

Malaria

From Plasmodium life cycle to organ pathology

Mechanisms • Morphology • Clinicopathologic correlations

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What determines the severity of malaria?

- The liver stage amplifies parasites before symptoms begin.
- Rupture of infected erythrocytes drives febrile attacks and anemia.
- In *P. Falciparum*, adhesion of infected red cells compromises the microcirculation.
- Tissue injury reflects parasite burden, perfusion failure, and host inflammation.

Malaria is an intraerythrocytic protozoal infection

- Plasmodium is an intracellular parasitic protozoan.
- Human infection alternates between hepatic and erythrocytic stages.
- Disease results from circulating parasitized RBCs and systemic responses.
- The erythrocytic stage explains characteristic clinical paroxysms.

Five human-infecting Plasmodium species

Species	Robbins emphasis
P. falciparum	High parasitemia; severe malaria and cerebral involvement
P. vivax	Hypnozoites; Duffy-related red-cell invasion
P. ovale	Latent hepatic hypnozoites and relapse
P. malariae	Usually lower parasitemia
P. knowlesi	Listed among human malarial parasites

The published burden reflects a major global disease

247 million

Estimated malaria cases in 2021

619,000

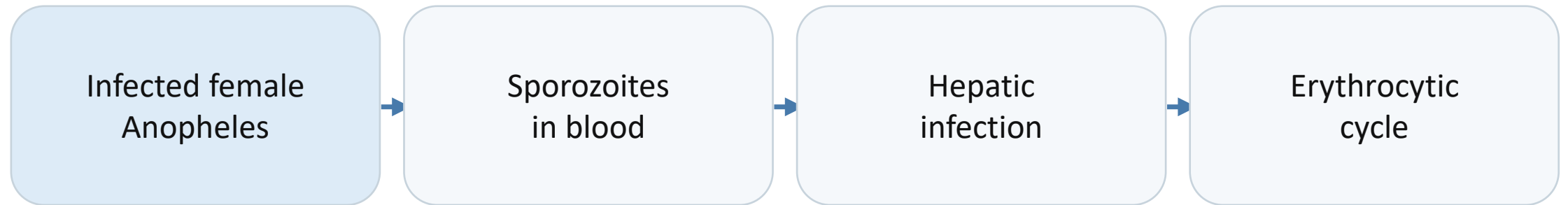
Estimated malaria deaths in 2021

Historical figures reproduced (2021 estimates); Not a current surveillance update.

The African region bears most documented cases

- 95% of estimated cases and 96% of deaths to the WHO African region (2021).
- Malaria is a major cause of mortality in children younger than 5 years there.
- Vectors are also distributed across Asia and Latin America.
- Geography informs exposure history but does not determine an individual diagnosis.

The mosquito bite starts human infection



Vector-mediated transmission introduces sporozoites, not erythrocytic schizonts.

Vector: Female Anopheles mosquito

Transmission is not limited to mosquito bites

- Infected female *Anopheles* mosquitoes are the principal vector.
- The textbook also records transmission by blood transfusion.
- Contaminated needles offer another blood-borne route.
- A travel history is informative, but blood exposure is also relevant.

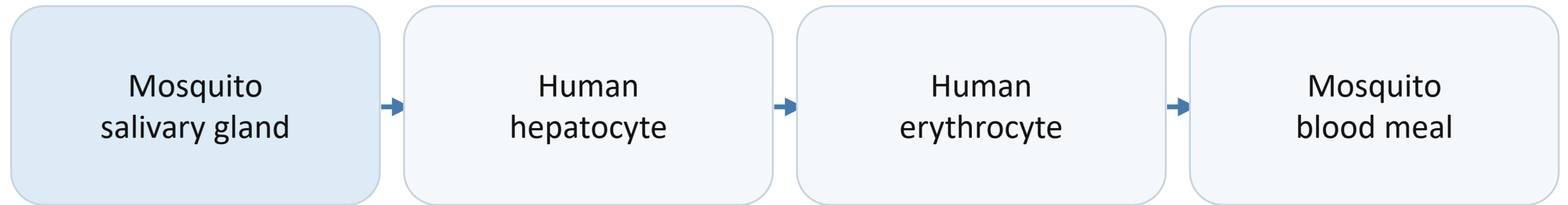
Uncomplicated malaria has a multisystem symptom complex

- Fever and chills may occur with headache and muscle aches.
- Fatigue is common; Gastrointestinal symptoms may accompany illness.
- Nausea, vomiting, and diarrhea are nonspecific associated features.
- Symptoms alone do not identify the infecting Plasmodium species.

Severe malaria involves organ dysfunction

- Renal failure is a major severe manifestation.
- Seizures, confusion, and coma signal cerebral involvement.
- Severe anemia and pulmonary edema occur particularly with *P. Falciparum*.
- An individual patient may develop several organ complications together.

The life cycle crosses three biological compartments

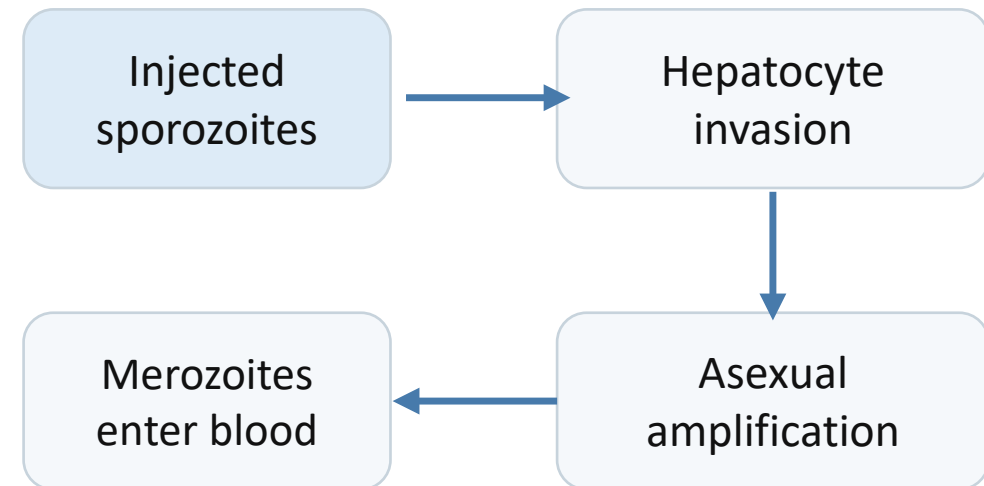


The human hepatic stage is initially silent; Blood stages generate symptoms.

Sporozoites are the infectious mosquito-derived form

- Sporozoites are present in female mosquito salivary glands.
- A blood meal transfers sporozoites into the human circulation.
- They invade hepatocytes shortly after entering the bloodstream.

HUMAN HEPATIC PHASE



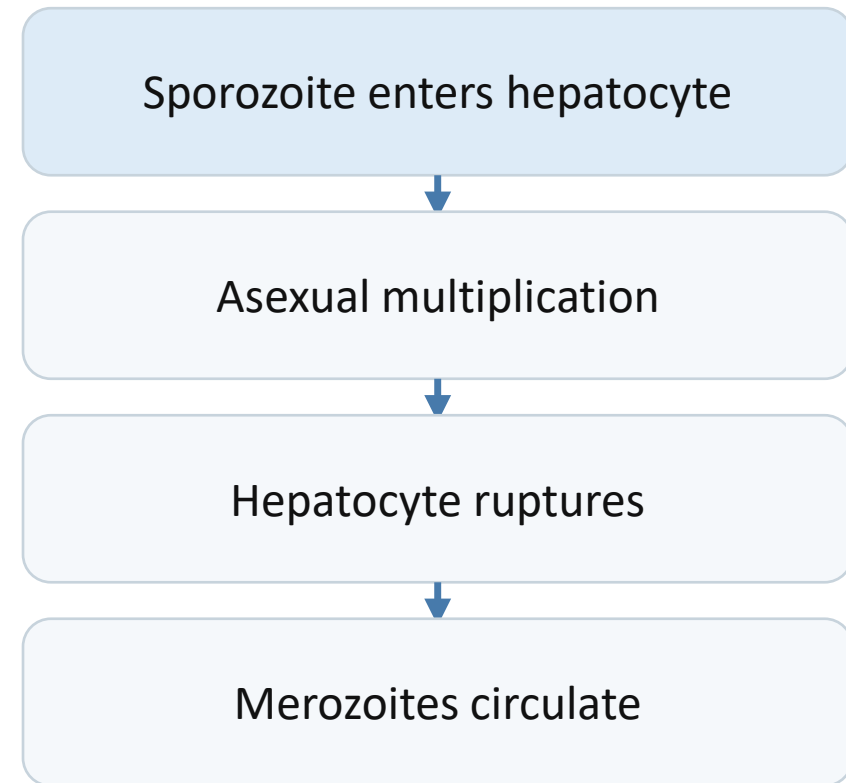
Schematic: Hepatocytes precede the erythrocytic infection

Hepatic invasion initiates asymptomatic amplification

- Sporozoites bind to the hepatocyte surface before entering.
- Host attachment involving thrombospondin/properdin-related receptors.
- Infected liver cells support asexual parasite multiplication.
- The exoerythrocytic stage is typically clinically silent.

