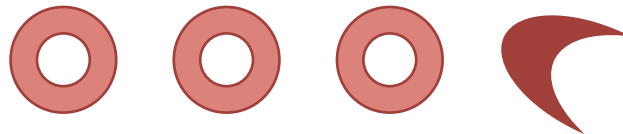


Sickle Cell Disease

Inherited hemoglobinopathy: molecular mechanism, morphology and clinicopathologic consequences



Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Trace the β -globin mutation to HbS polymerization and red-cell injury.
- Explain why hypoxia, dehydration, acidosis and slowed flow accentuate sickling.
- Recognize characteristic blood, marrow and splenic pathology.
- Relate hemolysis and vaso-occlusion to acute crises and chronic organ damage.
- Connect diagnostic tests and disease-modifying treatment to their mechanistic targets.

One mutation, two major injury pathways

Deoxygenated HbS polymerizes within red cells

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graph TD; A[Deoxygenated HbS polymerizes within red cells] --> B[Cumulative membrane injury<br/>Premature red-cell destruction<br/>Chronic hemolytic anemia]; A --> C[Adhesion and vascular stagnation<br/>Microvascular occlusion<br/>Ischemia and tissue infarction];
```

- Cumulative membrane injury
- Premature red-cell destruction
- Chronic hemolytic anemia

- Adhesion and vascular stagnation
- Microvascular occlusion
- Ischemia and tissue infarction

Both pathways arise from abnormal HbS behavior but do not track perfectly together.

Hemoglobin is a four-chain molecule

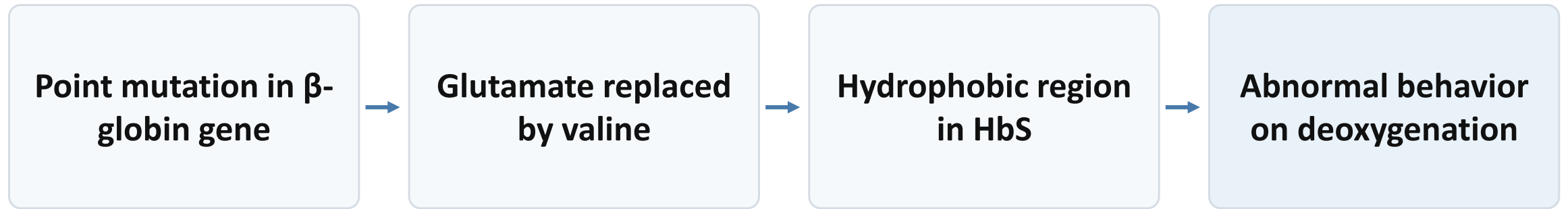
Normal adult hemoglobins

- HbA: $\alpha_2\beta_2$ — predominant adult hemoglobin
- HbA₂: $\alpha_2\delta_2$ — minor adult fraction
- HbF: $\alpha_2\gamma_2$ — fetal hemoglobin

Disease-associated form

- HbS: $\alpha_2\beta S_2$ in homozygous sickle cell anemia
- The mutation changes β -globin properties, not the basic tetrameric architecture
- Mixtures of hemoglobins influence sickling behavior

A missense mutation changes β -globin



The molecular substitution alters physicochemical interactions between hemoglobin molecules.

HbS differs because valine is hydrophobic

Normal β -globin residue

- Glutamate carries a charged side chain.
- Surface interactions maintain soluble hemoglobin behavior.

Mutant β S-globin residue

- Valine has a hydrophobic side chain.
- Deoxygenation facilitates inappropriate HbS association.
- Higher-order HbS polymers distort the red cell.

Inheritance: Two HbAS parents

Gametes: A or S from each heterozygous parent

	A	S
A	AA	AS
S	AS	SS

Each pregnancy has a one-in-four chance of HbSS, a two-in-four chance of HbAS, and a one-in-four chance of HbAA.

Sickle cell trait is not sickle cell anemia

HbAS: Sickle cell trait

- One sickle allele; HbA plus HbS.
- Most red cells resist sickling under usual oxygen conditions.
- Prolonged severe hypoxia may elicit sickling.

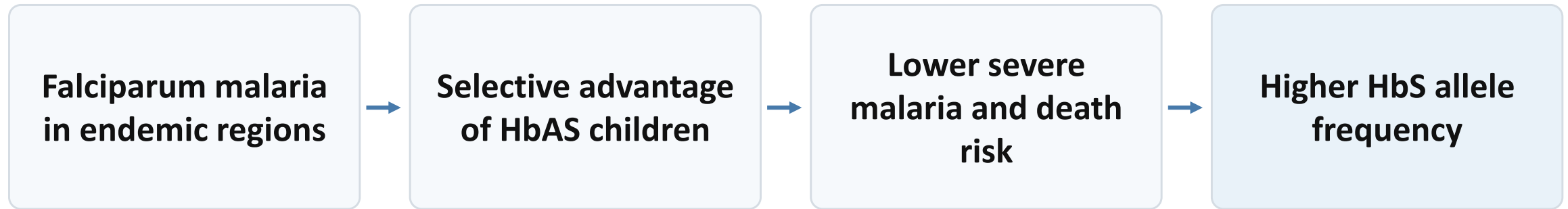
HbSS: Sickle cell anemia

- Two sickle alleles; HbS predominates.
- Polymerization occurs with ordinary physiologic deoxygenation.
- Chronic hemolysis and clinically important vascular injury result.

Hemoglobin mixtures modify disease severity

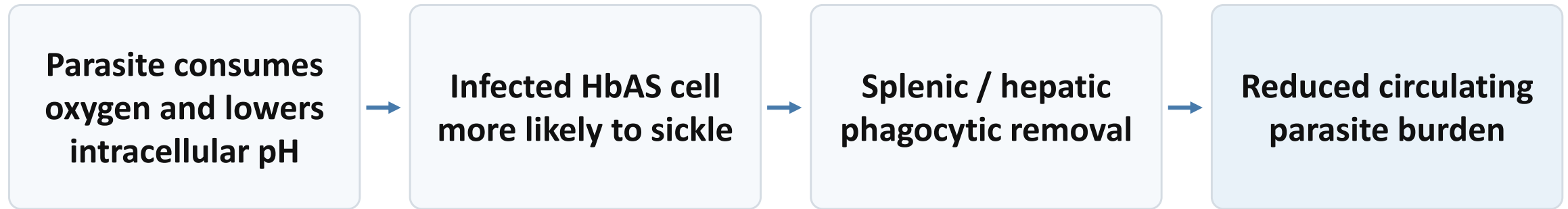
Hemoglobin context	Key molecular property	Clinicopathologic implication
HbAS	HbA interferes with HbS assembly	Mostly asymptomatic trait
HbSS	Predominantly HbS	Sickling disease
HbSC	HbS plus HbC; Cell dehydration	Symptomatic, often less severe than HbSS
HbF-rich cells	HbF strongly inhibits HbS polymerization	Lower sickling tendency

Malaria drove positive selection for HbAS



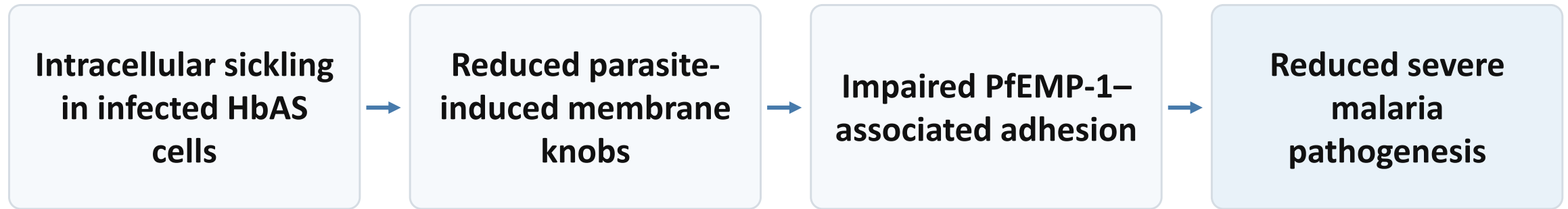
A population-genetic explanation for the distribution of HbS, not a benefit of HbSS disease.

Malaria protection: Enhanced red-cell clearance



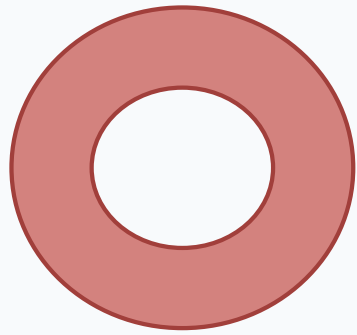
Proposed mechanism; Mechanistic details are not fully established.

Malaria protection: Impaired adhesion



Proposed mechanism; Parasite PfEMP-1 is involved in endothelial adhesion.

Deoxygenation is the polymerization switch



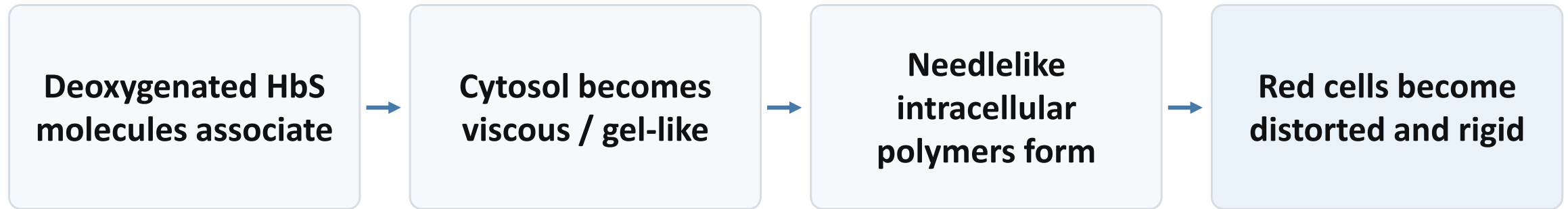
Oxygenated | deoxygenated

Schematic

- Oxygenated HbS remains more soluble.
