascular with
urinary hemoglobin/iron
loss

Atypical venous thrombosis

Hepatic, portal, or cerebral
site

Marrow failure

Aplastic anemia with a
possible PNH clone

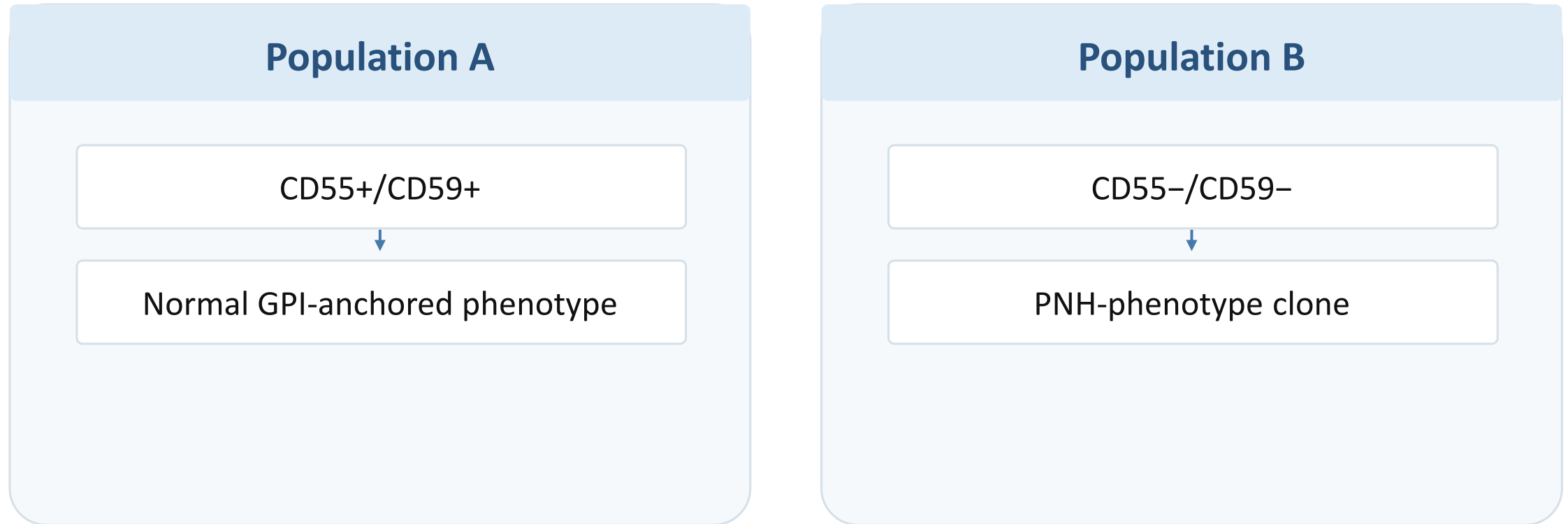
Flow cytometry demonstrates the cellular defect

A test for PNH looks for absent or decreased GPI-linked surface proteins.

Loss of erythrocyte CD59 and describes CD55/CD59 double-negative cells.

The method can demonstrate coexistence of affected and unaffected populations.

Mixed populations are the hallmark of clonal mosaicism



Conceptual phenotype labels, not a reproduced clinical flow plot.

What a CD55/CD59 pattern means

Cell phenotype	Interpretation
CD55+ / CD59+	GPI-linked regulators retained
CD55– / CD59–	Typical loss of both regulators in PNH clone
Mixed positive and negative groups	Residual normal hematopoiesis coexists with mutant clone

This table is an educational reconstruction of the Robbins Fig. 14.13 description.

Contemporary diagnostic practice uses multiple lineages

High-sensitivity testing can assess erythrocytes, granulocytes, and monocytes.

Leukocyte clone fractions are less distorted by prior red-cell transfusion and selective hemolysis.

The selected lineage and gating strategy must be documented.

FLAER interrogates the GPI anchor itself

Fluorescent aerolysin derivative (FLAER) binds GPI anchors.

Granulocyte/monocyte assays combine FLAER with lineage and GPI-linked markers.

Interpret results with laboratory-specific controls and analytical sensitivity.

Why red-cell clone size may underestimate burden

Erythrocytes

PNH red cells may be destroyed by complement
Transfused cells contribute normal phenotypes
Measured fraction may underrepresent marrow clone

Granulocytes / monocytes

Represent another progeny compartment
Less affected by RBC transfusion and lysis
Useful for clonal assessment

Flow-cytometry interpretation requires controls

One absent signal in one lineage is not sufficient for comprehensive characterization.