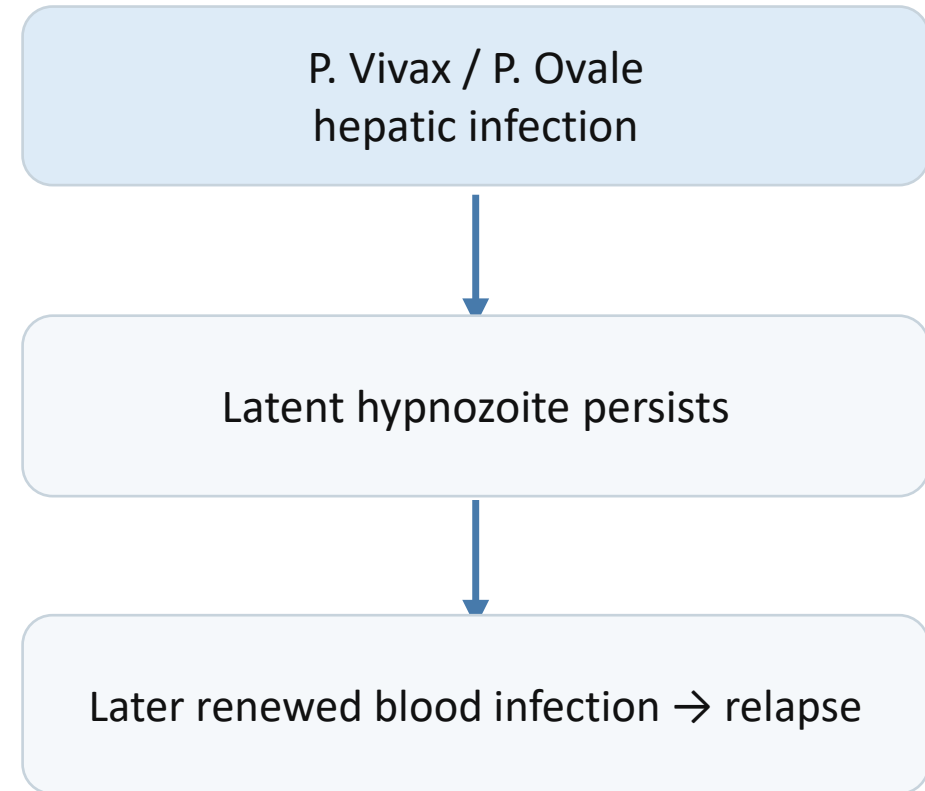
One infected hepatocyte can release many merozoites

- Release of up to 30,000 merozoites per infected hepatocyte.
- Merozoites are the progeny that begin erythrocytic infection.
- This amplification precedes the symptomatic blood stage.



Hypnozoites provide a mechanism for relapse

- P. Vivax and P. Ovale can persist as latent hepatic hypnozoites.
- Dormant forms may produce recurrent malaria weeks to months later.
- Relapse is not explained solely by the ongoing RBC cycle.



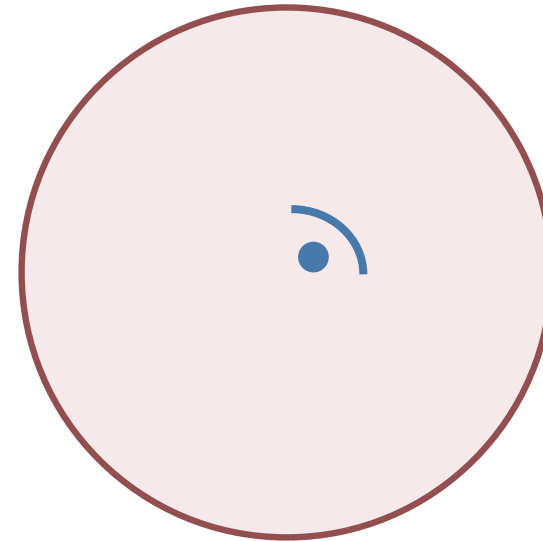
The hepatic and blood stages have distinct roles

Hepatic stage	Erythrocytic stage
Begins with sporozoite invasion	Begins with merozoite invasion
Asexual multiplication in hepatocytes	Trophozoite → schizont in RBCs
Asymptomatic in Robbins description	Fever and chills follow RBC rupture
Hypnozoites in vivax/ovale	Gametocytes may enter mosquito

Merozoites invade red cells by receptor interaction

- Merozoites use lectin-like adhesion molecules.
- They bind sialic acid residues on erythrocyte glycophorin.
- Active membrane penetration initiates an intracellular RBC stage.

Erythrocyte



Merozoite attachment precedes membrane penetration

Schematic — not a Giemsa-stained micrograph

An intracellular digestive vacuole supports parasite growth

- Within infected erythrocytes, parasites reside in a membrane-bound digestive vacuole.
- Secreted enzymes hydrolyze host hemoglobin.
- Hemoglobin consumption is part of trophozoite development.
- Hemozoin pigment later accumulates in tissue macrophages.

Trophozoites and schizonts are distinct blood stages

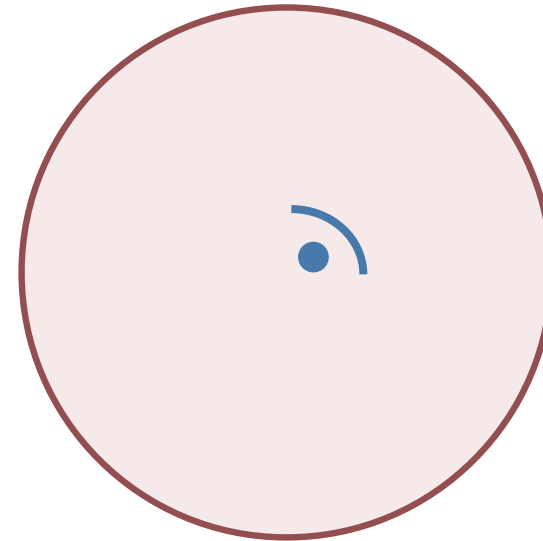


Schematic parasite stages; Diagnostic interpretation requires authentic blood-smear microscopy

The trophozoite has a single chromatin mass

- The ring/trophozoite follows successful erythrocyte invasion.
- Its single chromatin mass distinguishes it from the later schizont.
- Giemsa-stained peripheral blood permits stage recognition.

