

Defects in Innate Immunity

Inherited dysfunction of leukocytes and complement

Clinicopathologic mechanisms and disease patterns

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Locate the functional lesion in major inherited leukocyte disorders.
- Relate receptor, trafficking, and oxidative defects to infectious phenotypes.
- Explain how complement-component and regulatory deficiencies produce distinct disease patterns.
- Use a mechanism-first differential for representative clinical presentations.

Two principal classes of innate defects

Leukocyte function

Adhesion and migration

Phagolysosomal traffic

Microbicidal activity

Innate receptor/cytokine signaling

Complement system

Initiation or amplification

Central C3 effector function

Terminal membrane attack

Restraint of activation

Innate defenses: Cellular and humoral arms

Cellular defenses

Neutrophils and macrophages

Recognition, ingestion, and killing

Leukocyte recruitment to tissues

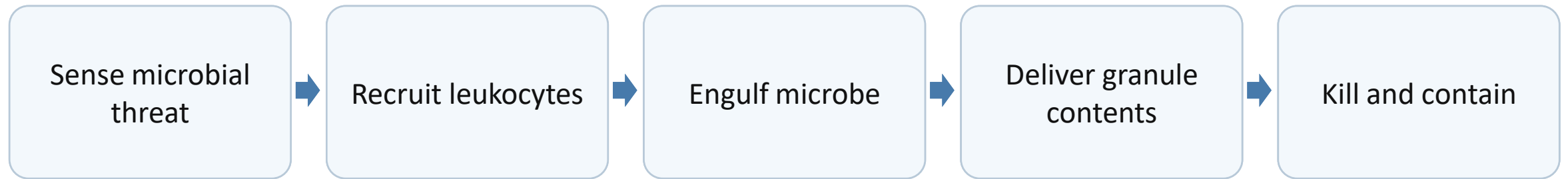
Humoral defenses

Complement proteins in plasma

Opsonization and inflammation

Terminal lysis of susceptible microbes

The critical checkpoints in pathogen clearance



Functional sequence — schematic

Leukocyte exit from blood requires ordered steps



Functional sequence — schematic

Leukocyte adhesion deficiency type 1

- Defective $\beta 2$ integrin chain shared by LFA-1 and Mac-1.
- Impairs firm leukocyte adhesion to activated endothelium.
- Migration to infected tissue is consequently reduced.

Normal: $\beta 2$ integrin engagement



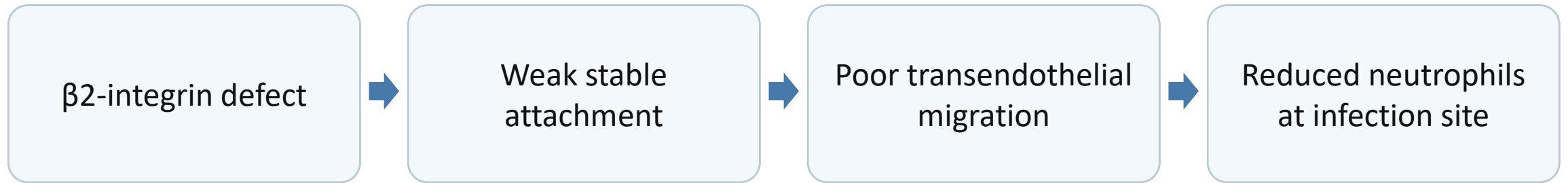
LAD-1: Adhesion failure



Outcome: Impaired tissue entry

Schematic

LAD-1 disrupts the firm-adhesion checkpoint



Causal sequence — schematic

Why circulating phagocytes cannot compensate

- Microbial killing requires phagocytes to reach the infected tissue.
- The adhesion defect acts upstream of ingestion and killing.
- Even intact intracellular killing is ineffective if cells cannot localize to the focus.
- LAD-1 to recurrent, potentially severe bacterial infections.

Leukocyte adhesion deficiency type 2

- A fucosyltransferase mutation impairs synthesis of sialyl-Lewis X.
- Sialyl-Lewis X serves as a ligand for E- and P-selectins.
- Loss of this ligand weakens the early adhesion/rolling interaction.

Fucosyltransferase mutation



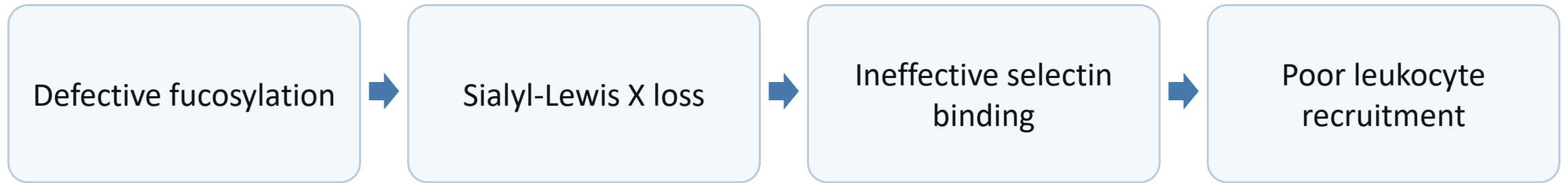
Absent selectin ligand



Defective early endothelial
tethering

Schematic

LAD-2 affects an earlier recruitment step



Causal sequence — schematic

LAD-1 versus LAD-2: Same endpoint, different lesion

Feature	LAD-1	LAD-2
Primary lesion	β 2 integrin common chain	Fucosyltransferase
Adhesion component	LFA-1 / Mac-1	Sialyl-Lewis X
Predominant checkpoint	Firm adhesion	Selectin-mediated tethering / rolling
Consequence	Defective leukocyte tissue entry	Defective leukocyte tissue entry

