

Injurious Effects of Host Immunity

Mechanisms and clinicopathologic examples

Dr Abu Suraih Sakhri

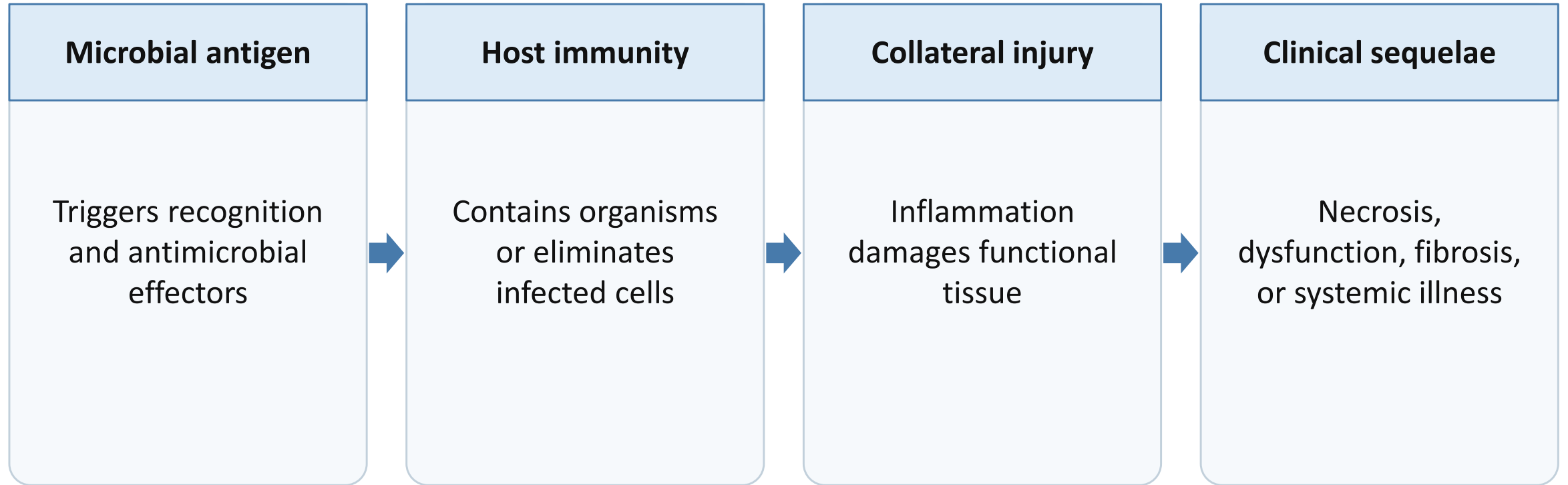
MBBS, MD (Pathology)

www.abusuraisakhri.com

Learning outcomes

- Explain why a protective antimicrobial response may also destroy host tissue.
- Connect T-cell, antibody, immune-complex, and cytokine effectors to lesions.
- Interpret the characteristic infectious and postinfectious examples.
- Distinguish direct microbial injury from host-response injury.