Erythrocyte

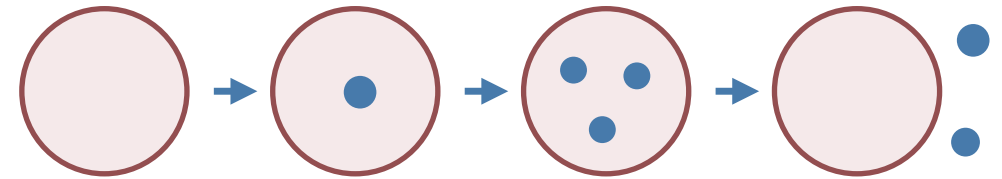


Early intraerythrocytic stage: One chromatin mass

Schematic — not a Giemsa-stained micrograph

The schizont contains multiple chromatin masses

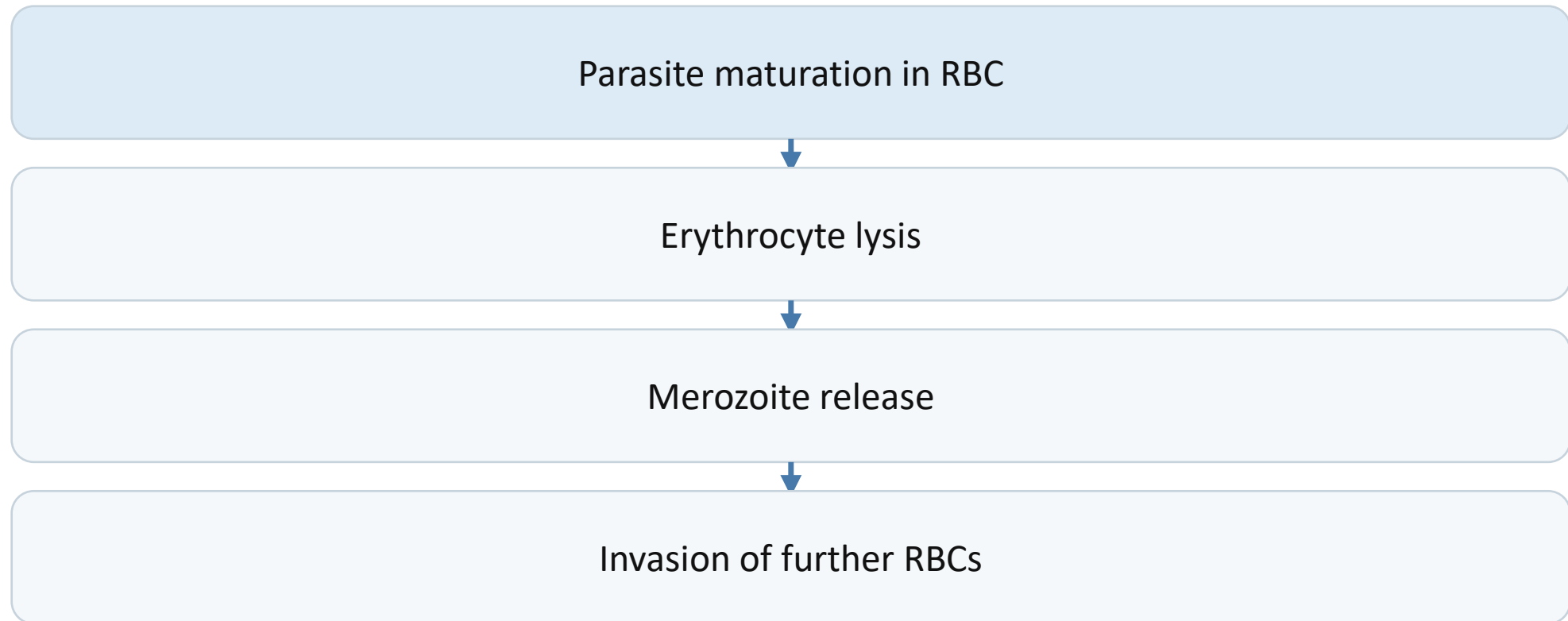
- Schizonts show multiple chromatin masses.
- Each chromatin mass develops toward an individual merozoite.
- Mature blood stages precede RBC lysis and reinvasion.



Early trophozoite Growing parasite Schizont Merozoites

Schematic parasite stages; Diagnostic interpretation requires authentic blood-smear microscopy

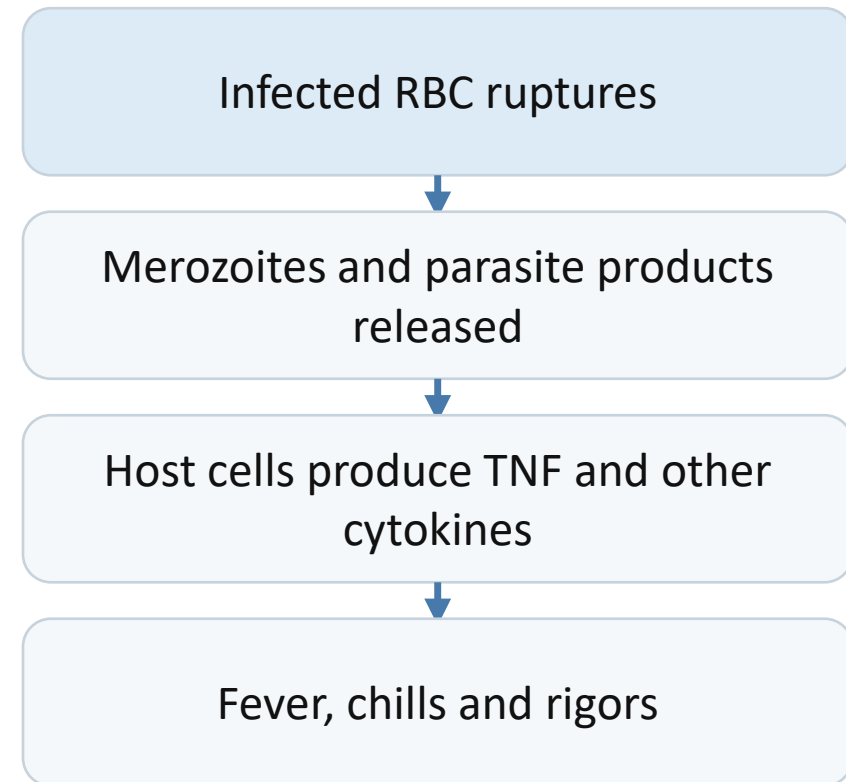
RBC rupture perpetuates parasitemia and symptoms



Repeated cycles propagate infection and host inflammatory responses

Cytokine release explains malarial fever

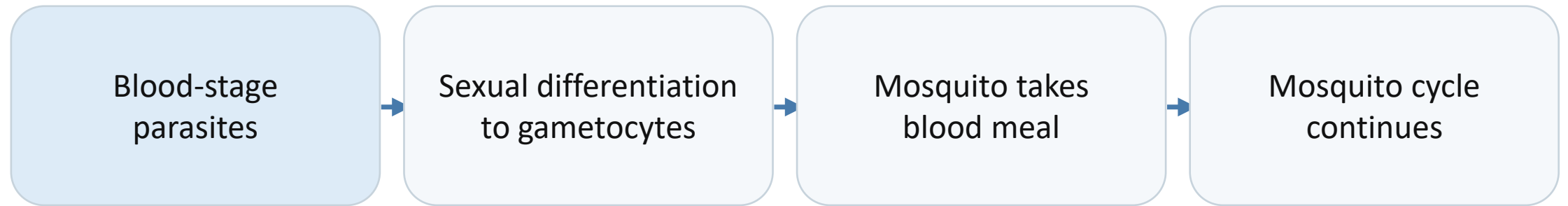
- Clinical paroxysms coincide with merozoite release.
- Host mediators, including TNF, drive fever.
- The fever is a host response—not a direct heating effect of parasites.



Fever periodicity varies among parasite species

- Paroxysmal attacks can recur with erythrocytic schizogony.
- Periodicities within an approximately 24–72-hour range.
- The interval depends on the parasite species.
- A fixed fever schedule is not required to suspect malaria.

Gametocytes sustain transmission back to mosquitoes



Gametocytes are the human blood forms infective to mosquitoes.