Application: Recurrent bacterial infection and failed adhesion

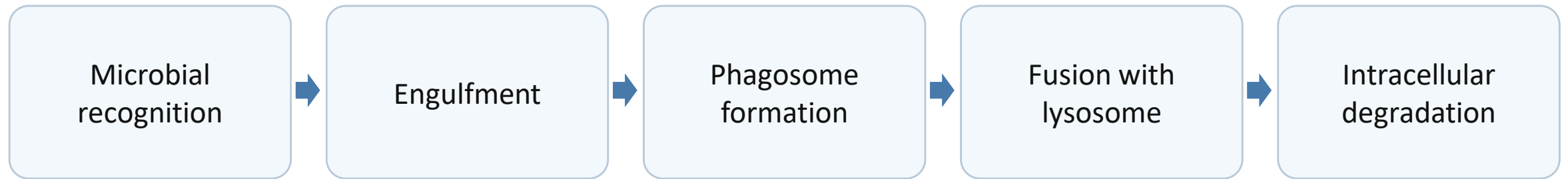
ILLUSTRATIVE TEACHING VIGNETTE

Teaching vignette: A child has repeated severe bacterial infections. Phagocytic cells are present in the circulation, but migration from blood into affected tissue is inefficient.

Question: Which functional checkpoint has failed?

Mechanistic answer: Endothelial adhesion / tissue recruitment; Molecular distinction requires evaluating integrin versus selectin-ligand function.

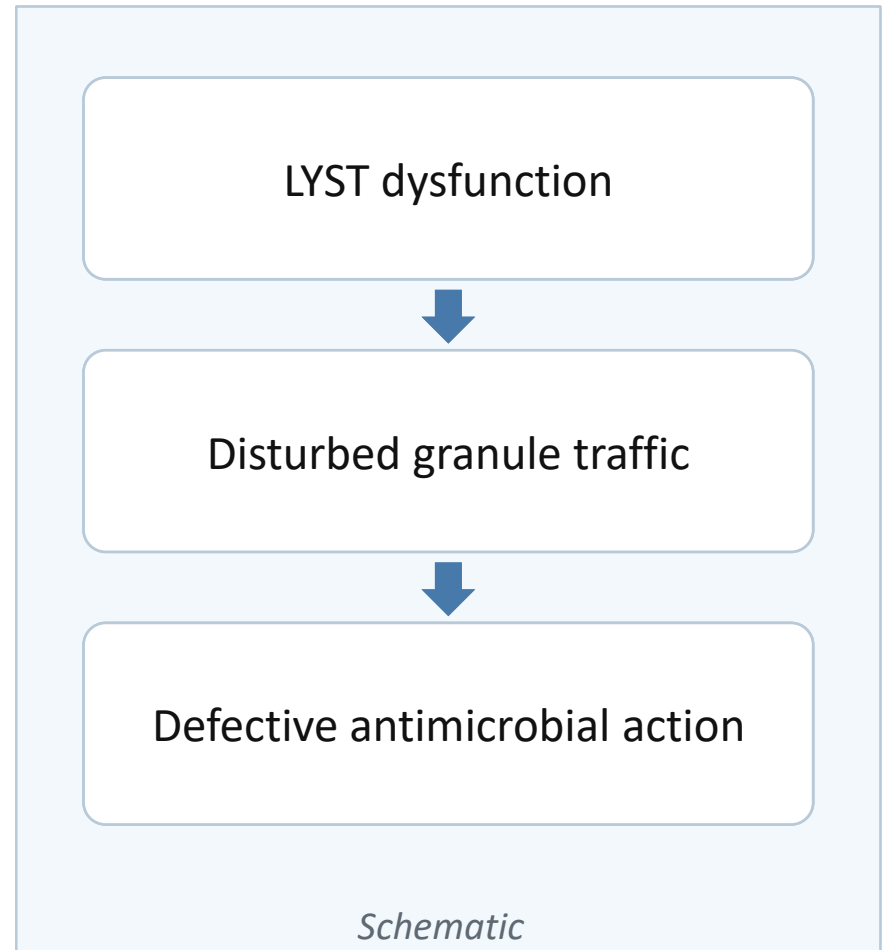
Phagocytosis proceeds through linked compartments



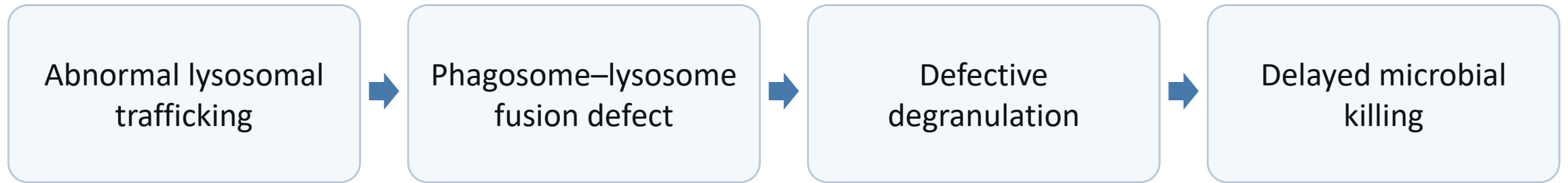
Functional sequence — schematic

Chédiak–Higashi syndrome: Molecular basis

- Autosomal recessive disorder involving the LYST gene.
- LYST encodes a regulator implicated in lysosomal trafficking.
- Abnormal intracellular granule handling compromises phagocyte function.