- Deoxygenated HbS has increased tendency to polymerize.
- Reoxygenation may reverse early, not yet fixed, shape change.

Schematic cell silhouettes — not a peripheral blood smear.

Molecular assembly progresses to long fibers



A time-dependent process: Sickling depends on both kinetics and microvascular transit.

Sickling is governed by local conditions

Variable	Promotes sickling	Reduces sickling
Oxygenation	Deoxygenation	Reoxygenation before irreversible injury
Cell Hb concentration	Dehydration / higher MCHC	Lower HbS concentration
Intracellular pH	Reduced pH	Less acidic conditions
Circulatory transit	Slow flow / prolonged deoxygenation	Fast transit
Hb composition	Higher effective HbS fraction	HbA or especially HbF

HbA delays polymer growth in HbAS cells

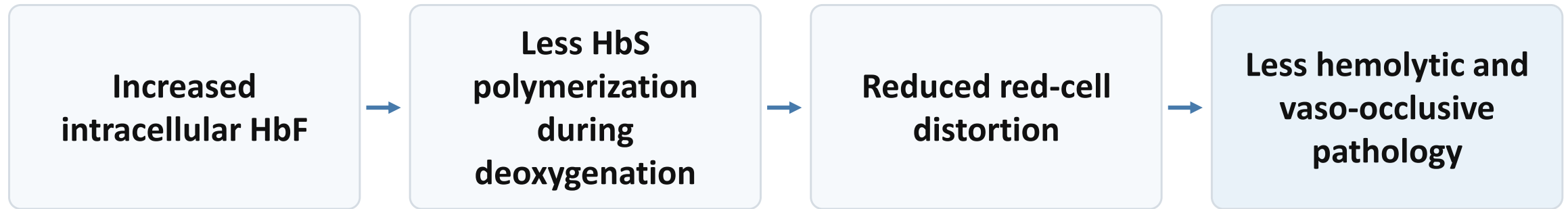
HbAS red cells

- Approximately 40% HbS' description.
- The remaining HbA interferes with HbS polymerization.
- Prolonged, relatively severe hypoxia is usually needed for sickling.

HbSS red cells

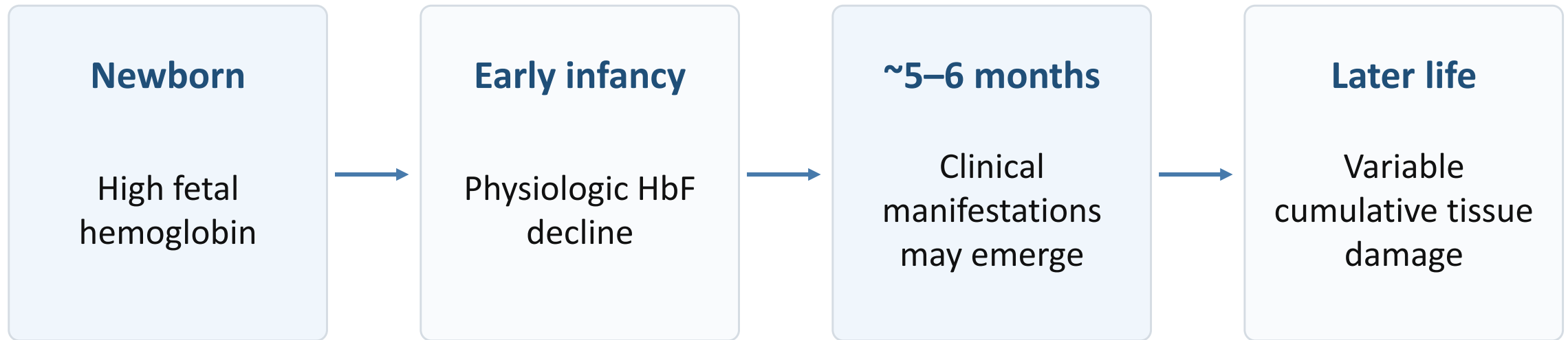
- Almost all hemoglobin is HbS.
- The inhibitory effect of HbA is absent.
- Sickling becomes important at typical tissue oxygen tensions.

HbF is a strong inhibitor of HbS polymers



High HbF expression is a major naturally occurring and therapeutic modifier.

Why symptoms often begin after infancy



Timing for HbSS; Onset and severity vary among individuals.

Persistent fetal hemoglobin can attenuate disease

Typical HbF decline

- HbF falls during infancy.
- HbS becomes the major hemoglobin species.
- Vaso-occlusive and hemolytic manifestations appear.

Persistently high HbF

- HbF interferes strongly with HbS assembly.
- Sickling frequency and severity may decline.
- This illustrates a genetic modifier of phenotype.

HbSC is a distinct sickling phenotype

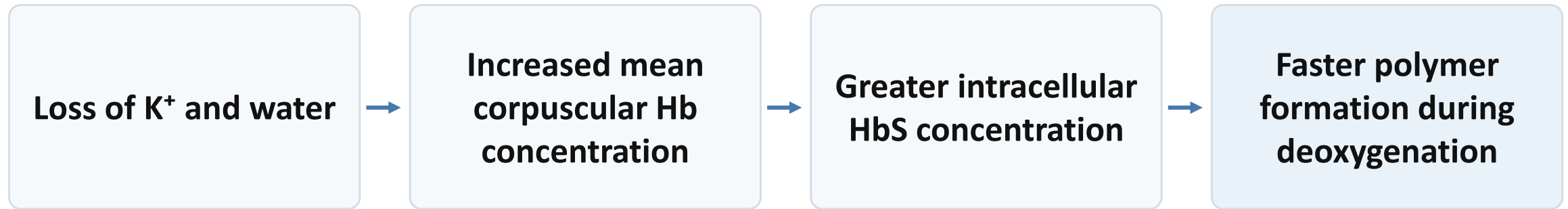
HbAS trait

- HbS diluted by a larger HbA component.
- Sickling usually requires severe or prolonged hypoxia.

Compound HbSC

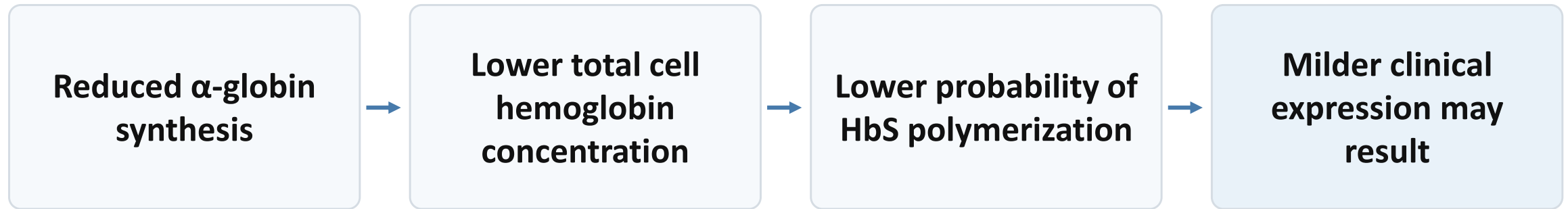
- HbS constitutes a larger share of total hemoglobin.
- Aging red cells lose salts and water.
- The resultant HbS concentration permits symptomatic disease.

Cell dehydration amplifies HbS polymerization



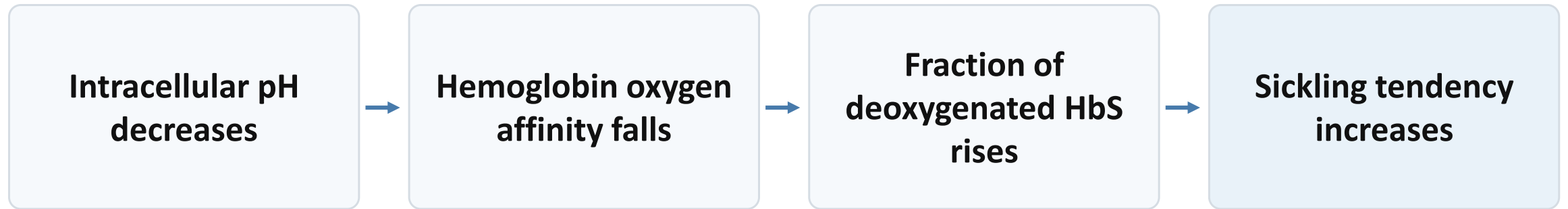
HbS concentration strongly affects the probability of aggregation.

Coexistent α -thalassemia may lessen sickling



The effect of accompanying α -thalassemia in HbSS.

Acidosis favors deoxygenated HbS



The effect is mediated partly by the oxygenation state of HbS.

Transit time determines where cells sickle

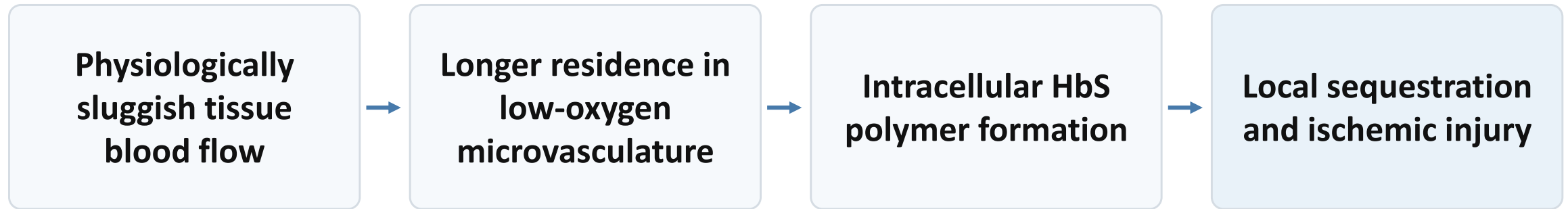
Rapid microvascular transit

- Deoxygenated exposure may be brief.
- Polymerization may not reach a critical threshold before cells exit.
- Major occlusion is less likely under ordinary flow.

Slow microvascular transit

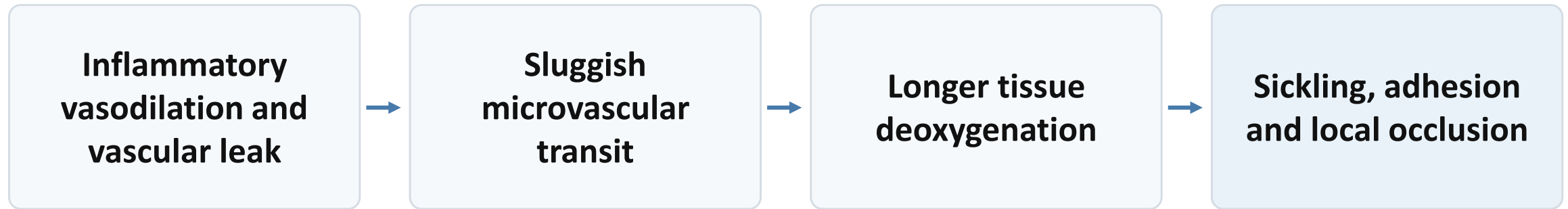
- Red cells remain deoxygenated longer.
- HbS polymers can assemble during transit.
- Rigid cells arrest and reinforce local obstruction.

The spleen and marrow are high-risk beds



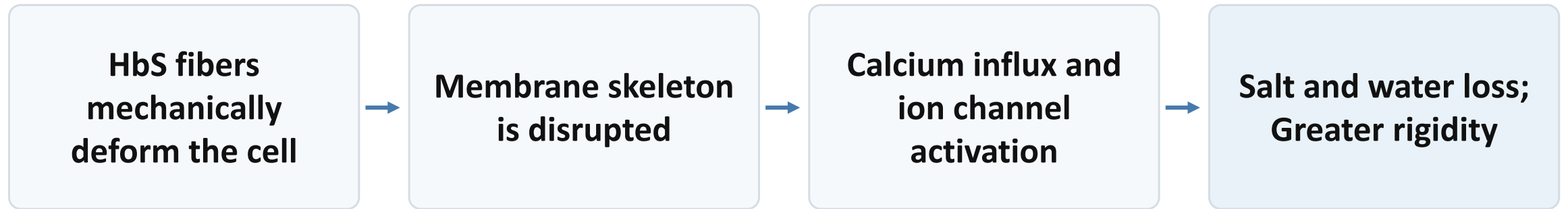
Normal slow transit in the spleen and bone marrow.

Inflamed vessels become more permissive to stasis



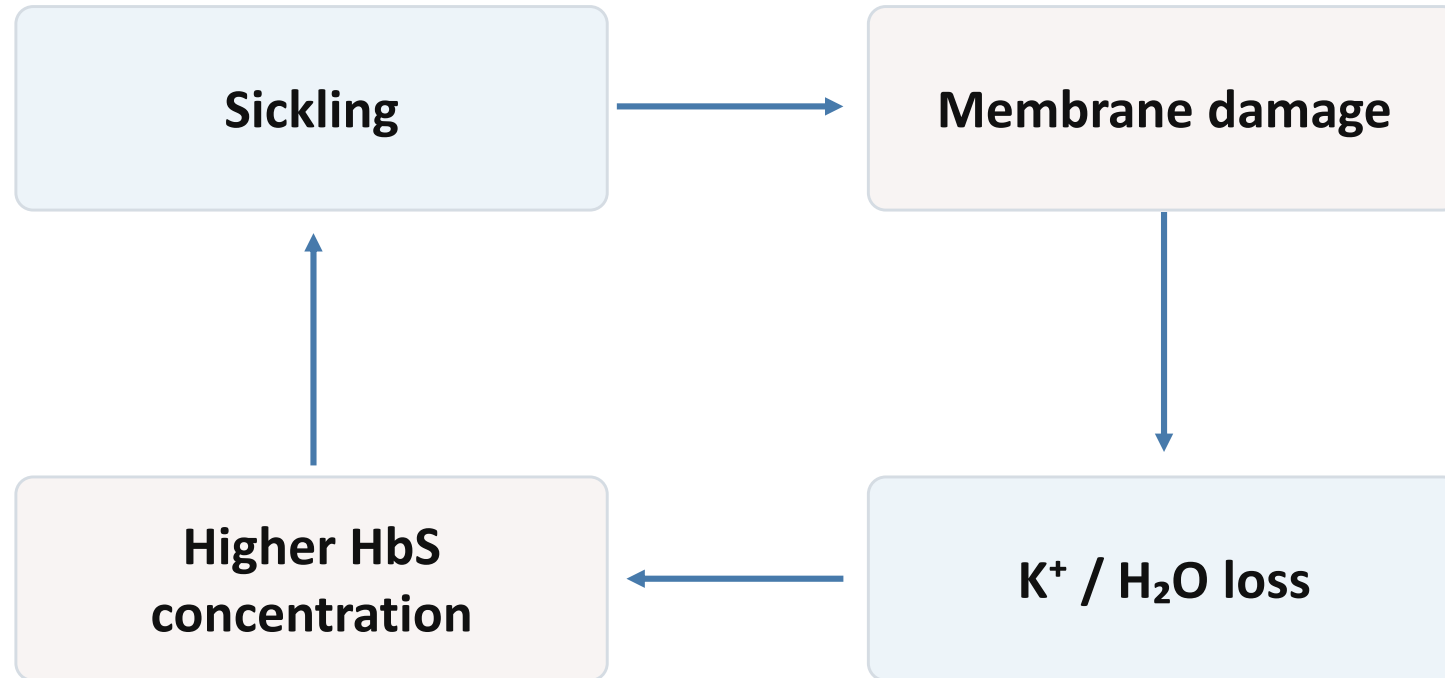
Inflammation also enhances endothelial adhesion molecule expression.

Repeated sickling injures the cell membrane



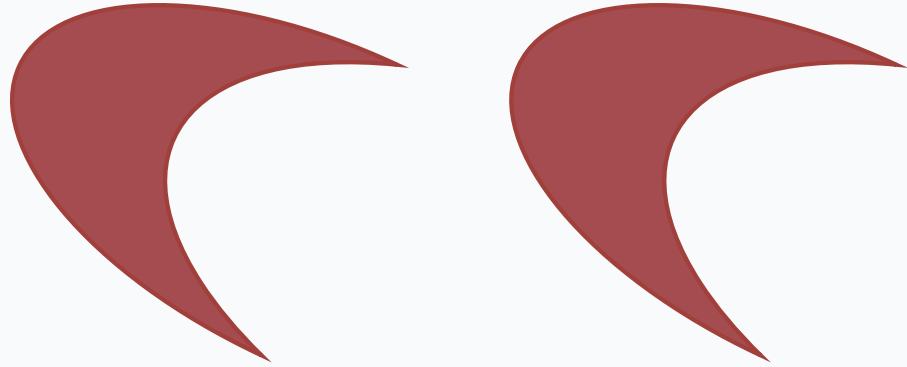
Membrane injury persists when an early sickling episode reverses.

A dehydration–rigidity feedback loop



Recurrent episodes favor dense, poorly deformable erythrocytes.

Reversible and irreversible sickling differ



Earlier | permanently damaged

Schematic

- Early distortions may reverse on oxygenation.
- Repeated cycles create cumulative, permanent membrane damage.
- Some cells remain sickled even when oxygenated.

Schematic silhouettes — irreversibility refers to sustained cell shape and stiffness.

Sickle cells are removed through two routes

Sickled cells have reduced survival