A compartment-specific view prevents stage confusion

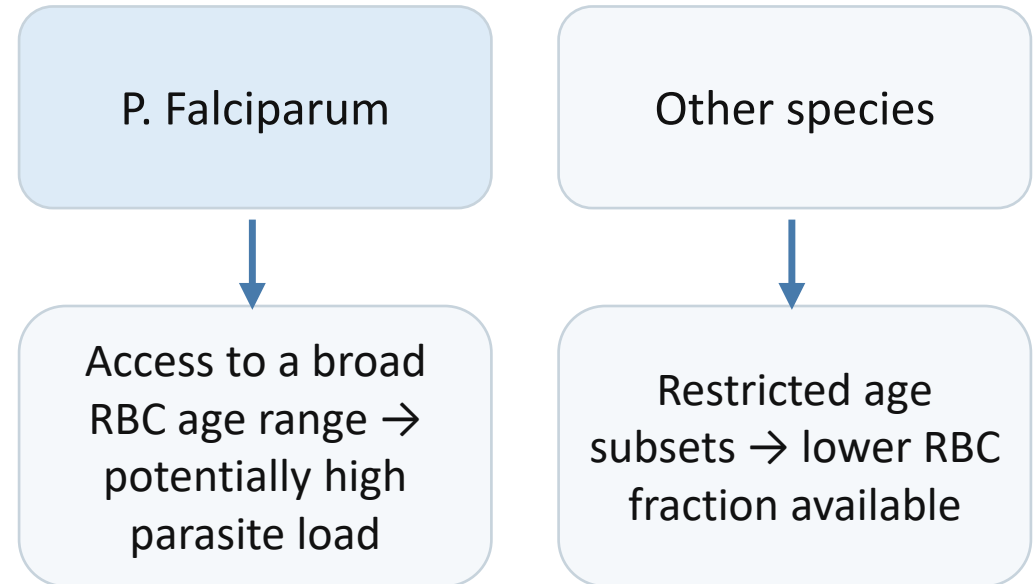
Biological form	Compartment / role
Sporozoite	Female mosquito salivary glands → hepatocytes
Merozoite	Released from liver or RBC; invades red cells
Trophozoite	Growing intracellular erythrocytic stage
Schizont	Asexual dividing blood-stage parasite
Gametocyte	Blood-stage sexual form infective for mosquito
Hypnozoite	Latent hepatic form in <i>P. vivax</i> / <i>P. ovale</i>

Lower parasitemia is typical of several non-falciparum species

- P. Vivax, P. Ovale, P. Knowlesi and P. Malariae with lower parasitemia.
- These infections may still produce anemia and splenic changes.
- Splenic rupture and nephrotic syndrome are described as uncommon outcomes.
- Lower parasitemia does not imply absence of clinical significance.

P. Falciparum can infect erythrocytes of any age

- Falciparum infection is not restricted to young or old red cells.
- Broader host-cell availability supports greater parasitemia.
- Parasite burden alone does not explain microvascular injury.



Falciparum virulence has two major mechanisms

Cell-entry advantage



Infection of RBCs at multiple ages raises parasite burden

Vascular adhesion

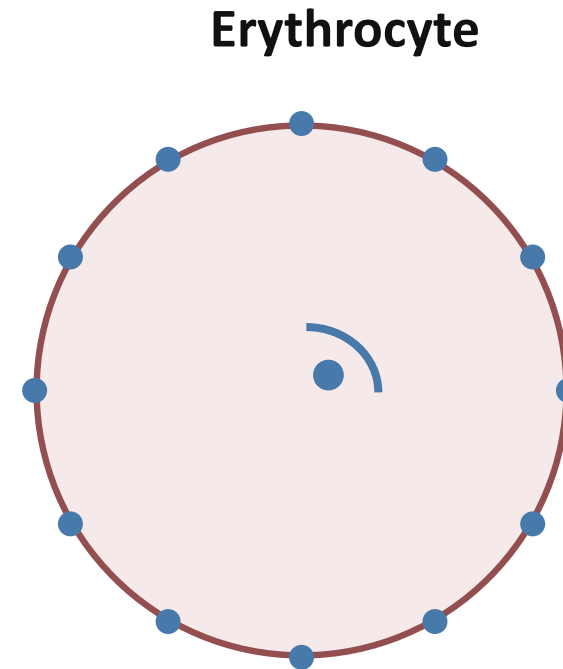


PfEMP1-bearing infected RBCs adhere in small vessels

High parasitemia plus sequestration drive severe pathology

PfEMP1 remodels the infected RBC surface

- Falciparum erythrocyte membrane protein 1 (PfEMP1) is parasite-derived.
- PfEMP1 associates with protruding knobs on infected RBCs.
- This change allows adhesion to endothelial molecules.



Adhesive PfEMP1 is displayed in surface knobs

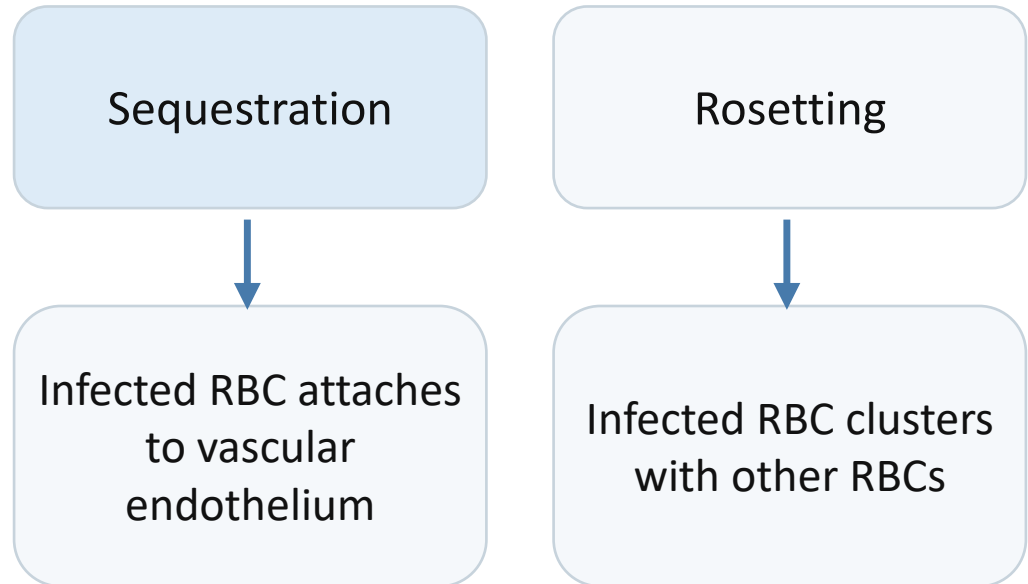
Schematic — not a Giemsa-stained micrograph

Endothelial ligands participate in sequestration

Ligand named in Robbins	Role in falciparum pathology
CD36	Endothelial adhesion partner for PfEMP1
ICAM-1	Endothelial adhesion partner for PfEMP1
VCAM-1	Endothelial adhesion partner for PfEMP1
E-selectin	Endothelial adhesion partner for PfEMP1
Thrombospondin	Adhesion-associated ligand

Sequestration and rosetting are related but distinct

- Both are described for *P. Falciparum* infection.
- Adhesion impedes blood passage through microvessels.
- The consequence is local hypoperfusion, not merely anemia.

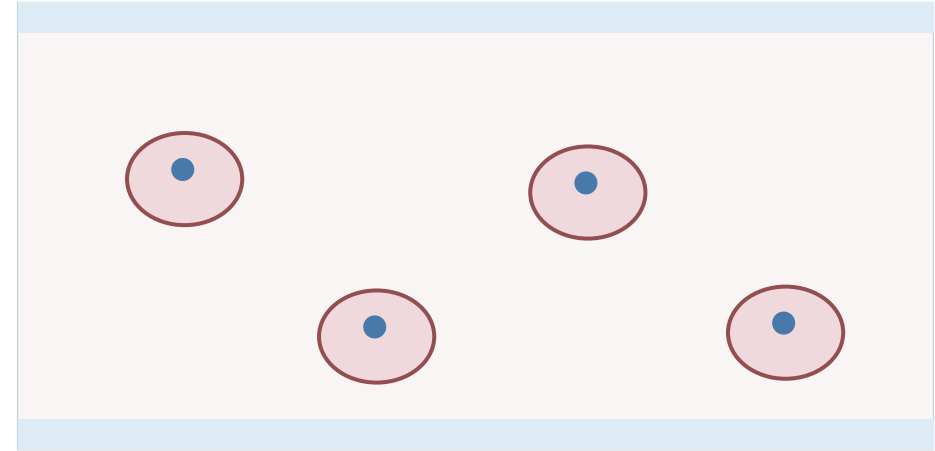


Microvascular obstruction produces ischemia

- Adherent parasitized red cells accumulate in small vessels.
- Local perfusion falls when flow is obstructed.
- Ischemia follows impaired oxygen delivery to tissue.