The central paradox: Defense can cause disease



Three mechanisms of microbial tissue damage

Direct cellular damage

Entry, replication, or direct
cytopathic effects

Microbial toxins / enzymes

Toxin-related cell injury
and tissue destruction

Host immune response

Immune effectors harm
infected or bystander
tissue

Immune injury is mechanistically diverse

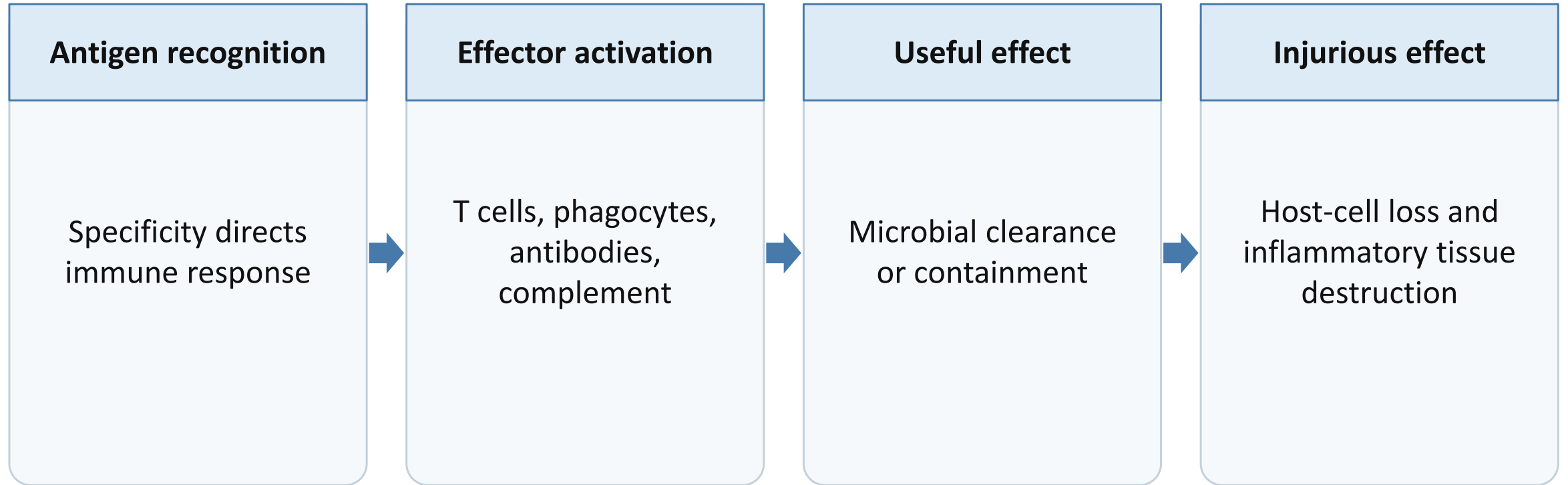
Cellular immunity

- CD8+ T cells kill infected cells
- Th1 cells activate macrophages
- Th17 cytokines recruit inflammatory leukocytes

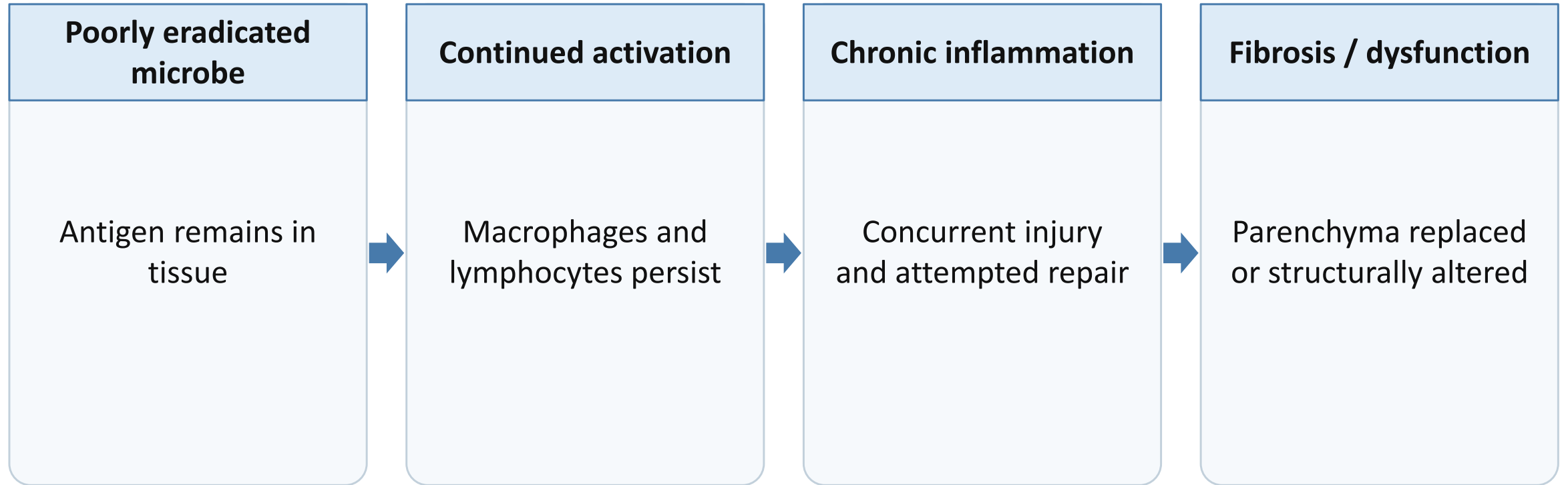
Humoral and soluble effectors

- Cross-reactive antibody can bind host tissues
- Antigen–antibody complexes activate inflammation
- Cytokines can produce systemic damage

Protective and destructive outputs share effectors



Why persistent antigen changes the outcome



T cells create two distinct injury patterns

CD8+ cytotoxicity

- MHC I presents intracellular microbial peptide
- Cytotoxic lymphocytes eliminate infected target cells
- Hepatocytes are targets in viral hepatitis