```
graph TD; A[Sickled cells have reduced survival] --> B[Extravascular hemolysis]; A --> C[Intravascular hemolysis];
```

- Poor deformability traps cells in phagocytic organs.
- Mononuclear phagocytes remove severely damaged cells.
- Extravascular hemolysis predominates.

- Sickled cells are mechanically fragile.
- Some rupture within the circulation.
- Intravascular hemolysis also occurs.

The proportion of irreversibly sickled cells correlates with severity of hemolysis.

Hemolysis and vaso-occlusion are not identical

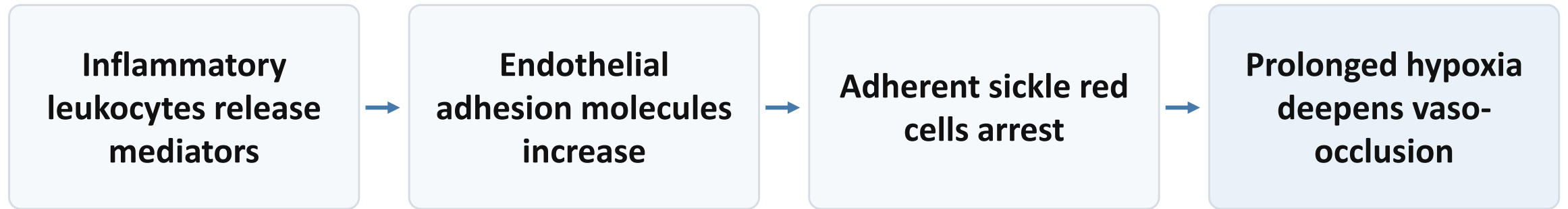
Chronic hemolysis

- Tracks cumulative membrane injury and irreversible sickling.
- Produces anemia, bilirubin generation and free plasma hemoglobin.

Microvascular occlusion

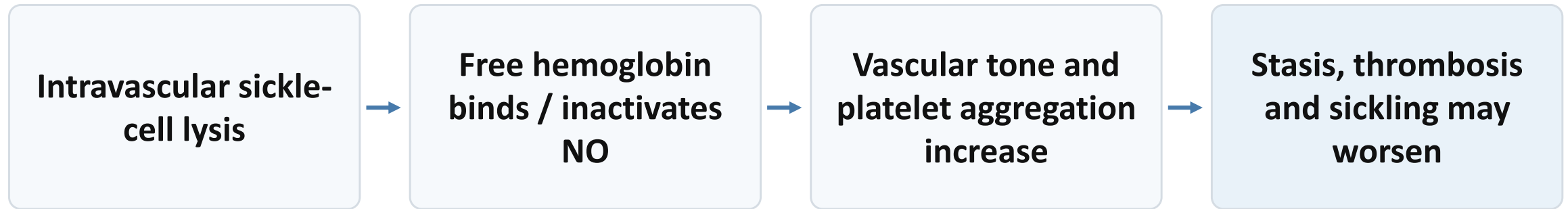
- Depends also on red-cell adhesion and vascular conditions.
- Not simply proportional to irreversibly sickled cell count.
- Produces tissue hypoxia, pain and infarction.

Adhesion links inflammation to occlusion



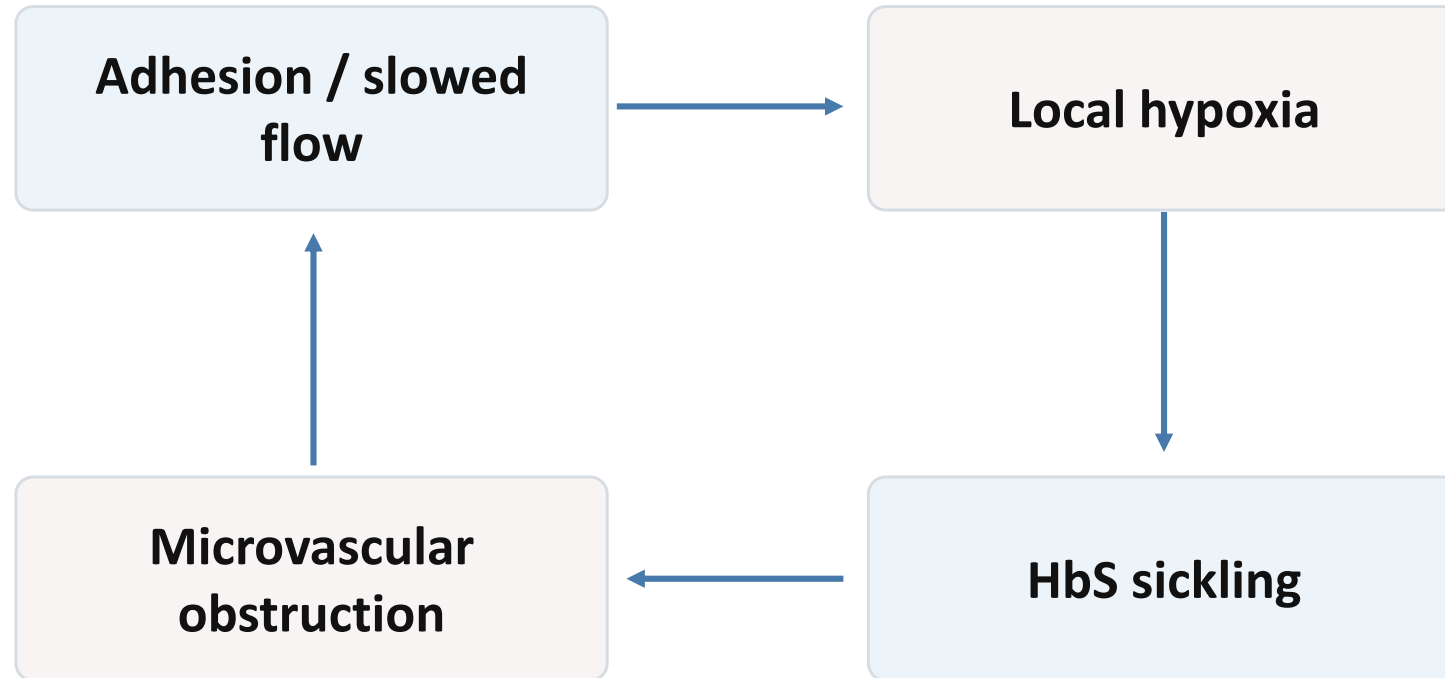
Adhesion is a dynamic process involving sickle cells and activated endothelium.

Free hemoglobin may deplete nitric oxide



Nitric-oxide depletion as a possible contributor, not the sole cause of occlusion.

Microvascular occlusion creates a vicious cycle



Each turn can increase deoxygenation and promote further sickling.

Two parallel paths explain the core phenotype

HbS polymerization in deoxygenated cells

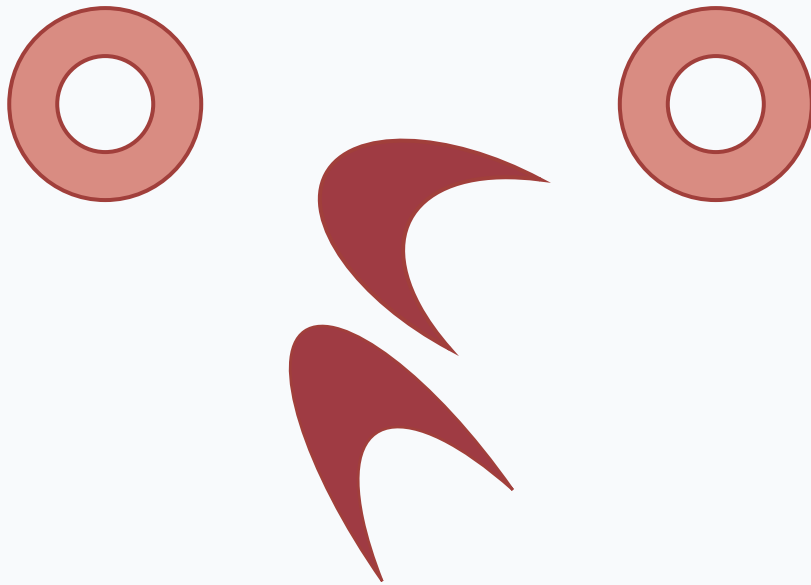
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graph TD; A[HbS polymerization in deoxygenated cells] --> B[• Membrane injury → shortened red-cell survival  
• Anemia → increased marrow erythropoiesis  
• Heme turnover → jaundice / pigment stones]; A --> C[• Adhesive rigid cells → obstruction  
• Infarction → painful crises  
• Chronic ischemia → multisystem injury];
```