Confirm GPI deficiency with an appropriate multiparameter panel and multiple cellular populations.

Consider technical gating, specimen quality, and recent transfusion before interpretation.

PNH vs immunohemolytic anemia

Feature	PNH	Immunohemolytic anemia
Primary lesion	Acquired GPI-anchor defect	Red-cell reactive antibody
Complement vulnerability	Lost CD55/CD59 protection	Antibody-associated mechanisms vary
Key diagnostic approach	GPI-protein flow cytometry	Direct antiglobulin testing
RBC destruction	Characteristically intravascular	Often extravascular in warm type

PNH among causes of intravascular hemolysis

Category	Example mechanism	Distinguishing principle
GPI-anchor defect	PNH / complement MAC	Deficient GPI-linked proteins
Mechanical trauma	Valve or microvascular shear	Physical fragmentation
Immune complement	Some antibody-associated hemolysis	Evidence of immunoglobulin/complement binding
Infection / toxin	Parasite or toxin-mediated injury	Trigger-specific context

Clinical case: Chronic hemolysis without dark urine

A patient has persistent laboratory features of hemolysis but reports no nocturnal attacks of visibly red urine. Does this exclude PNH?

Assess whether PNH could still produce chronic hemolysis.

Name the most direct phenotypic test.

Predict whether all circulating red cells must be abnormal.

Case interpretation: The name can mislead

Chronic hemolysis is compatible with PNH.

Flow cytometry for deficient GPI-linked proteins is the defining diagnostic approach.

Mixed normal and deficient populations are expected when normal stem-cell progeny persist.

Clinical case: Hepatic-vein thrombosis

A patient presents with unexplained hepatic venous thrombosis and anemia. What unified hematologic process should be considered?

Identify the thrombotic complication pattern.

Connect red-cell complement sensitivity to the initiating clone.

Select a test that could support the hypothesis.

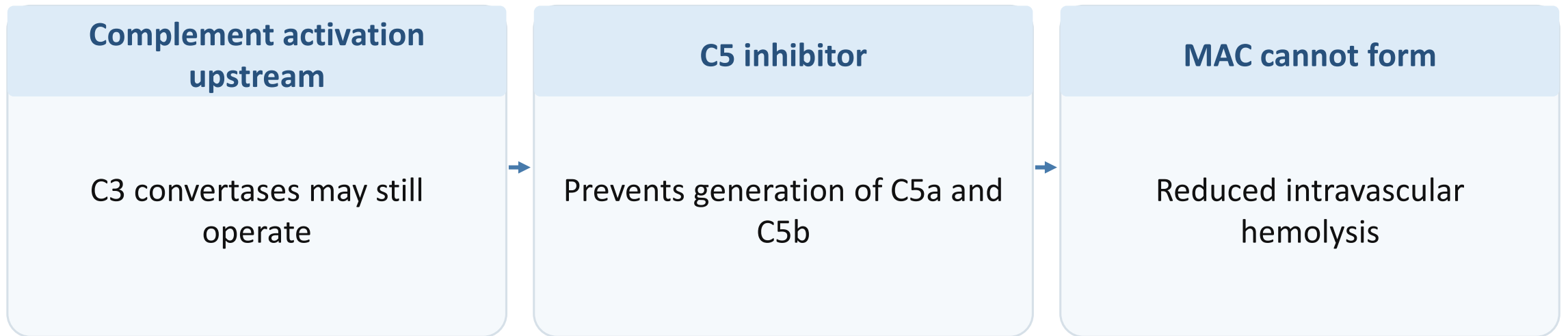
Case interpretation: Recognize the vascular clue

PNH can present with thrombosis in atypical venous territories.

The PIGA-mutant hematopoietic clone generates complement-sensitive cells.

Peripheral-blood flow cytometry can identify GPI-deficient populations.

Complement inhibition intervenes at C5



Why C5 inhibition changes the clinical course

Blocking terminal complement prevents formation of the lytic C5b–9 complex.

Reductions in hemolysis and transfusion requirements.

It also reports a large reduction in thrombotic risk with C5 inhibition.