CD4+ inflammatory pathways

- Th1-derived IFN- γ activates macrophages
- Th17-derived mediators recruit myeloid cells
- Granulomas and chronic inflammation may result

Antibody-related injury: Two mechanisms

Cross-reactive antibody

- Microbial epitope resembles a host determinant
- Antibody recognizes host tissue
- Rheumatic carditis provides the exemplar

Immune-complex deposition

- Microbial antigens associate with antibody
- Complexes deposit or form in tissue
- Poststreptococcal nephritis provides the exemplar

Local injury and systemic inflammation differ

Local tissue reaction

- Destruction confined to infected or targeted tissue
- Granuloma, hepatitis, carditis, nephritis
- Repair can replace tissue with scar

Systemic response

- Inflammatory mediators reach distant organs
- Cytokine excess can accompany severe viral illness
- Severe COVID-19 illustrates systemic injury

Morphology records the dominant effector

Macrophage-rich

Granuloma with
epithelioid macrophages
and lymphocytes

Cytotoxic / mononuclear

Inflammatory hepatocyte
injury with cell death

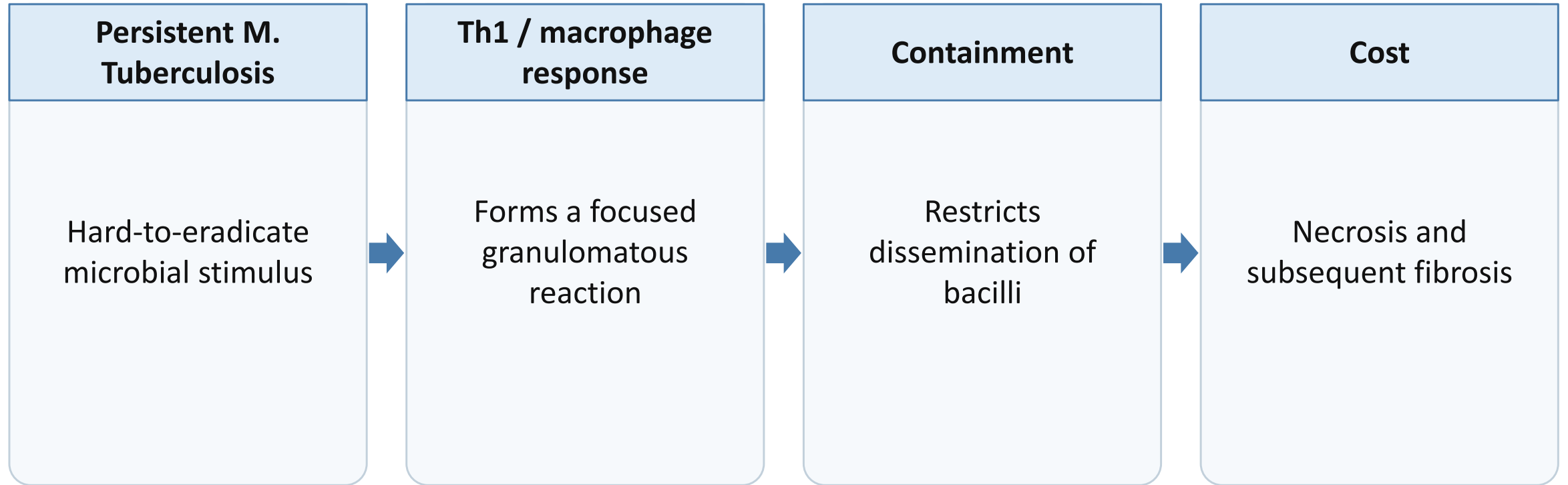
Neutrophilic / proliferative

Immune-complex nephritis
with leukocyte influx

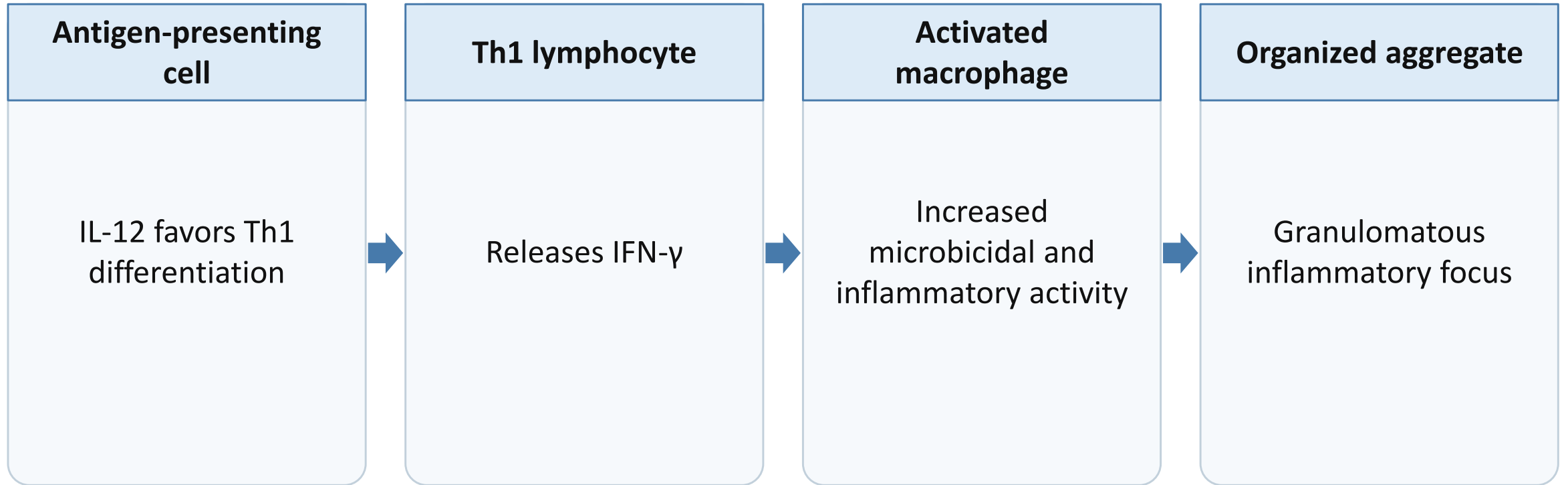
Three questions to ask at the microscope

- What effector dominates: Activated macrophages, lymphocytes, or neutrophils?
- What structure is injured: Parenchymal cell, vessel, valve, or glomerulus?
- Is the insult ongoing, or is the lesion postinfectious?
- Which microbial tests can establish the specific cause?

Tuberculosis: The classic containment–injury trade-off



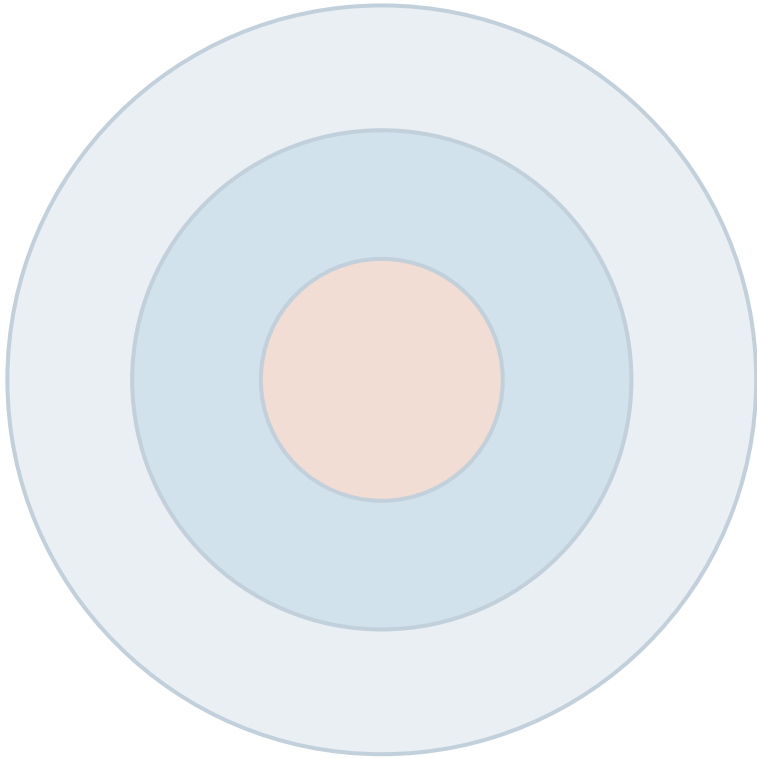
Th1 cells provide the signal for granulomas



Macrophages can injure the tissue they defend

- IFN- γ promotes macrophage antimicrobial functions and inflammatory activity.
- Activated macrophages also release cytokines that sustain local leukocyte recruitment.
- Persistent activation couples microbial containment to continuing collateral damage.
- Repair of destroyed tissue may culminate in fibrosis.