- Membrane injury → shortened red-cell survival
- Anemia → increased marrow erythropoiesis
- Heme turnover → jaundice / pigment stones

- Adhesive rigid cells → obstruction
- Infarction → painful crises
- Chronic ischemia → multisystem injury

The paths interact through inflammation, free hemoglobin and tissue oxygen delivery.

Peripheral blood: Characteristic cell patterns

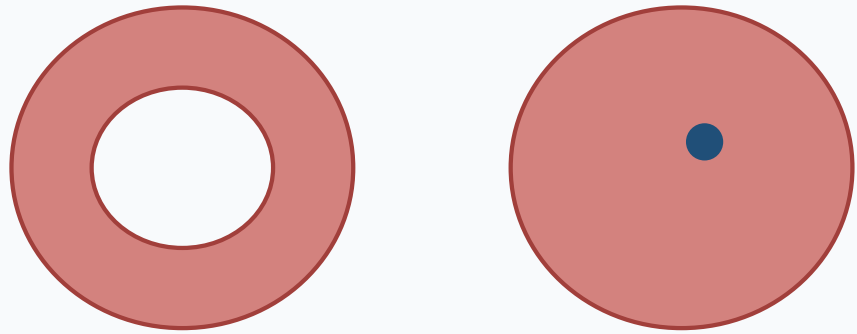


Cell silhouettes (schematic)

- Irreversibly sickled cells have elongated curved or pointed contours.
- Target cells accompany altered red-cell hydration.
- Anisocytosis and poikilocytosis are present.
- Reticulocytosis signals compensatory erythropoiesis.

Original schematic of cell shapes; Not authentic patient microscopy.

Howell–Jolly bodies signal loss of splenic function



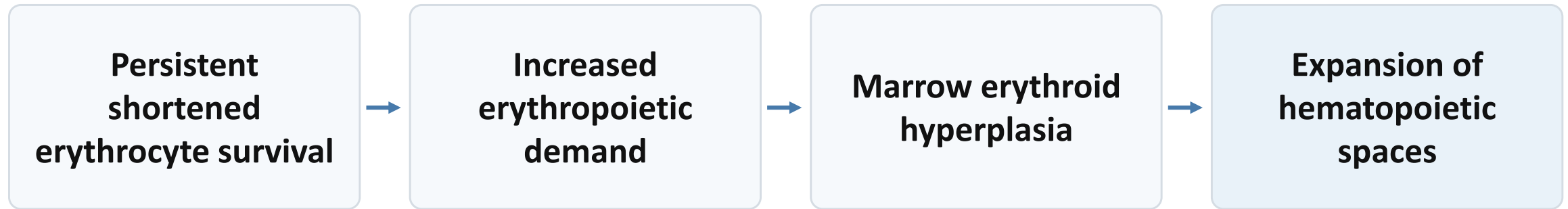
Red cell | nuclear remnant

Schematic

- Small nuclear remnants may persist within circulating erythrocytes.
- Normally the spleen removes these inclusions.
- Their appearance in sickle cell disease supports functional asplenia.