Phagolysosomal fusion is functionally impaired

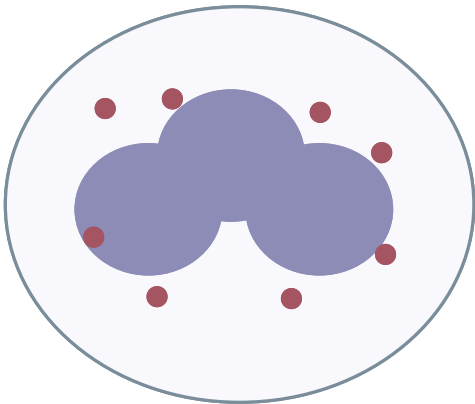


Causal sequence — schematic

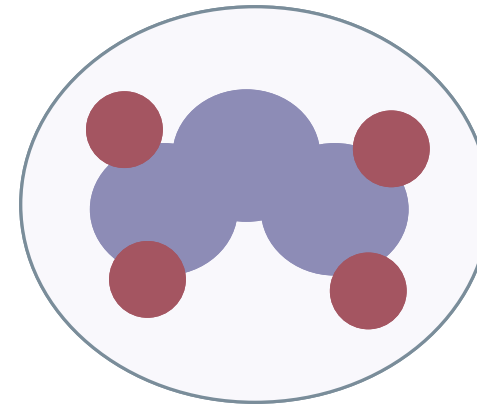
Giant leukocyte granules: A morphologic clue

Abnormally large cytoplasmic granules visible on peripheral-blood smears.

Usual granule distribution



Chédiak–Higashi: Giant granules



Chédiak–Higashi impairs multiple phagocyte tasks

- Neutropenia decreases available circulating neutrophils.
- Defective degranulation disrupts antimicrobial delivery.
- Delayed microbial killing permits persistence after phagocytosis.
- These abnormalities together increase susceptibility to infection.

LYST dysfunction affects tissues beyond leukocytes

Melanocytes

Abnormal pigment handling

Albinism

Nervous system

Lysosomal-related cellular
dysfunction

Neurologic abnormalities

Platelets

Granule-related functional
abnormality

Bleeding tendency

A multisystem pattern distinguishes Chédiak–Higashi

- The leukocyte phenotype alone resembles other phagocyte defects.
- Albinism raises suspicion for a broader intracellular-trafficking disorder.
- Neurologic and bleeding manifestations localize pathology beyond neutrophils.
- Giant cytoplasmic granules provide a distinctive morphologic clue.

Application: Enlarged granules and infections

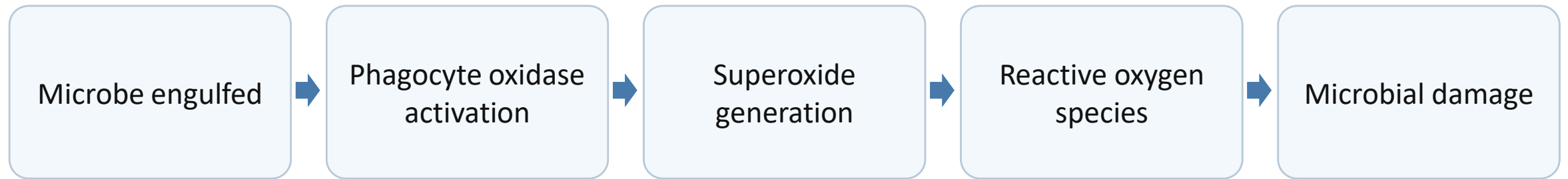
ILLUSTRATIVE TEACHING VIGNETTE

Teaching vignette: A child with recurrent infections also has reduced pigmentation, bleeding problems, and giant cytoplasmic granules in leukocytes.

Question: Does the principal defect involve adhesion, granule traffic, or ROS production?

Mechanistic answer: LYST-associated lysosomal trafficking / phagolysosomal function (Chédiak–Higashi syndrome).

Oxygen-dependent killing follows ingestion



Functional sequence — schematic

Respiratory burst: The chemical purpose

- The phagocyte oxidase complex uses NADPH and oxygen.
- Its activity generates superoxide, a major reactive oxygen species.
- The acute oxygen consumption is termed the respiratory burst.