Granuloma architecture is a tissue-level strategy



Schematic — cellular organization, not histology

Central focus

May contain caseous necrosis

Inner cellular zone

Epithelioid macrophages and giant cells

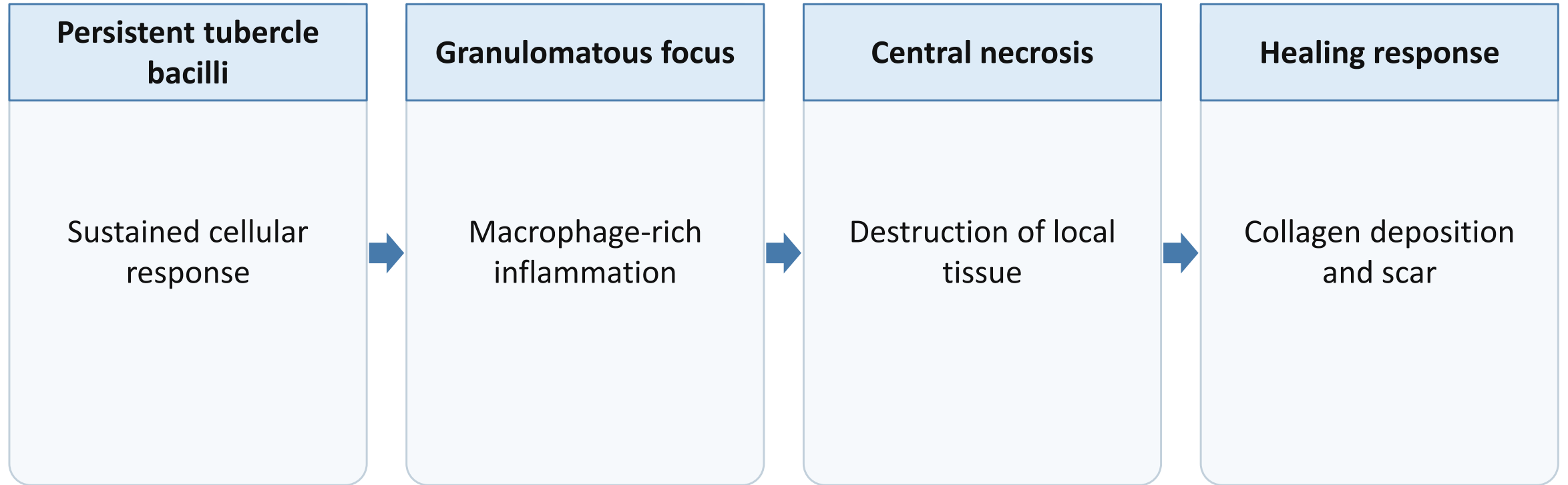
Peripheral reaction

Lymphocytes and later fibroblasts

Epithelioid transformation signifies sustained activation

- Activated macrophages acquire abundant cytoplasm and an epithelial-like appearance.
- Cells aggregate into a compact granulomatous focus.
- Fusion of macrophages can produce multinucleated giant cells.
- Lymphocytes commonly surround or intermix with the macrophage population.