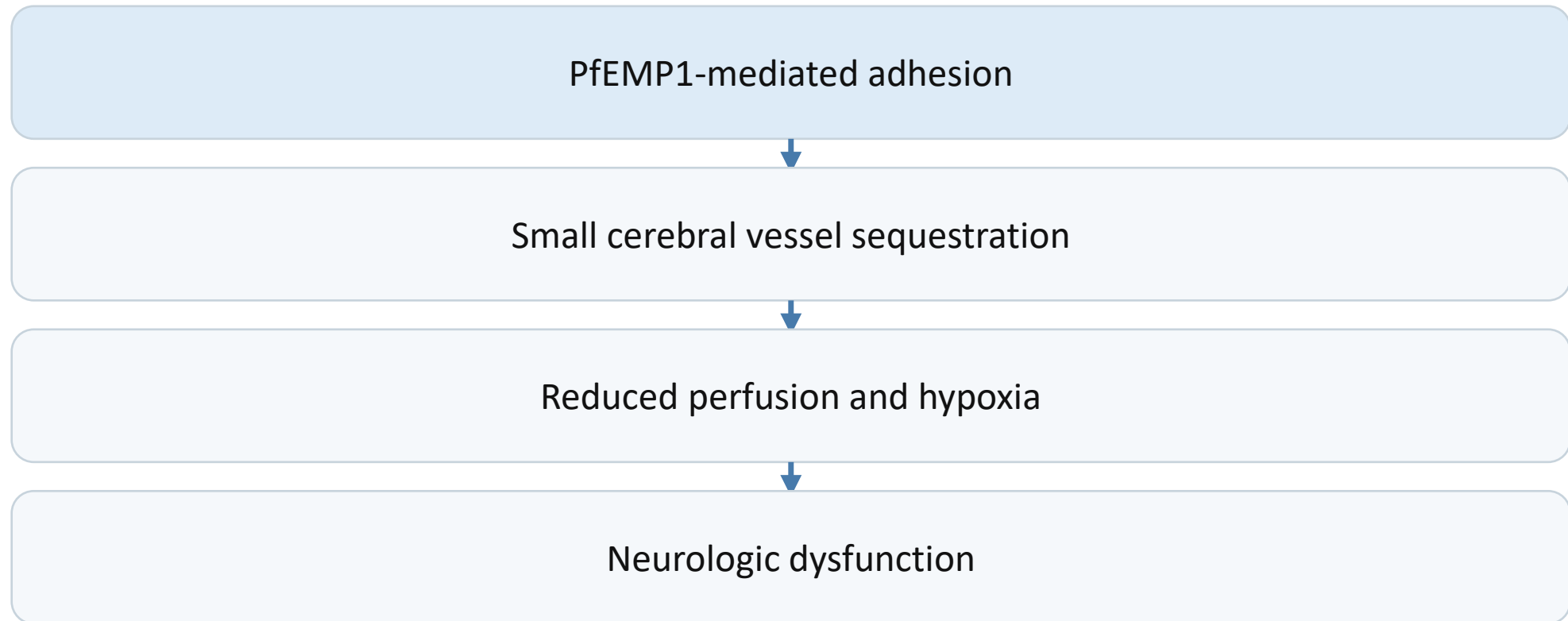
Schematic

Parasite-infected RBCs



Adherent parasitized cells narrow functional microvascular flow

Cerebral malaria is a microcirculatory disorder



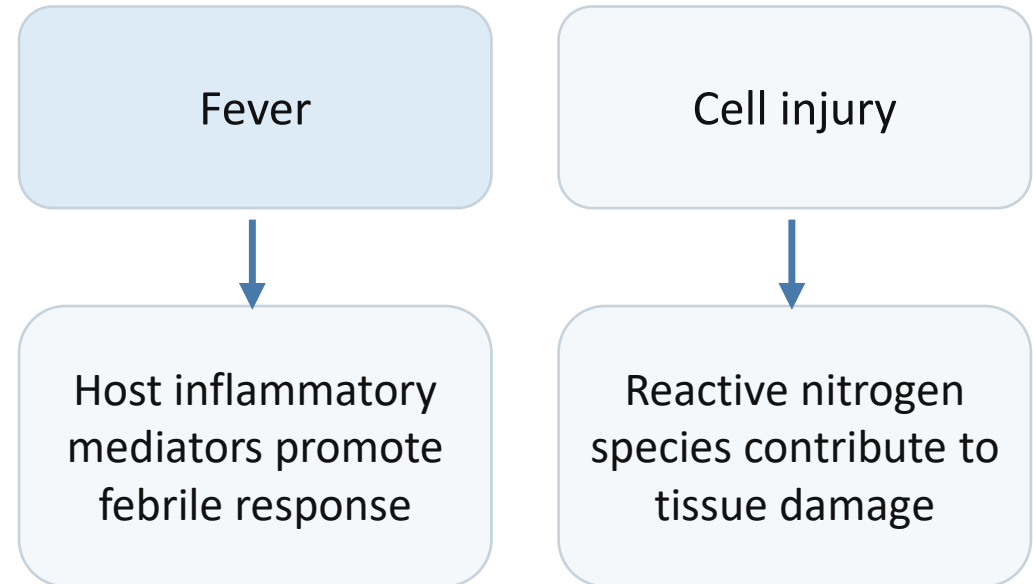
Mechanistic chain underlying confusion, seizures and coma

Parasite GPI-linked proteins activate inflammation

- Falciparum GPI-linked parasite proteins are released from infected red cells.
- They include merozoite surface-associated antigens.
- Host cells respond by producing cytokines.
- Inflammatory signaling complements the mechanical effects of sequestration.

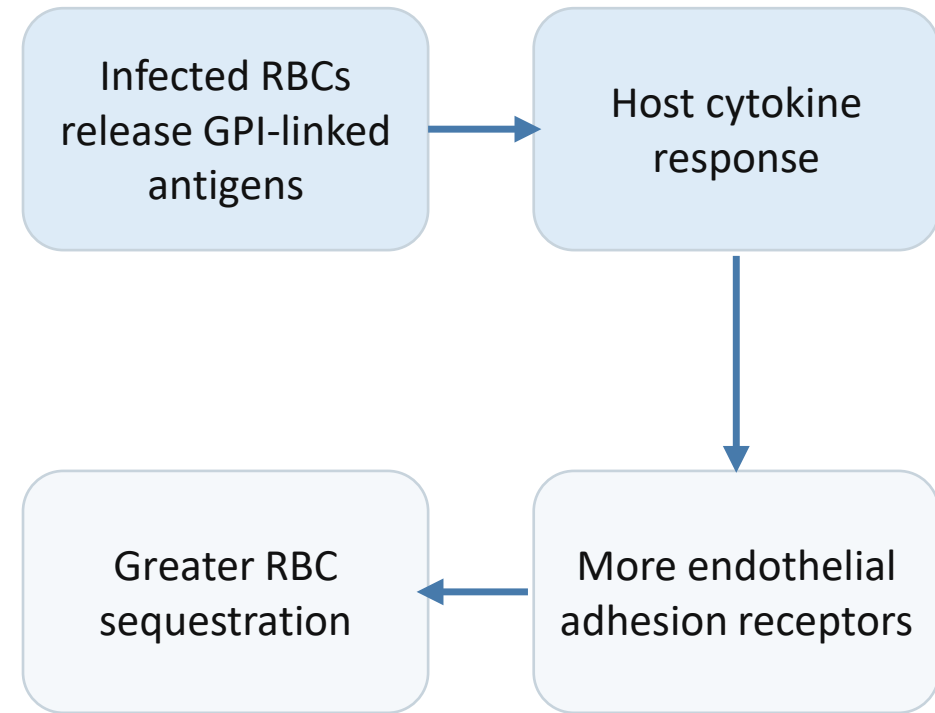
Cytokines contribute to systemic tissue injury

- Cytokine production follows exposure to parasite components.
- Reactive nitrogen intermediates add inflammatory injury.
- Organ dysfunction can reflect more than vascular occlusion.