NADPH + O₂



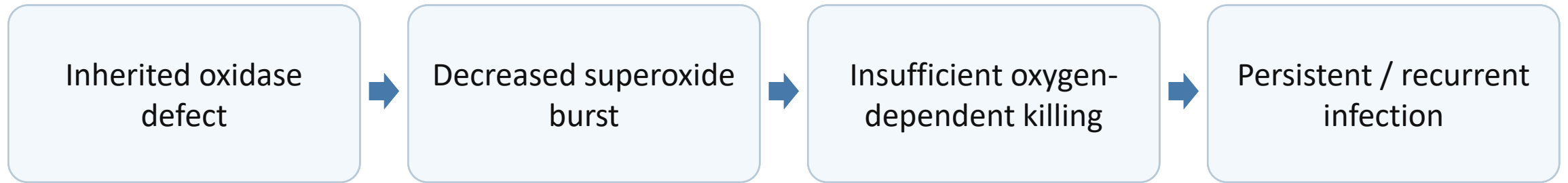
Phagocyte oxidase



Superoxide (O₂•⁻)

Schematic

Chronic granulomatous disease is an oxidase defect



Causal sequence — schematic

CGD includes X-linked and recessive forms

Genetic pattern	Affected oxidase element	Example protein
X-linked	Membrane-associated component	gp91phox
Autosomal recessive	Cytoplasmic component	p47phox
Autosomal recessive	Cytoplasmic component	p67phox

The gp91phox-associated CGD mechanism

- A membrane-bound oxidase component is defective.
- Assembly/activity of the microbicidal oxidase is compromised.
- The resulting oxidative burst is insufficient for normal killing.

Membrane component defect



Oxidase dysfunction



Microbial persistence

Schematic

Cytoplasmic-component CGD has the same endpoint

- P47phox and p67phox are cytoplasmic oxidase components.
- Autosomal recessive variants involving these components.
- Different molecular lesions converge on reduced oxidative microbicidal activity.

Cytoplasmic component defect



Oxidase dysfunction



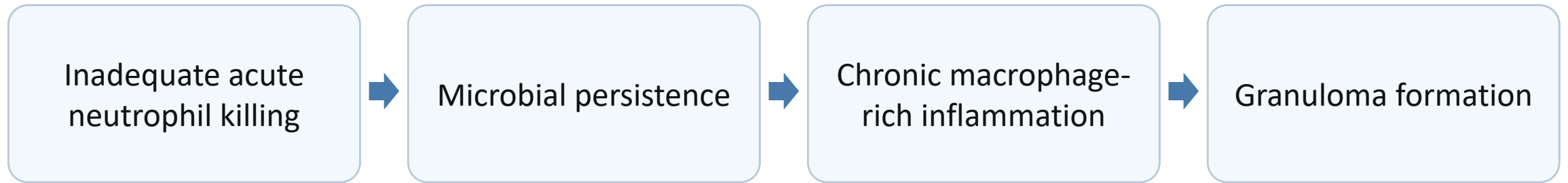
Microbial persistence

Schematic

CGD manifests through failed intracellular killing

- Neutrophils can encounter and ingest microbes, yet oxygen-dependent killing is impaired.
- Recurrent bacterial infections.
- The infection phenotype reflects failure after cellular recruitment and phagocytosis.
- This differs mechanistically from impaired leukocyte extravasation in LAD.

Why granulomas form in CGD



Causal sequence — schematic

Granulomas in CGD are a secondary response

- The term “granulomatous” describes the host response, not the primary molecular lesion.
- Activated macrophages accumulate and attempt to contain persistent microbes.
- A granuloma may wall off organisms that were not rapidly cleared.
- The underlying defect remains oxidase-dependent microbicidal activity.

Chédiak–Higashi versus CGD

Feature	Chédiak–Higashi	CGD
Major lesion	LYST-dependent lysosomal traffic	Phagocyte oxidase
Defective step	Granule handling/fusion	ROS generation
Distinctive clue	Giant leukocyte granules	Macrophage-rich granulomas
Additional findings	Albinism, neurologic, platelet defects	Chronic inflammatory containment

Application: Persistent infection and granulomas

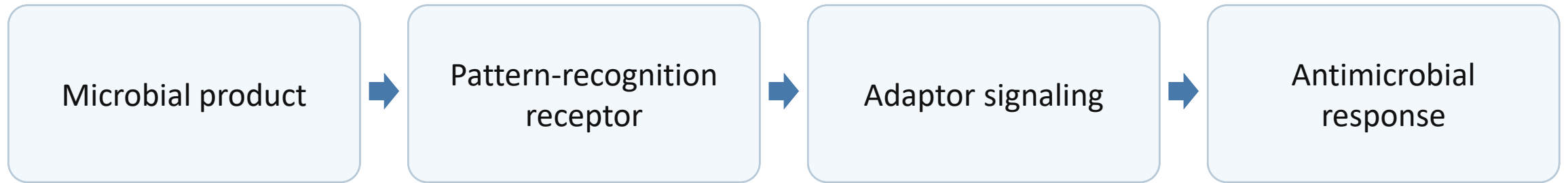
ILLUSTRATIVE TEACHING VIGNETTE

Teaching vignette: Recurrent bacterial infections are accompanied by macrophage-rich granulomatous inflammation despite the presence of phagocytes.

Question: Which leukocyte killing pathway should be considered?

Mechanistic answer: Impaired phagocyte oxidase–dependent superoxide generation (CGD).