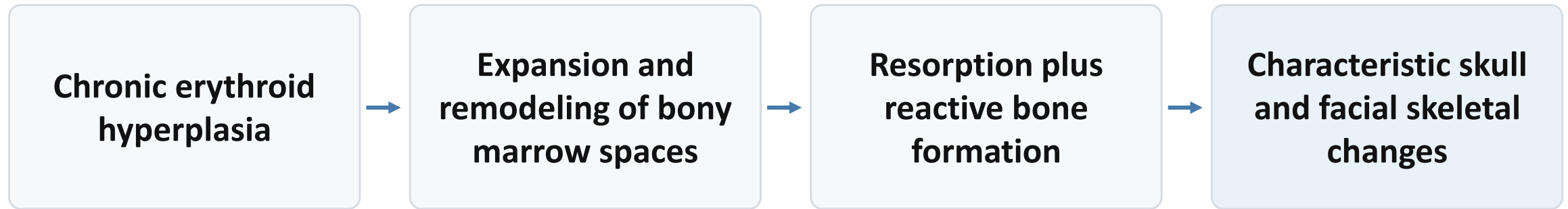
Schematic depiction of a red cell with an inclusion; Not a micrograph.

Marrow expands to compensate for hemolysis



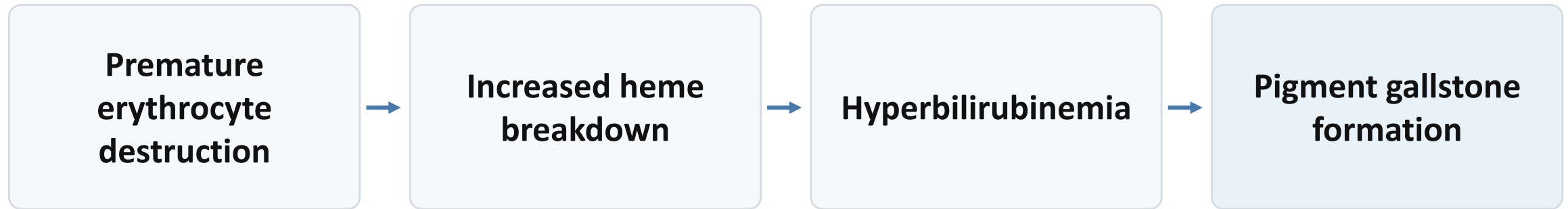
Extramedullary hematopoiesis may develop when compensatory demand is substantial.

Marrow expansion remodels the skeleton



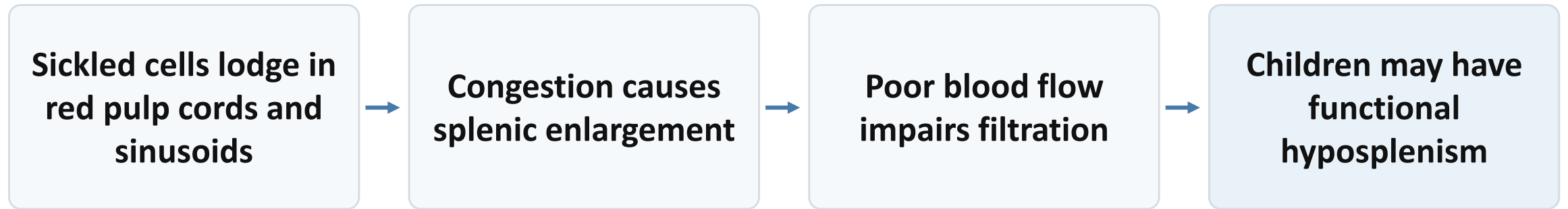
Prominent cheekbones and a “crewcut” skull appearance.

Hemoglobin turnover produces pigment stones



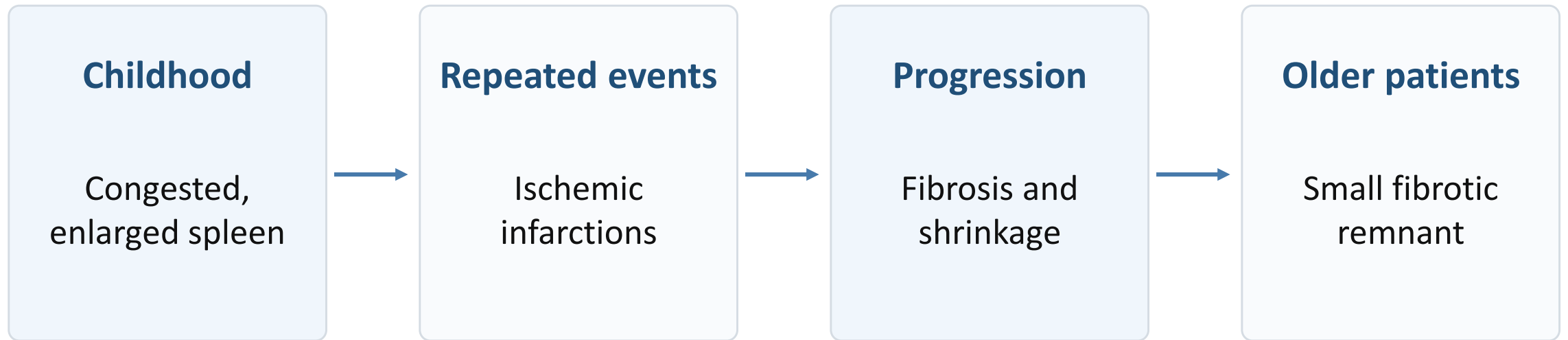
This is a consequence of sustained hemolysis rather than microvascular infarction.

Early spleen: Sequestration and congestion



Pronounced early red-pulp congestion and trapping.

Repeated infarction leads to autosplenectomy



Functional loss may precede near-complete anatomic involution.