C5 blockade does not repair the stem-cell mutation

Effect achieved

- Suppresses terminal complement attack
- Reduces complement-mediated RBC lysis
- Can reduce downstream clinical complications

What remains

- PIGA-mutant clone persists
- GPI-anchor deficiency remains
- Marrow disease needs independent assessment

Residual anemia under C5 blockade: A further mechanism

C3 deposition can continue when proximal complement activation is not blocked.

C3-opsonized red cells may undergo extravascular clearance.

This is one reason control of intravascular lysis does not guarantee normal hemoglobin.

Complement-targeted drugs require infection precautions

Terminal complement has an important role in defense against *Neisseria meningitidis*.

Serious or fatal meningococcal infection as a treatment hazard.

Inhibitor choice must be paired with infection-prevention planning.

The infection risk is clinically actionable, not a theoretical footnote.

Risk reduction does not eliminate meningococcal risk

CDC recommends meningococcal vaccination for people receiving complement inhibitors.

Vaccination and antimicrobial approaches may offer incomplete protection.

Suspected meningococcal disease requires urgent evaluation despite prevention measures.

Marrow-directed therapy addresses a different component

Immunosuppressive therapy can help some patients with accompanying marrow aplasia.

It targets immune marrow suppression rather than directly replacing GPI anchors.

Distinguish treatment of hemolysis from treatment of marrow failure.

Hematopoietic transplantation is potentially curative

Replacing the abnormal hematopoietic stem-cell compartment can remove the source of the clone.

Transplantation as the curative strategy.

It is usually reserved for serious concurrent aplastic anemia or myeloid malignancy because of treatment risk.

Management logic depends on the dominant phenotype

Hemolysis / thrombosis

Complement-directed
treatment and complication
assessment

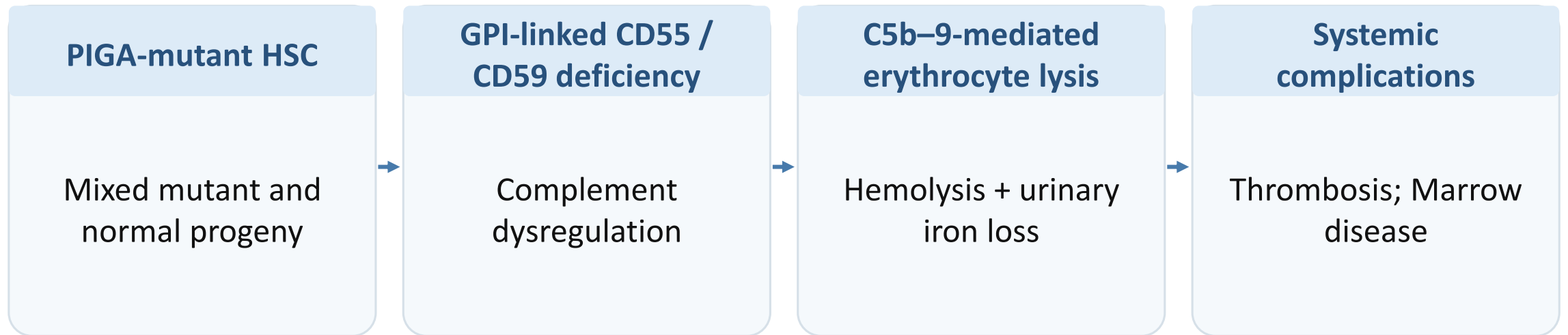
Marrow aplasia

Evaluate hematopoietic
failure; Consider marrow-
directed therapy

Myeloid malignancy

Specialist neoplasm-
directed evaluation;
Transplantation may be
relevant

High-yield synthesis: Mutation to clinical harm



Check your understanding

Which statement identifies the mechanistic distinction most important for understanding PNH?

- A. CD55 blocks terminal C9 insertion; CD59 degrades C3 convertase.
- B. CD55 accelerates convertase decay; CD59 blocks MAC formation.
- C. PIGA directly encodes the CD59 protein.
- D. PNH affects only mature erythrocytes.

Mechanistic answer: B

CD55 acts mainly at the C3/C5 convertase stage.

CD59 protects at terminal membrane attack complex assembly.

A PIGA mutation disrupts the shared GPI anchoring of multiple proteins.

Clinical integration: Diagnostic priorities

Think of PNH when hemolysis coexists with unusual venous thrombosis or marrow aplasia.

Demonstrate GPI-linked protein deficiency in blood-cell populations by flow cytometry.

Interpret clonal mosaicism and the difference between red-cell and leukocyte fractions.

Assess hemolytic, thrombotic, and marrow components separately.

Selected source references

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