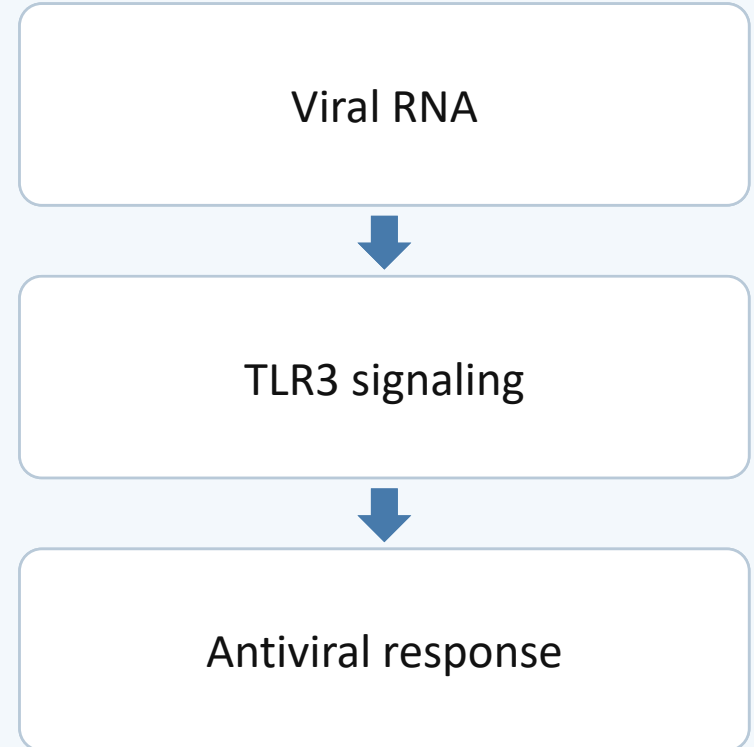
Pattern-recognition receptors initiate rapid defense



Causal sequence — schematic

TLR3 detects viral RNA

- Toll-like receptor 3 (TLR3) senses viral RNA.
- Its signaling contributes to protective antiviral responses.
- Inherited defects of this pathway are associated with herpes simplex encephalitis.

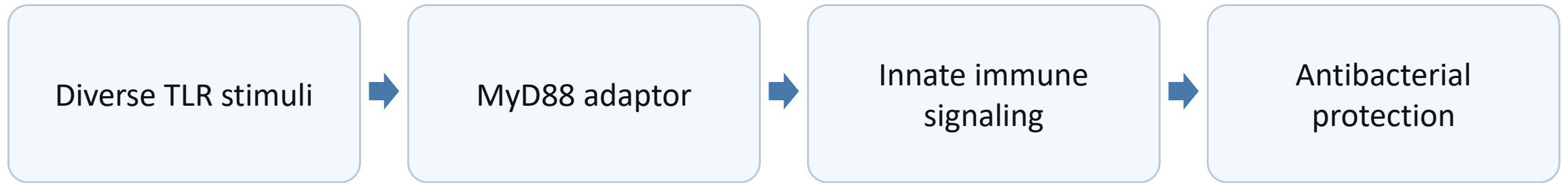


Schematic

A tissue-specific clue: Herpes simplex encephalitis

- TLR3 defects with recurrent herpes simplex encephalitis.
- This illustrates that an innate signaling lesion need not produce the same infections as a phagocyte defect.
- The pathogen and affected organ may help localize the molecular pathway.
- The association does not imply that every case of herpes encephalitis is hereditary.

MyD88 transmits signals from multiple TLRs



Causal sequence — schematic

MyD88 deficiency predisposes to destructive bacterial infection

- MyD88 is downstream of several Toll-like receptors.
- Defects affect signaling triggered by multiple microbial stimuli.
- Severe destructive bacterial infections, especially pneumonia.
- The phenotype differs from TLR3-associated herpes encephalitis.