Splenic destruction changes infection risk

Progressive loss of splenic filtration

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graph TD; A[Progressive loss of splenic filtration] --> B[Reduced clearance of organisms from blood<br/>Impaired defense against encapsulated bacteria]; A --> C[Howell–Jolly bodies persist<br/>Risk of serious bacterial sepsis and meningitis];
```

- Reduced clearance of organisms from blood
- Impaired defense against encapsulated bacteria

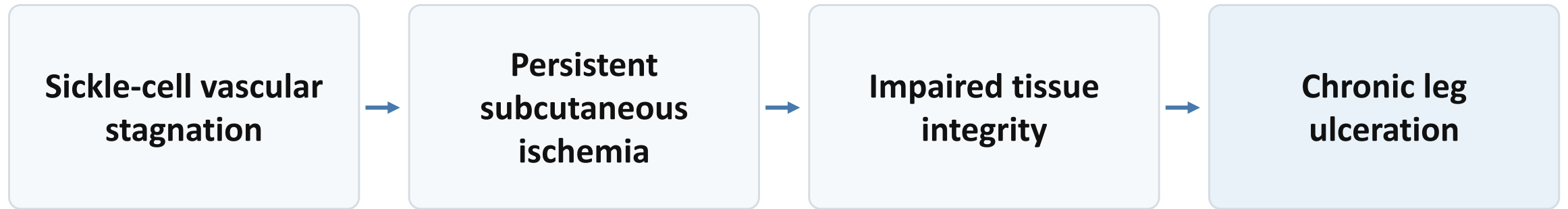
- Howell–Jolly bodies persist
- Risk of serious bacterial sepsis and meningitis

Source additionally notes impaired alternative-pathway opsonization of uncertain origin.

Infarction is a systemic process

Affected site	Dominant injury	Potential consequence
Bone / marrow	Microvascular infarction	Severe painful bone crisis
Brain	Ischemic vascular injury	Stroke
Kidney	Medullary sickling / injury	Concentrating defect
Spleen	Recurrent infarction	Functional / anatomic asplenia
Retina	Vascular obstruction	Visual impairment
Pulmonary circulation	Vascular disease	Respiratory dysfunction

Chronic leg ulcers reflect local stasis



Ulcers particularly in adults; They are uncommon in children.

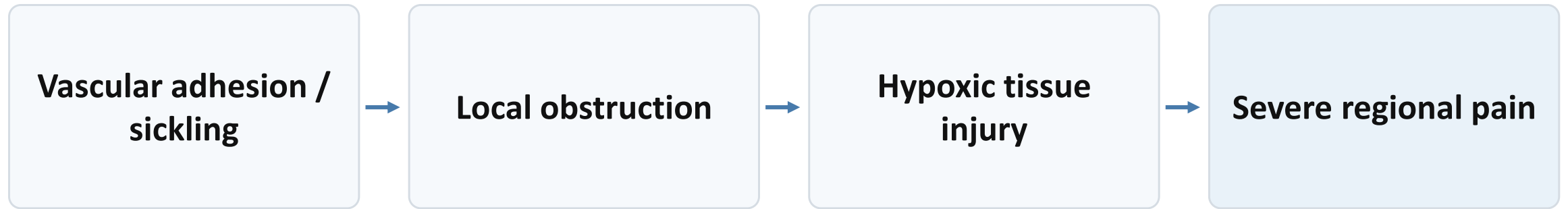
Baseline phenotype: Chronic hemolytic anemia

- Hematocrit commonly around 18%–30% in sickle cell anemia.
- Reticulocytosis reflects persistent marrow compensation.
- Unconjugated bilirubin generation explains chronic jaundice and pigment stones.
- Irreversibly sickled cells may be visible on the peripheral blood film.

Acute crises have different mechanisms

Crisis	Immediate process	Characteristic pattern
Vaso-occlusive	Microvascular obstruction / infarction	Regional severe pain
Acute chest	Pulmonary inflammation + sickling	Fever, cough, pain, infiltrates
Splenic sequestration	Rapid trapping of blood in spleen	Enlarging spleen, hypovolemia
Aplastic	Parvovirus B19 suppresses erythropoiesis	Abrupt anemia with impaired marrow output

Pain crises are episodes of tissue infarction



Infection, dehydration and acidosis can precipitate crises, but an obvious trigger is often absent.

Hand–foot syndrome is a pediatric manifestation

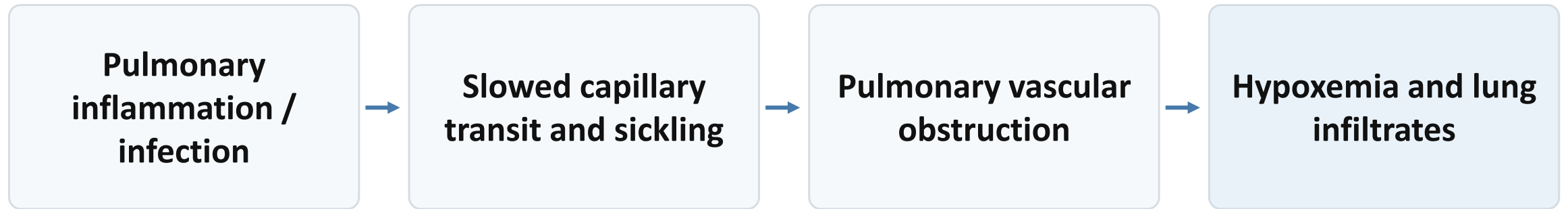
What occurs

- Acute vaso-occlusive bone injury in the hands and feet.
- Pain and swelling constitute dactylitis.
- Often occurs in childhood.

Diagnostic implication

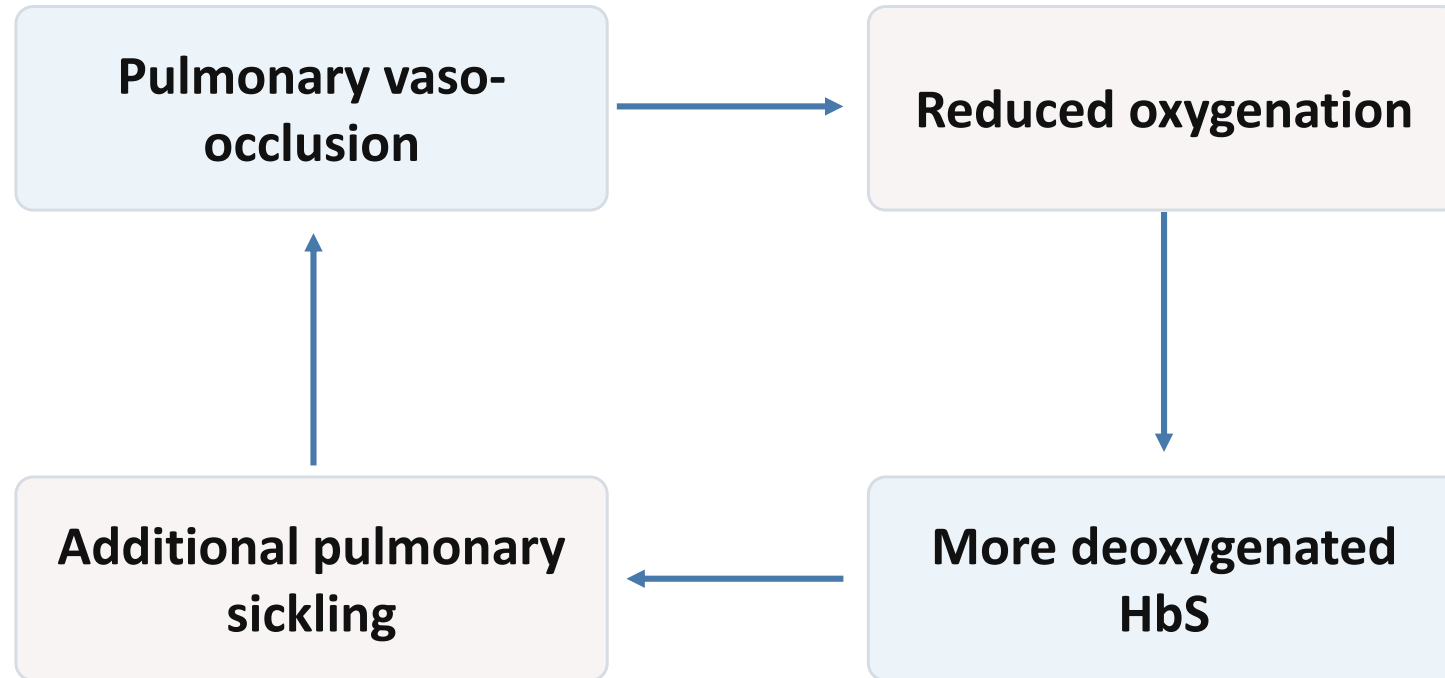
- Bone infarction can mimic acute osteomyelitis.
- Clinical context and investigation are needed to distinguish them.
- Do not infer infection merely from painful swelling.

Acute chest syndrome is pulmonary vaso-occlusion



Typical features: Fever, cough, chest pain and pulmonary infiltrates.

Acute chest syndrome can self-amplify



This feedback can become rapidly life-threatening; Exchange transfusion may be needed.

Stroke reflects cerebral vascular injury

Vascular obstruction compromises brain oxygenation

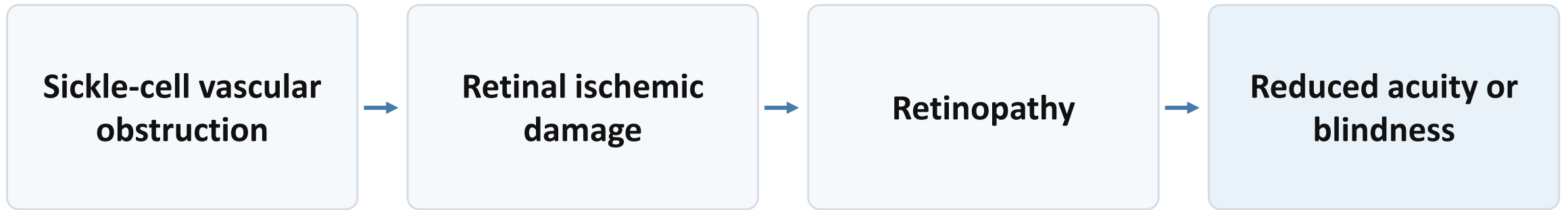
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graph TD; A[Stroke reflects cerebral vascular injury] --> B[Vascular obstruction compromises brain oxygenation]; B --> C[Sickle red-cell adhesion<br/>Endothelial vascular interactions]; B --> D[Proposed NO depletion<br/>Vasoconstriction and ischemia];
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- Sickle red-cell adhesion
- Endothelial vascular interactions

- Proposed NO depletion
- Vasoconstriction and ischemia

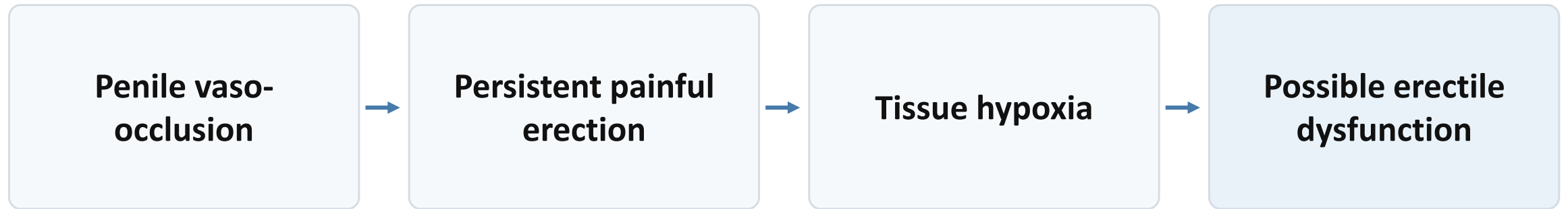
The relative contribution of these factors as proposed mechanisms.

Retinopathy can threaten sight



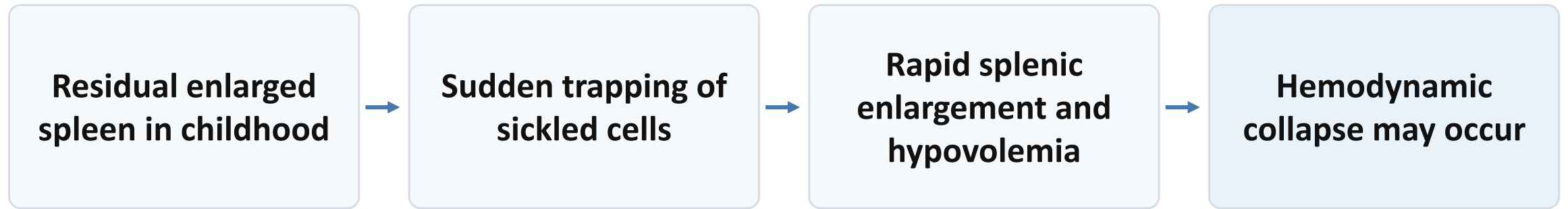