Inflammation can intensify vascular sequestration

- Cytokines induce expression of endothelial PfEMP1 ligands.
- More adhesion receptors facilitate sequestration.
- Sequestration then contributes to local ischemia.

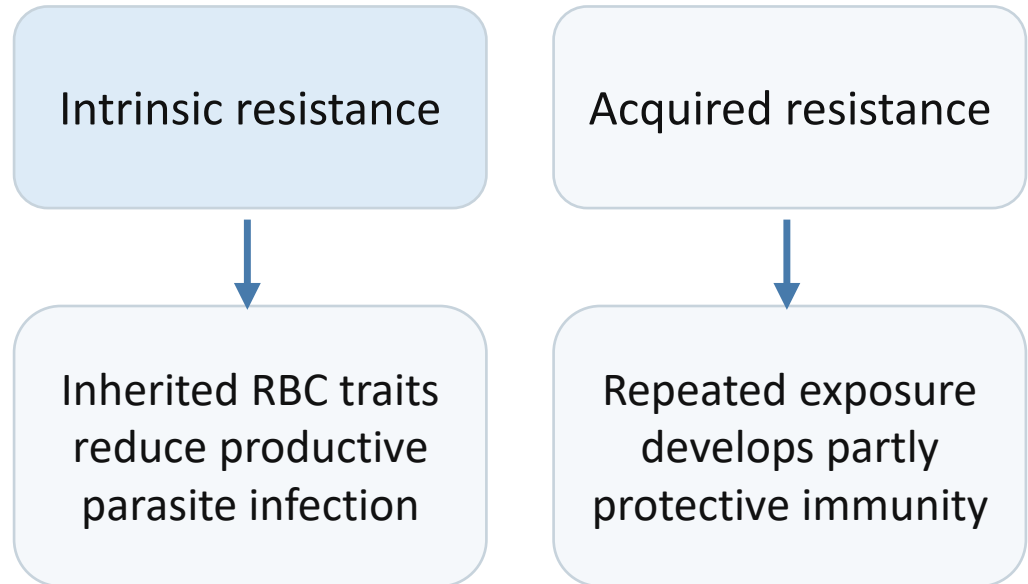


Falciparum infection produces several clinical end points

Pathogenic process	Major clinical consequence
High erythrocytic parasite burden	Severe anemia
Cerebral microvascular sequestration	Seizures, confusion, coma
Systemic / microcirculatory injury	Renal failure
Inflammation and vascular dysfunction	Pulmonary edema; possible death

Host resistance is intrinsic or acquired

- These mechanisms operate at different biological levels.
- Intrinsic resistance is related to erythrocyte phenotype.
- Acquired resistance does not necessarily prevent reinfection.



Heterozygous RBC variants can confer an advantage

- Selected inherited RBC variants reduce susceptibility to productive Plasmodium infection.
- Some confer protection in heterozygous carriers but cause disease in homozygotes.
- This can maintain otherwise harmful variants in endemic populations.
- The benefit varies with the variant and parasite context.

Globin variants are one protective category

- Hemoglobin S and hemoglobin C among protective globin variants.
- The source identifies heterozygous-state protection as an evolutionary pattern.
- The diagnosis and pathobiology of each hemoglobinopathy remain distinct.

Hemoglobin S (HbS)

Hemoglobin C (HbC)

Thalassemias

Other RBC traits

Inherited RBC variation → reduced productive infection in some heterozygous carriers

Thalassemias form a second resistance category

- α - and β -thalassemias reduce globin-chain production.
- They are listed among erythrocyte traits that may inhibit malaria.
- Protection is not equivalent to eliminating infection risk.
- The source does not assign a single molecular protective mechanism to all variants.

Enzyme and membrane variants also affect susceptibility

- G6PD deficiency is the red-cell enzyme example.
- DARC, band 3, and spectrin appear among membrane-related examples.
- Protective mechanisms for many listed traits are incompletely understood.

G6PD deficiency

Duffy / DARC
absence

Band 3 variants

Spectrin variants

Inherited RBC variation → reduced productive infection in
some heterozygous carriers

Duffy antigen illustrates receptor-specific resistance

- Duffy (DARC) in *P. Vivax* entry.
- Duffy-negative populations historically show reduced susceptibility.
- Do not generalize this receptor model to every *Plasmodium* species.

P. Vivax targets the RBC Duffy antigen



Duffy absence changes the available entry receptor



Susceptibility to classical vivax invasion is reduced

Repeated exposure produces partial clinical immunity

- Endemic exposure can generate partially protective immune responses.
- Individuals may have fewer symptoms even with persistent or repeated infections.
- Antibodies and T lymphocytes contribute to reduced manifestations.
- This is partial immune protection—not sterile lifelong immunity.

Antigenic variation permits immune escape

PfEMP1 and other surface antigens are recognized



Parasites express alternate antigen-encoding genes



Newly expressed surface proteins change antigenicity



Existing antibody responses may become less effective

P. falciparum expresses variable surface-antigen repertoires

Malaria immunity has several effector components

- Antibodies against Plasmodium antigens help limit disease.
- T lymphocytes contribute to adaptive resistance.
- Cytotoxic T lymphocytes may play a role against falciparum infection.
- Parasite antigenic switching challenges durable protective responses.

The peripheral blood smear is central to diagnosis

- Giemsa-stained peripheral blood is the morphologic diagnostic specimen.
- Intraerythrocytic asexual parasite forms are identifiable.
- Microscopic recognition connects the lifecycle directly with diagnosis.
- Accurate interpretation depends on genuine slide morphology.

Blood-stage forms have different nuclear patterns



Schematic parasite stages; Diagnostic interpretation requires authentic blood-smear microscopy

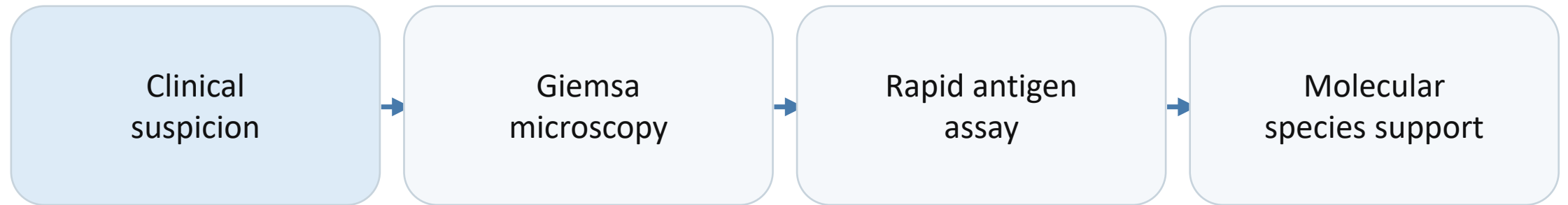
Antigen-based rapid diagnostic tests provide early evidence

- Immunochromatographic tests detect parasite antigens.
- These are useful for a rapid response.
- Robbins specifies confirmation with blood-smear examination.
- Assay availability and use should be interpreted within the relevant diagnostic setting.

Molecular testing improves parasite detection

- PCR and related molecular assays are more sensitive than conventional microscopy in the source.
- Species confirmation may assist selection of appropriate therapy.
- A very low parasitemia result does not by itself establish symptomatic disease.
- Methods should be chosen for a defined diagnostic question.

The meaning of a positive test depends on context



These are complementary methods, not a single universally mandated sequence.