Cytokine deficiency can be inherited or acquired

Inherited defect

Mutation in a cytokine gene

Mutation in a cytokine receptor

Interruption of protective signaling

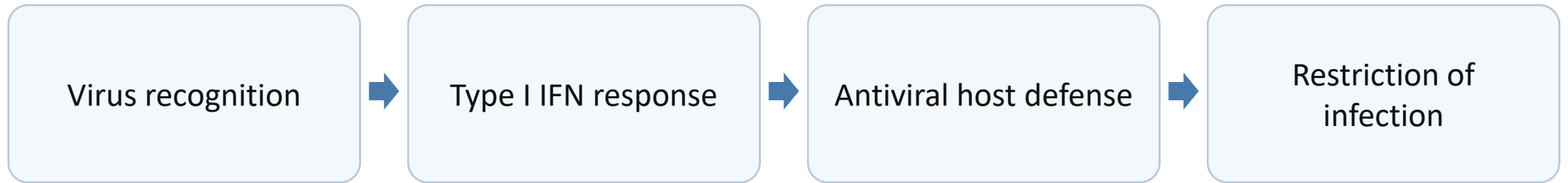
Acquired defect

Autoantibody directed at a cytokine

Neutralization of cytokine activity

Functional loss despite intact coding genes

Type I interferons are major antiviral cytokines

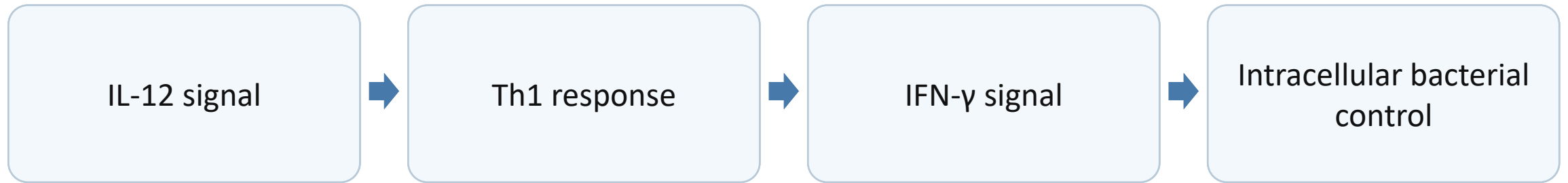


Causal sequence — schematic

Defective type I IFN immunity and severe viral disease

- Inherited defects in type I IFN pathways can increase viral susceptibility.
- Autoantibodies to type I interferons can create acquired cytokine dysfunction.
- Severe forms of COVID-19 among associated viral presentations.
- A pathway deficiency is a risk mechanism, not a deterministic clinical outcome.

IL-12 and IFN- γ form a macrophage-defense axis



Causal sequence — schematic

Mendelian susceptibility to mycobacterial disease

- Mutations affecting IL-12 or IFN- γ receptor signaling impair protective responses.
- Environmental mycobacteria of low usual virulence may cause disease.
- This phenotype is termed Mendelian susceptibility to mycobacterial disease.

IL-12 / IFN- γ receptor defect



Reduced cellular defense



Environmental mycobacterial
infection

Schematic

Innate signaling defects: Use the organism pattern

Pathway impaired	Robbins-associated clinical pattern
TLR3 signaling	Recurrent herpes simplex encephalitis
MyD88 signaling	Severe pyogenic bacterial infections; pneumonia
Type I interferon immunity	Viral disease; severe COVID-19 forms
IL-12 / IFN- γ axis	Infection by environmental mycobacteria

Complement has three initiation routes

Classical pathway

Antigen–antibody complexes
activate C1

Involves early components
including C2 and C4

Alternative pathway

Amplification on microbial
surfaces

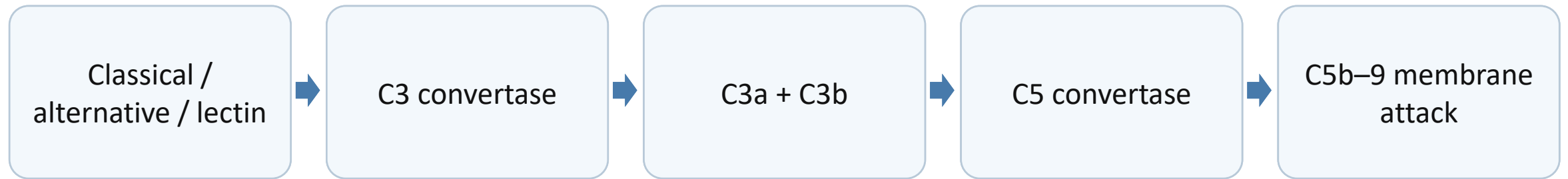
Can operate without antibody

Lectin pathway

Mannose-binding lectin
recognizes carbohydrates

Converges on subsequent
complement steps

The C3 cleavage step is the shared hub



Functional sequence — schematic

Complement protects in three distinct ways

Inflammation

C3a / C5a

Vascular reactions and
leukocyte recruitment

Opsonization

C3b / iC3b

Enhanced phagocyte ingestion

Direct lysis

C5b–C9

Membrane attack complex

C2 and C4 deficiencies affect classical activation

- C2 deficiency is described as the most common complement protein deficiency.
- C2 or C4 deficiency can reduce classical pathway activity.
- Some affected individuals have bacterial or viral infections; Others remain asymptomatic.

Early classical pathway defect



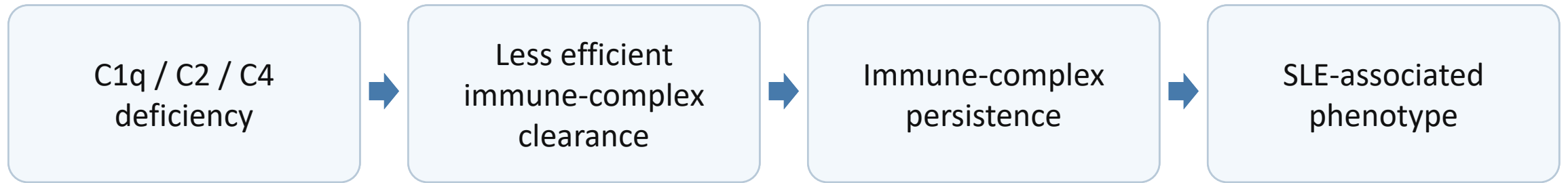
Alternative pathway may persist



Variable clinical expression

Schematic

Early classical deficiency can present as autoimmunity



Causal sequence — schematic

Why an immune deficiency may resemble SLE

- Complement participates in removal of immune complexes.
- Early classical components contribute to this clearance.
- SLE may dominate in some patients deficient in C1q, C2, or C4.
- The clinical phenotype therefore need not be recurrent infection alone.

Properdin and factor D: Alternative-pathway defects

- Properdin and factor D support alternative-pathway complement activity.
- Inherited deficiency of either is uncommon.
- These defects with recurrent pyogenic infections.