The organ-level manifestation derives from the same occlusive vascular pathology.

Priapism is a vaso-occlusive complication



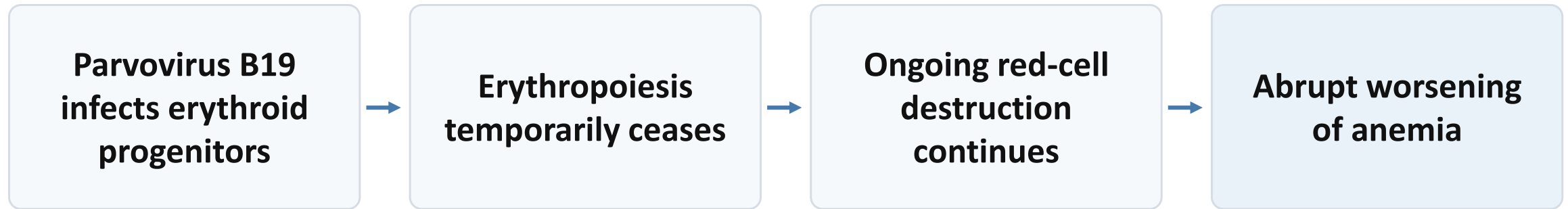
The complication in males after puberty.

Splenic sequestration can cause shock



This is mechanistically different from gradual autosplenectomy.

Parvovirus B19 causes aplastic crisis



The failure of compensatory production, rather than increased sickling alone, explains the acute drop.

Different crises demand different reasoning

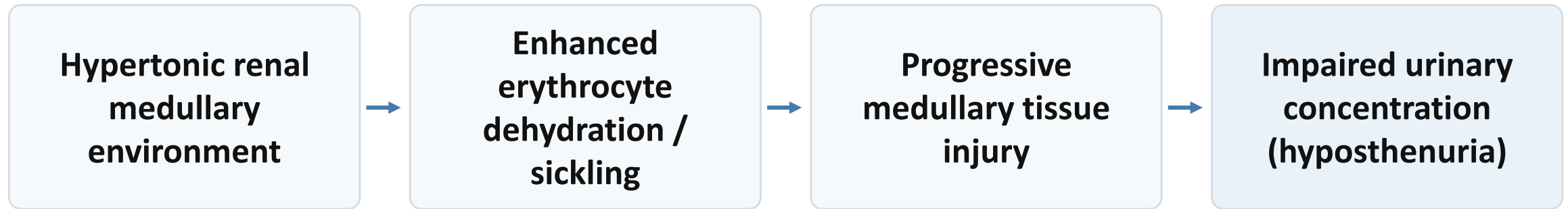
Sudden severe pain / hypoxemia

- Consider tissue ischemia and vaso-occlusion.
- A new pulmonary infiltrate and respiratory signs indicate acute chest syndrome.

Sudden anemia

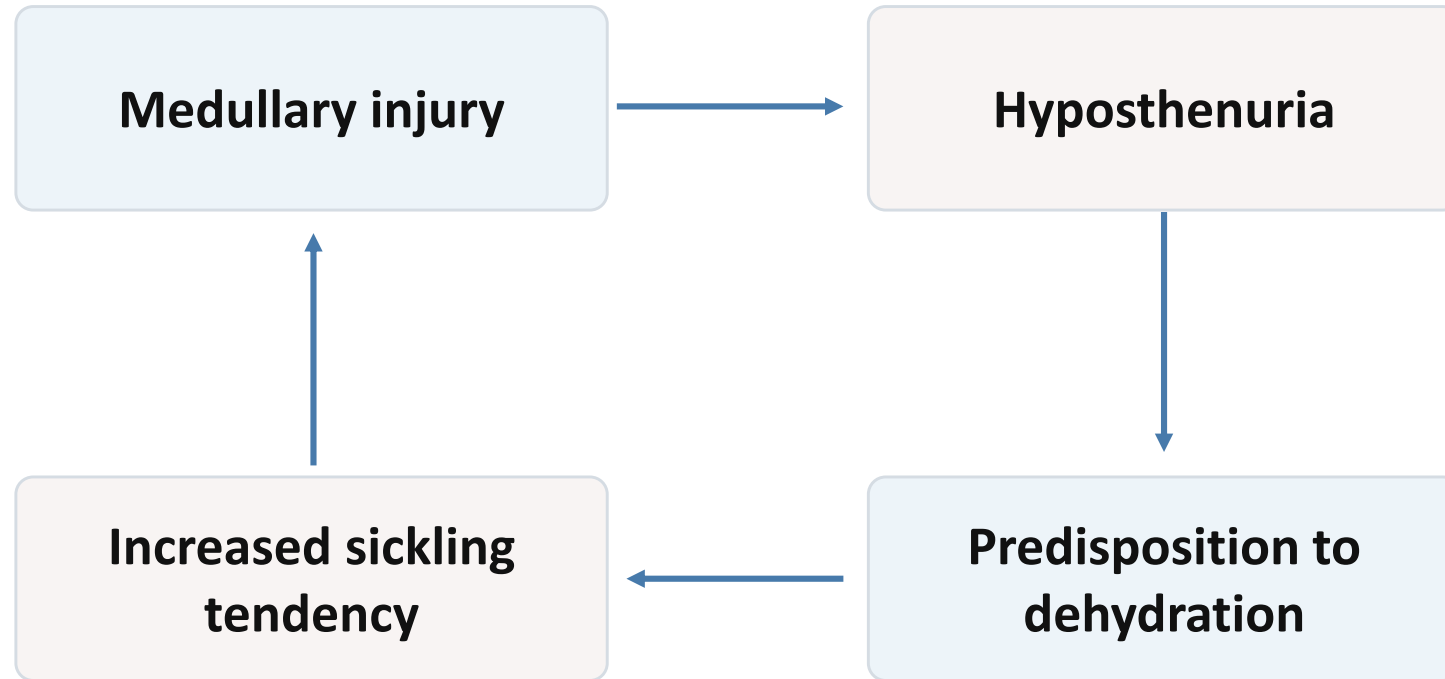
- Enlarging spleen suggests sequestration.
- Suppressed erythropoiesis suggests aplastic crisis.
- Same underlying disease; Different proximate mechanism.

Renal medulla promotes local sickling



Urinary concentrating defects aggravate dehydration risk.

Hyposthenuria increases vulnerability to crises

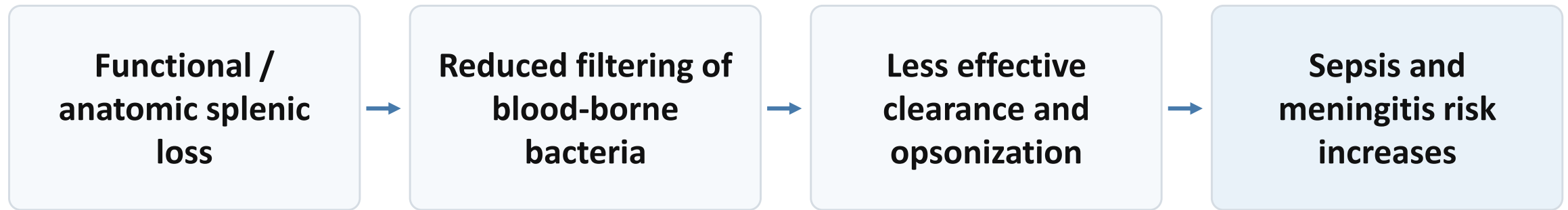


A physiologic feedback linking kidney pathology to subsequent vaso-occlusive events.

Chronic hypoxia affects multiple organs

Organ system	Mechanism or lesion	Clinical implication
Growth / development	Sustained anemia and tissue hypoxia	Impaired growth
Spleen	Congestion, infarction, fibrosis	Asplenia
Heart	Chronic hypoxic stress	Cardiac damage
Kidney	Medullary sickling	Hyposthenuria
Lungs	Chronic vascular / hypoxic injury	Pulmonary dysfunction

Asplenia predisposes to encapsulated infection



Robbins specifically highlights pneumococcus, H. Influenzae and meningococcus.

Prevention targets infectious vulnerability

Mechanistic vulnerability

- Progressive loss of splenic tissue and function.
- Impaired antibacterial defense, especially during childhood.

Measures

- Vaccination against key pathogens.
- Prophylactic antibiotics in appropriate patients.
- Both help lower serious infection incidence.

Clinical expression varies considerably

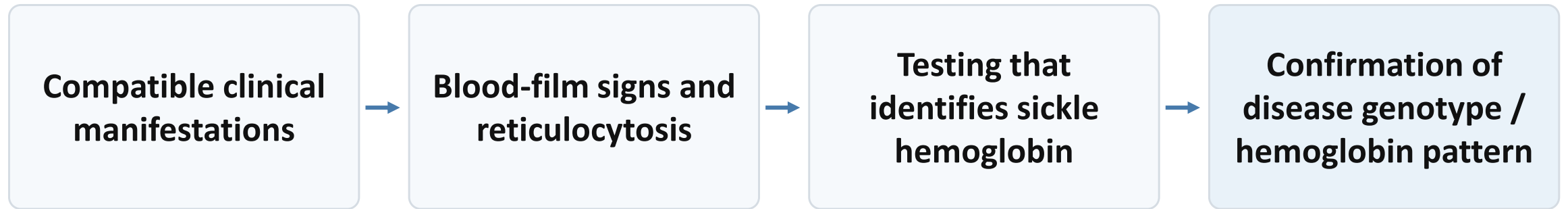
Milder course

- Fewer crises and less cumulative tissue damage.
- Modifier hemoglobins may alter polymerization.

More severe course

- Frequent vaso-occlusive episodes.
- Progressive organ impairment.
- Multiple genetic and environmental modifiers are suspected.

Diagnosis combines phenotype and Hb testing



Morphology suggests the disorder; Specific Hb testing establishes its presence.

Blood-film findings are supportive, not sufficient

Peripheral morphology

- Irreversibly sickled cells are distinctive.
- Target cells and reticulocytosis support hemolysis.
- Howell–Jolly bodies suggest asplenia.

Required confirmation

- Demonstrate sickle hemoglobin by appropriate testing.
- Distinguish HbSS, HbAS and other sickle-containing patterns.
- Account for phenotype variability.

Newborn and prenatal testing identify HbS early

Newborn screening

- Routine U.S. Heel-stick screening.
- Detects sickle hemoglobin before typical symptomatic age.
- Provides time to plan prevention and surveillance.

Prenatal assessment

- Fetal DNA may be assessed from prenatal sampling.
- Chorionic biopsy or amniocentesis are mentioned.
- Family genotype informs reproductive counseling.

Hydroxyurea modifies the disease mechanism

Hydroxyurea, an inhibitor of DNA synthesis

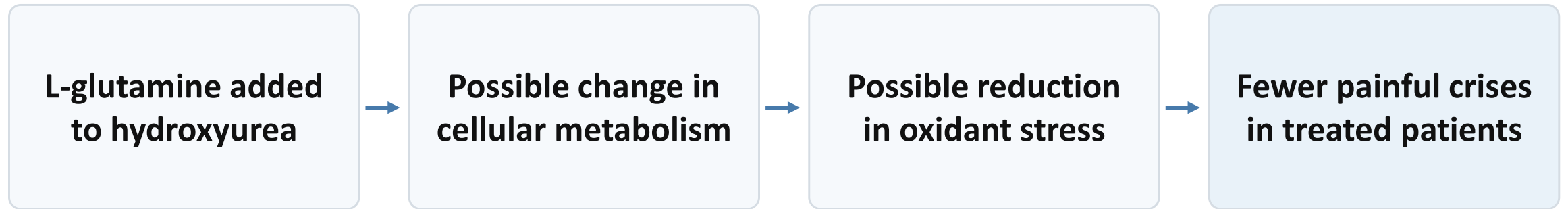
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graph TD; A[Hydroxyurea, an inhibitor of DNA synthesis] --> B[Raises red-cell HbF levels<br/>HbF inhibits HbS polymerization<br/>Reduces sickling burden]; A --> C[Reduces leukocyte production<br/>Provides anti-inflammatory effects<br/>Lessens vaso-occlusive crises];
```