Spleen enlargement reflects red-pulp congestion

- Parasitized red cells acquire altered membrane proteins.
- Splenic macrophages recognize and remove abnormal erythrocytes.
- Congestion and red-pulp hyperplasia contribute to splenomegaly.
- Marked enlargement in *P. Falciparum* infection.

Macrophage clearance links blood infection to spleen

Parasite proteins alter the erythrocyte membrane



Splenic macrophages recognize abnormal RBCs



Engulfment of parasitized erythrocytes



Red-pulp expansion and pigment accumulation

Hemozoin gives chronically infected tissues dark color

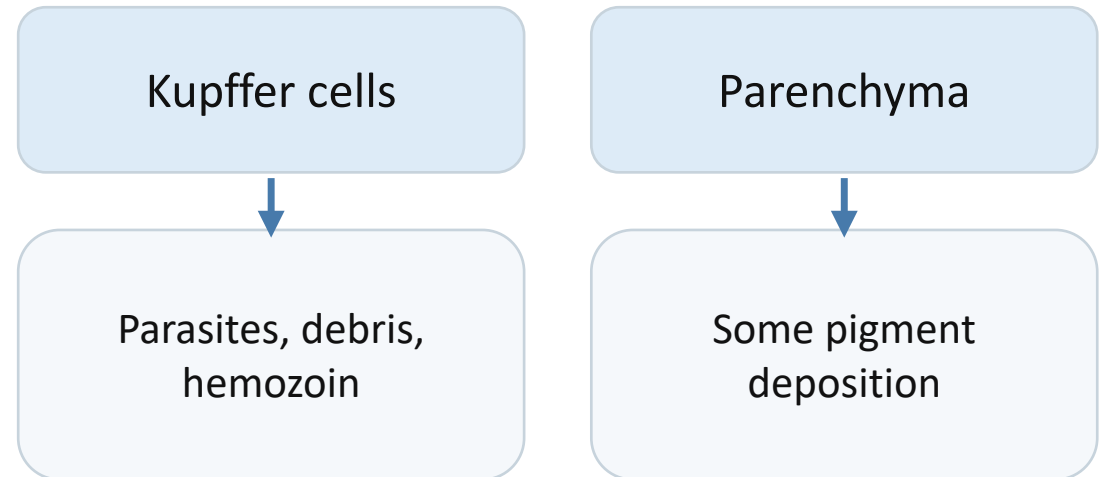
- Hemozoin is a granular brown-black malarial pigment.
- The pigment occurs within phagocytic cells.
- It is faintly birefringent.
- Pigmented macrophages help explain the gray-black spleen.

Chronic splenic infection remodels the organ

- The chronically involved spleen may become increasingly fibrotic.
- The capsule and trabeculae become thickened.
- A brittle, enlarged spleen.
- Structural remodeling follows prolonged congestion and phagocytic activation.

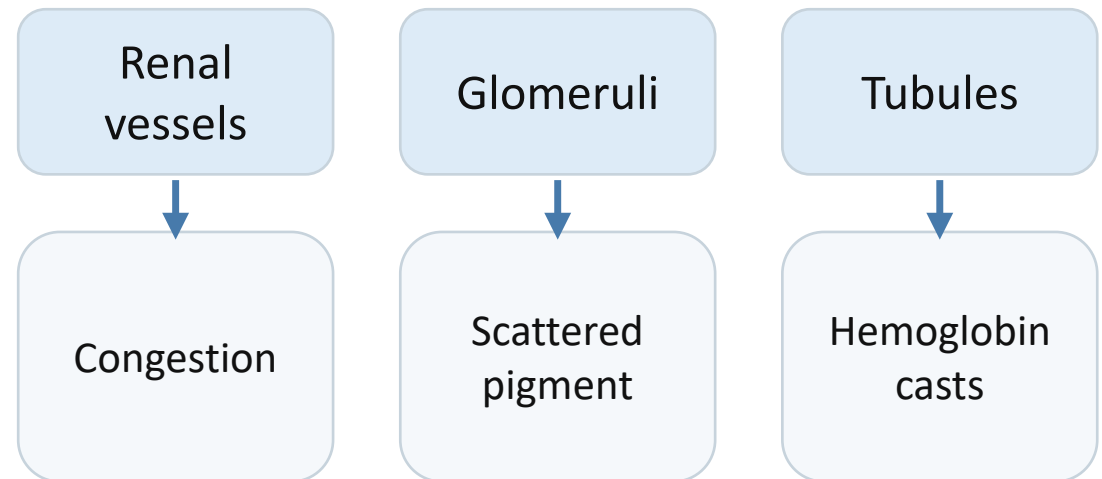
The liver becomes enlarged and pigmented

- The liver may enlarge as infection progresses.
- Kupffer cells contain pigment, parasites and cellular debris.
- Pigment may also appear within hepatocytes.

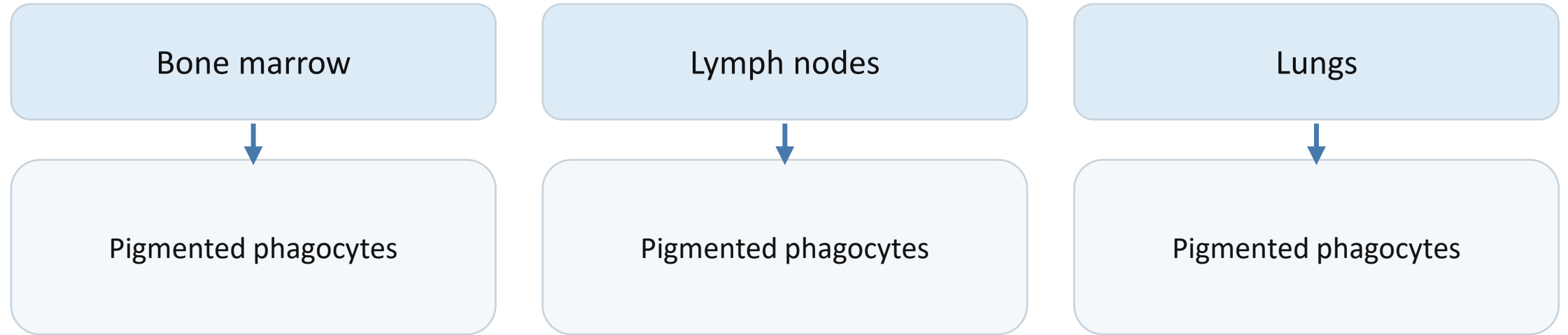


Renal pathology combines congestion and hemoglobin injury

- Kidneys may be enlarged and congested.
- Pigment is described within glomerular structures.
- Hemoglobin casts occur in tubules.



Pigmented phagocytes are not confined to one organ



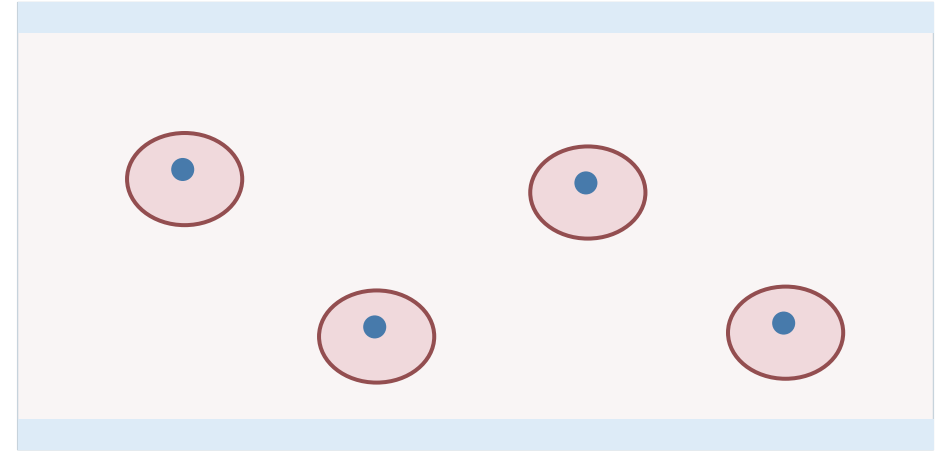
Subcutaneous tissues may also contain pigmented cells

Cerebral vessels accumulate parasitized RBCs

- *P. Falciparum*–infected red cells may pack cerebral small vessels.
- The finding provides a morphologic correlate of sequestration.
- Local vascular stasis produces tissue hypoxia.