Alternative pathway impairment



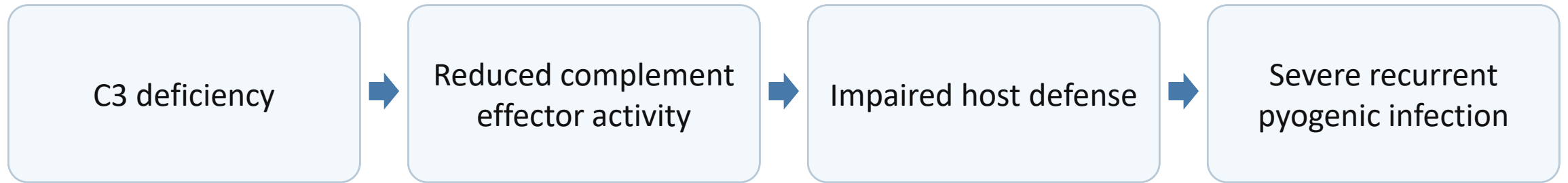
Reduced complement protection



Recurrent pyogenic infection

Schematic

C3 deficiency removes multiple complement defenses

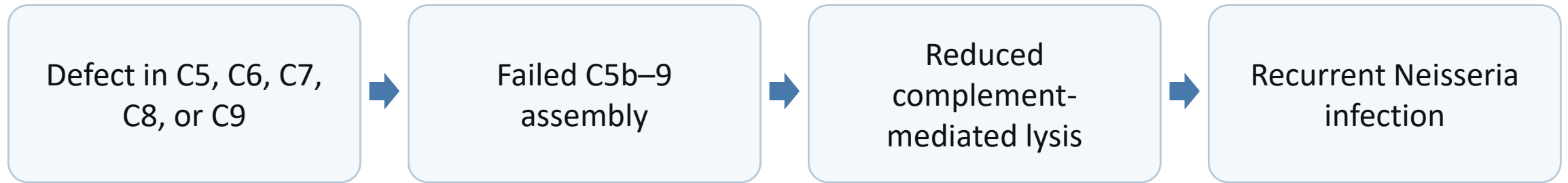


Causal sequence — schematic

C3 deficiency and immune-complex glomerulonephritis

- Increased immune-complex–mediated glomerulonephritis in C3 deficiency.
- C3 contributes to clearance of immune complexes as well as microbial defense.
- Even when complement is deficient, inflammation may still be driven through Fc receptors.
- A renal inflammatory complication can coexist with recurrent infection.

Terminal complement deficiency targets membrane attack



Causal sequence — schematic

Why Neisseria is a clue to terminal deficiency

- The membrane attack complex perforates susceptible microbial membranes.
- Neisseria because its thin cell wall permits complement-mediated lysis.
- Meningococcal or gonococcal infections may recur when terminal lysis is deficient.
- This pattern helps distinguish terminal defects from global C3 deficiency.

Mannose-binding lectin deficiency

- Mannose-binding lectin initiates the lectin pathway.
- Inherited dysfunctional forms are associated with susceptibility to infections.
- This defect interrupts recognition-dependent complement activation.

Defective mannose-binding lectin



Impaired lectin initiation



Reduced antimicrobial protection

Schematic

Complement regulators protect host tissues

C1 inhibitor

Restrains protease systems including C1 and kallikrein

Prevents uncontrolled vasoactive mediator generation

CD55 / CD59

Cell-surface, GPI-anchored complement regulators

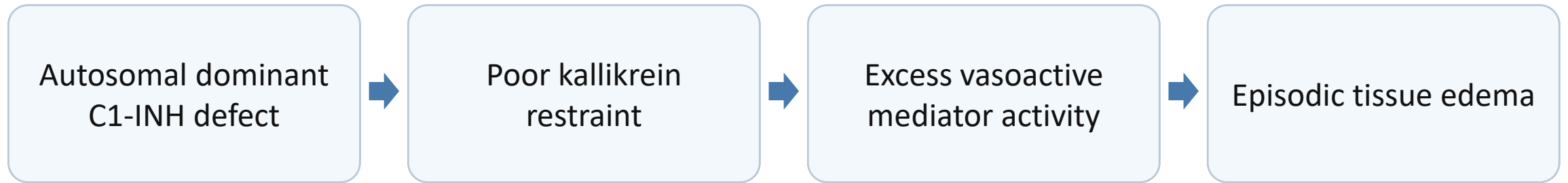
Help prevent complement injury to host cells

Factor H

Controls alternative-pathway amplification

Protects vascular and other host surfaces

Hereditary angioedema: C1 inhibitor deficiency

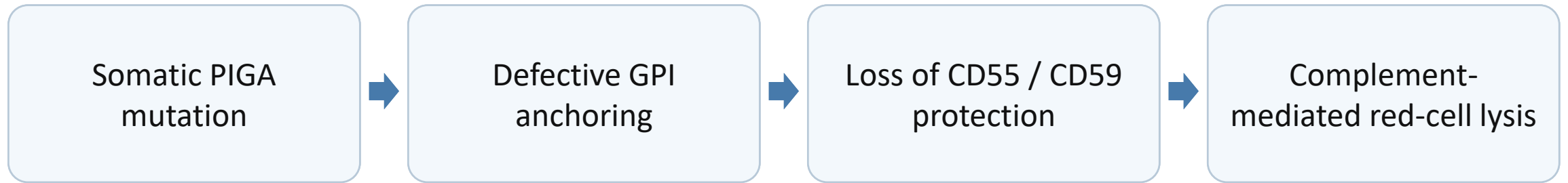


Causal sequence — schematic

Angioedema can threaten airway and gut

- Edema may involve skin, larynx, or gastrointestinal mucosa.
- Laryngeal swelling can cause life-threatening airway obstruction.
- Gastrointestinal attacks can produce nausea, vomiting, and diarrhea.
- Minor trauma or emotional stress may precede attacks; C1-INH concentrate for acute treatment.