- Raises red-cell HbF levels
- HbF inhibits HbS polymerization
- Reduces sickling burden

- Reduces leukocyte production
- Provides anti-inflammatory effects
- Lessens vaso-occlusive crises

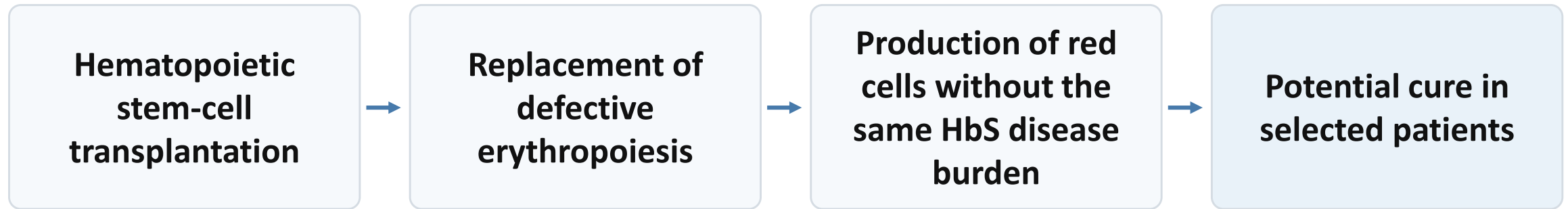
The precise HbF induction mechanism is not known.

L-glutamine is described as an adjunct



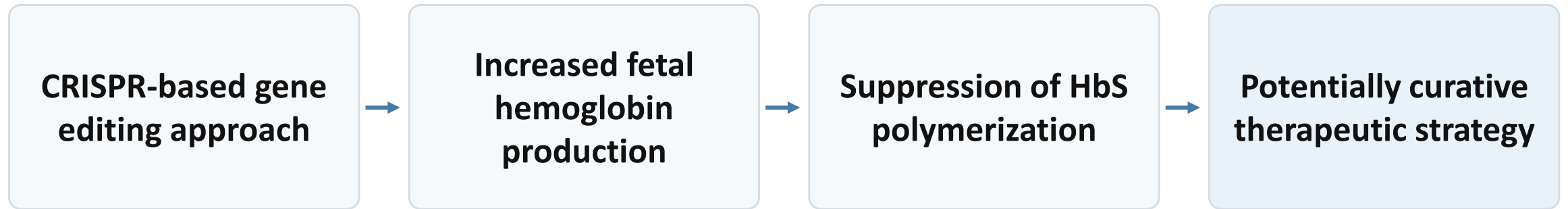
The proposed mechanism is uncertain in the Robbins section; This is not a dosing recommendation.

Stem-cell transplantation offers curative potential



Transplantation for disease not adequately controlled by other treatment.

Gene editing can reactivate fetal hemoglobin



Robbins 11th ed. Notes an approved gene-editing approach and substantial cost/access barriers.

Therapeutic targets follow pathophysiology

Intervention	Main mechanism	Intended disease impact
Hydroxyurea	More HbF; Fewer leukocytes	Fewer vaso-occlusive episodes
L-glutamine	Possible lower oxidant stress	Fewer painful episodes
Stem-cell transplantation	Reconstitutes hematopoiesis	Potential cure
Gene editing	Raises HbF expression	Prevents HbS sickling / potential cure
Vaccines / antibiotics	Reduces infection vulnerability	Prevents serious infection

Teaching case: Painful swollen hands

Clinical teaching scenario

A young child with known sickle cell disease develops acutely painful swelling of both hands and feet. The history does not establish an obvious precipitant.

Question for discussion

Which pathologic mechanism best explains this presentation, and what important clinical mimic should be considered?

Case analysis: Hand–foot syndrome

Mechanism

- Dactylitis is a childhood bone vaso-occlusive episode.
- HbS polymerization contributes to microvascular stasis and infarction.

Critical differential

- Acute osteomyelitis can resemble a bone crisis.
- Pain alone does not determine whether the lesion is infectious.

Teaching case: Sudden worsening of anemia

Clinical teaching scenario

A child with chronic HbSS-associated anemia develops a rapid decline in red-cell mass during an intercurrent viral illness, without a new focal painful infarction.

Question for discussion

Which crisis arises when erythroid progenitor production temporarily stops? How does it differ from splenic sequestration?

Case analysis: Production versus sequestration

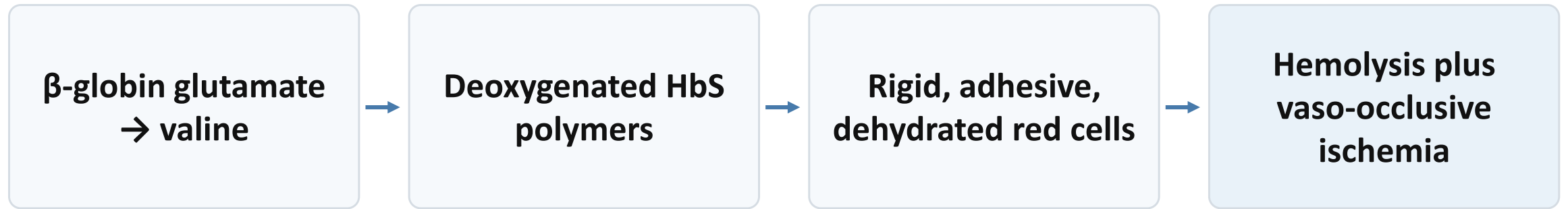
Aplastic crisis

- Parvovirus B19 suppresses erythroid progenitors.
- Low production cannot offset the shortened sickle-cell life span.

Sequestration crisis

- Circulating erythrocytes rapidly pool in an enlarged spleen.
- Hypovolemia and abrupt splenic enlargement are characteristic.

Mechanism review: Trace the causal sequence



Use this sequence to explain morphology, clinical manifestations and therapeutic targets.

Clinicopathologic review: Three patterns

Pattern	Recognize	Underlying mechanism
Chronic hemolysis	Anemia, reticulocytosis, pigment stones	Membrane damage and early RBC removal
Acute ischemia	Pain crisis, chest syndrome, stroke	Slowed flow, adhesion, sickling
Splenic dysfunction	Howell–Jolly bodies, infection risk	Congestion, infarction and fibrosis

References and source boundaries

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026), Chapter 14, “Sickle Cell Disease,” printed pp. 582–585.
- Primary pathology content and clinical examples are derived from the supplied Robbins section.
- Original editable diagrams are mechanistic schematics, not reproduced textbook figures.
- Authentic textbook blood-smear and splenic photomicrographs were not embedded because source image files / reuse clearance were unavailable.
- Current treatment protocols, dose regimens and eligibility criteria are intentionally outside this textbook-based lecture.