Schematic

Parasite-infected RBCs



Microvascular sequestration → impaired cerebral perfusion

Perivascular ring hemorrhages signal focal injury

- The source describes ring hemorrhages around involved brain vessels.
- Their formation is thought to reflect local hypoxia and stasis.
- These are tissue lesions, distinct from the bloodstream parasite stage.
- Vascular occlusion and hemorrhage may coexist.

Dürck granulomas accompany cerebral malaria

- Small focal inflammatory reactions may surround compromised vessels.
- Robbins calls these malarial or Dürck granulomas.
- More severe hypoxia leads to neuronal degeneration and softening.
- Meningeal inflammation may be scant.

Chronic anemia may impair myocardial oxygen delivery

- Progressive anemia and circulatory stasis can cause focal myocardial hypoxia.
- Some hearts show focal interstitial inflammatory infiltrates.
- The myocardial findings are not described as pathognomonic.
- Cardiac injury is a secondary consequence of systemic infection.

Pulmonary edema, shock, and DIC mark critical disease

- Pulmonary edema can be a fatal complication in a nonimmune host.
- Shock with disseminated intravascular coagulation is also described.
- Fatal disease may occur without all classic morphologic lesions.
- Severity assessment must integrate clinical organ dysfunction.

The organ lesions follow a shared causal framework

Organ	Dominant Robbins lesion	Pathophysiologic link
Spleen	Congestion, red-pulp hyperplasia, pigment	RBC clearance
Liver	Pigmented Kupffer cells	Phagocytic sequestration
Kidney	Congestion, pigment, hemoglobin casts	Perfusion + hemoglobin injury
Brain	Parasitized RBCs, hemorrhages, hypoxic lesions	Microvascular obstruction
Heart	Focal hypoxic changes	Anemia and stasis

Malaria and babesiosis share a diagnostic resemblance

Feature	Malaria	Babesiosis
Blood-stage form	Intraerythrocytic parasites	Rings may resemble falciparum
Hemozoin	Present in malaria tissue pathology	Absent in Babesia
Tetrads	Not a defining malaria feature	Maltese-cross tetrads may appear
Vector	Female Anopheles	Ixodes ticks

Contrast relies on the separate Robbins Babesiosis passage (pp. 357–358).

Case: Fever after exposure in an endemic region

A returning traveler reports episodic fever, chills, headache and fatigue. A peripheral blood sample is available.

Reasoning questions

- Which stages are likely to be seen in a Giemsa-stained blood film?
- Why do febrile episodes coincide with erythrocyte rupture?
- How would parasite species confirmation change interpretation?

Case: Coma with falciparum parasitemia

A patient with confirmed *P. Falciparum* infection develops confusion and seizures. Microvascular congestion is suspected.

Reasoning questions

- Explain how PfEMP1 changes infected RBC behavior.
- Name the vascular adhesion and perfusion consequences.
- Predict the cerebral histologic lesions.

Case: Malaria recurs after apparent resolution

Weeks after an initial episode, a patient develops another febrile illness following P. Vivax infection.

Reasoning questions

- Which hepatic parasite form accounts for a true relapse?
- Why is a purely erythrocytic explanation incomplete?
- Which other human Plasmodium species shares hepatic latency?

Circumsporozoite antigen is a vaccine target

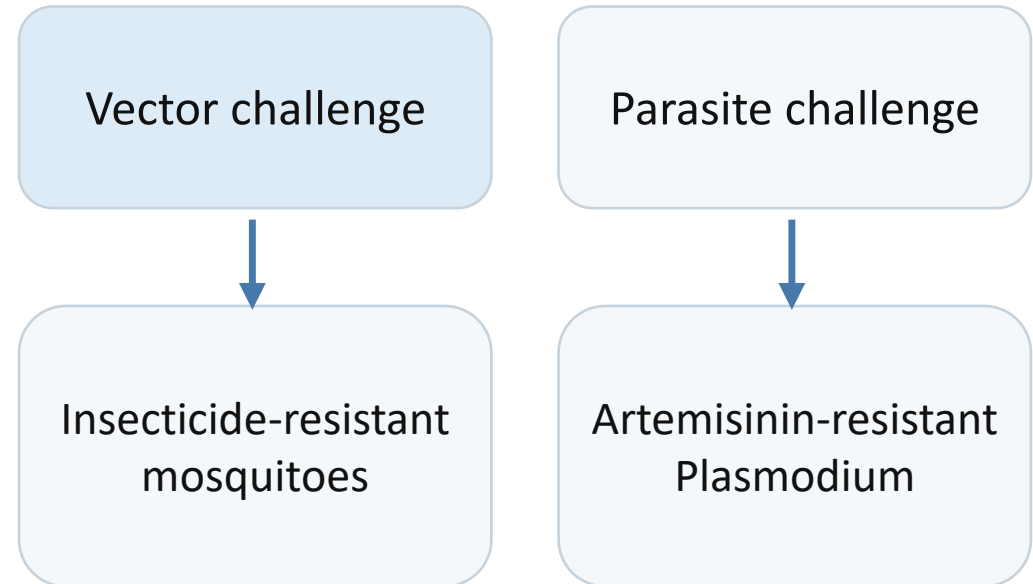
- RTS,S/AS01 recommendation for children in moderate- to high-transmission P. Falciparum regions.
- The antigen is displayed before liver-cell infection.
- This is a prevention mechanism rather than an erythrocytic treatment.



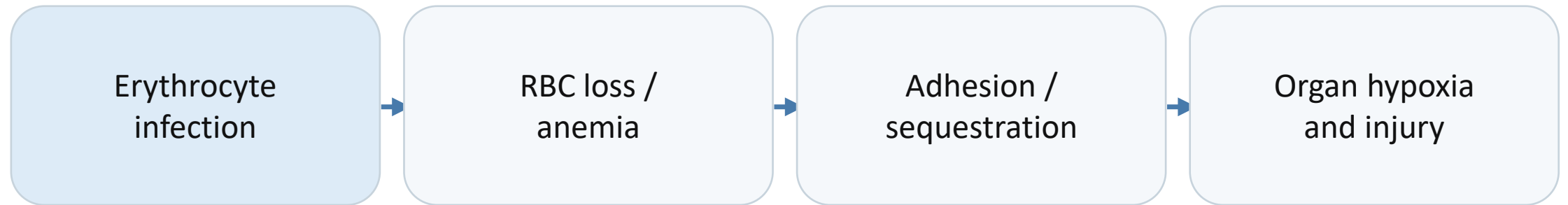
RTS,S/AS01 targets the pre-hepatic circumsporozoite stage.

Control faces both vector and parasite resistance

- Public-health control is impeded by resistant mosquito vectors.
- Antimalarial drug resistance is a separate parasite problem.
- The textbook specifically identifies artemisinin resistance.



Clinical severity arises through several converging routes



Inflammatory cytokines independently aggravate symptoms and tissue injury.

Four distinctions organize the pathology of malaria

- Sporozoite infects hepatocytes; Merozoite infects erythrocytes.
- Trophozoite and schizont are asexual blood stages; Gametocytes maintain transmission.
- Falciparum severity reflects parasite burden plus microvascular adhesion.
- Hemozoin and parasitized RBCs connect the blood infection to organ morphology.

Assess your understanding

- Why does the exoerythrocytic phase usually lack fever?
- Why does *P. Falciparum* cause disproportionate cerebral injury?
- What causes hepatosplenic dark pigment in chronic infection?
- Which species can relapse through latent hepatic hypnozoites?

Reference and source limitations

- Primary reference: Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Chapter 8, Infectious Diseases: Malaria and adjacent parasitic-infection context.
- The extracted Markdown interleaves figure captions and Babesiosis text; content was separated by context.
- No original chapter PDF or licensed photomicrographs were supplied; all presented figures are explicit native conceptual schematics.