PNH is an acquired regulatory defect

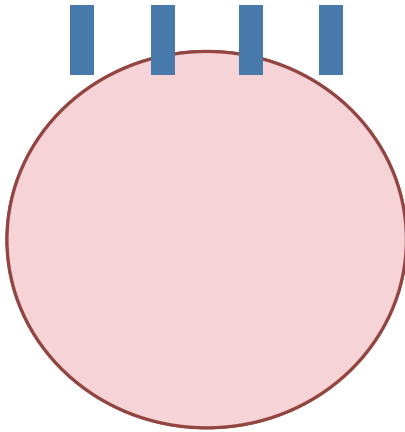


Causal sequence — schematic

Complement regulation in PNH: The cell-surface view

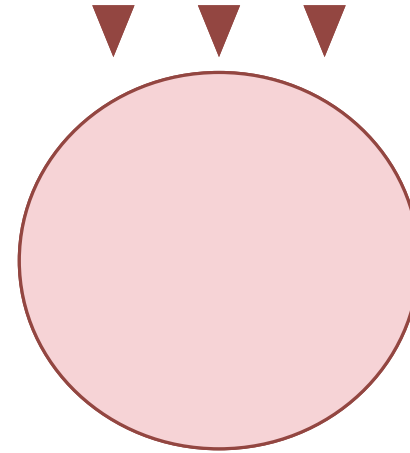
Without GPI-linked protective proteins, erythrocytes become vulnerable to terminal complement injury.

Protected host red cell: CD55 and CD59



CD55 / CD59 present

PNH red cell: Deficient regulators



Complement vulnerability

Factor H connects regulation to vascular injury

- Factor H constrains the alternative pathway through C3b regulation.
- Defects in alternative-pathway regulators are associated with atypical hemolytic uremic syndrome.
- Factor H gene variants have also been associated with age-related macular degeneration.

Regulatory failure



Excess host-surface complement activity



Tissue injury

Schematic

Complement defects: Phenotype-oriented comparison

Defect group	Dominant association in Robbins
C1q / C2 / C4	Variable infection; SLE in some
Properdin / factor D	Recurrent pyogenic infection
C3	Severe pyogenic infection; immune-complex GN
C5–C9	Recurrent Neisseria infection
C1 inhibitor	Episodic skin / airway / GI edema
GPI-linked regulators	PNH / red-cell complement lysis

A localization framework for innate immune defects

Presenting pattern	Potential checkpoint
Severe bacterial infection with poor tissue recruitment	Endothelial adhesion: LAD-1 / LAD-2
Giant granules with pigment / neurologic clues	Lysosomal trafficking: Chédiak–Higashi
Infection plus macrophage-rich granulomas	Oxidative killing: CGD
Recurrent HSV encephalitis or pyogenic pneumonia	TLR3 / MyD88 pathways
Environmental mycobacteria	IL-12 / IFN- γ signaling
Recurrent Neisseria	Terminal complement lysis

Application: Recurrent invasive Neisseria infection

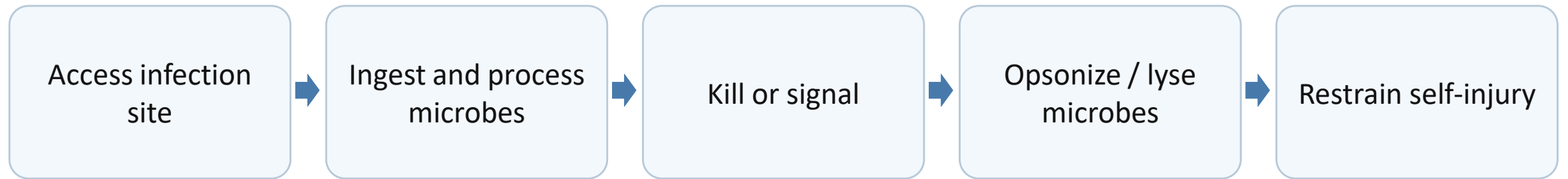
ILLUSTRATIVE TEACHING VIGNETTE

Teaching vignette: Repeated meningococcal or gonococcal infections occur in a patient without evidence in this vignette of a generalized leukocyte adhesion defect.

Question: Which complement function is particularly implicated?

Mechanistic answer: C5b–C9 membrane attack complex formation; Examine terminal pathway components.

Integrative synthesis: The failed-defense checkpoint



Functional sequence — schematic

Textbook reference and scope

- Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. (2026).
- Primary section: Defects in Innate Immunity, within Immunodeficiency Diseases.
- Mechanism context drawn from the supplied sections on normal innate immunity, inflammation, and complement; PNH details from the supplied hematology chapter.
- Teaching diagrams in this lecture are original editable schematics, not pathology specimens.