Caseation links immune reaction to irreversible loss



A granuloma is not synonymous with tuberculosis

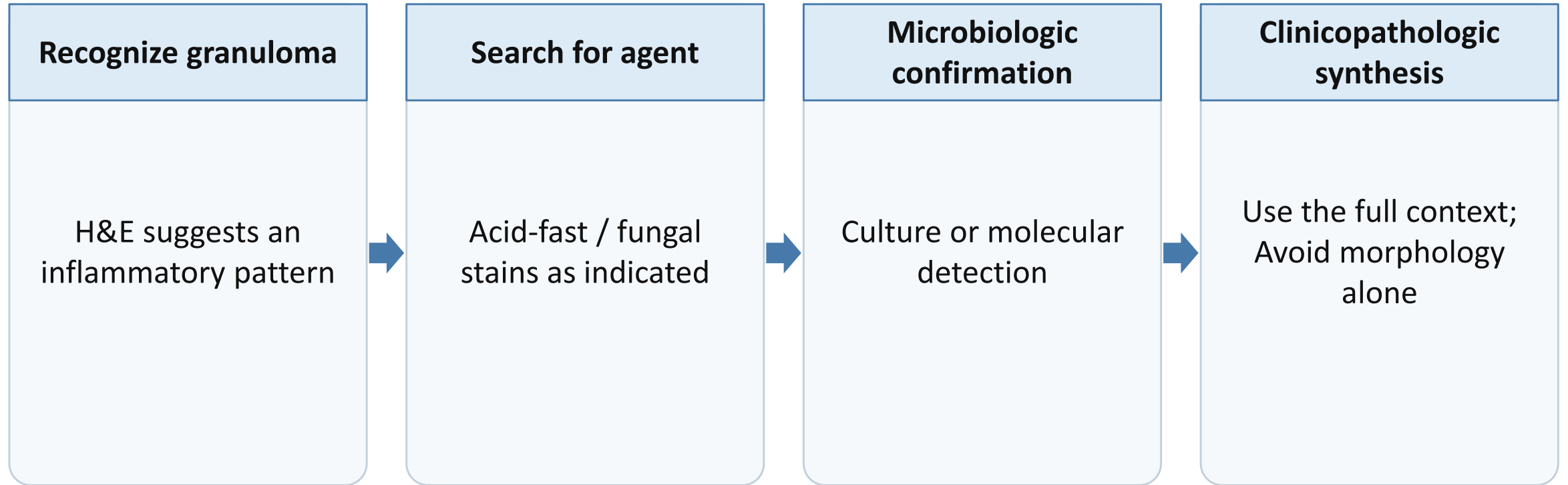
Infectious granuloma

- Tuberculosis: Classic caseating reaction
- Other microbes can form granulomas
- Specific organism must be demonstrated

Noninfectious granuloma

- Foreign material may stimulate giant cells
- Sarcoidosis and Crohn disease are examples
- Similar morphology has different etiologies

Proving the cause of a granulomatous lesion



Containment and scarring are simultaneous outcomes

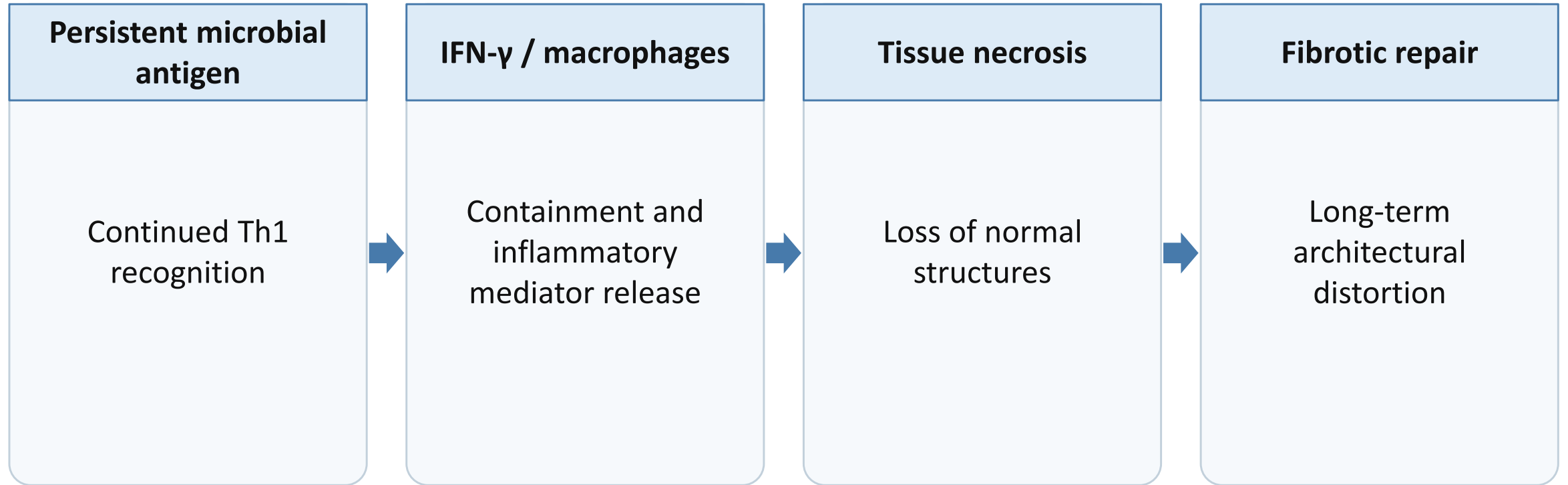
Protection

- Focal cellular response encases persistent bacilli
- Activated macrophages constrain infection

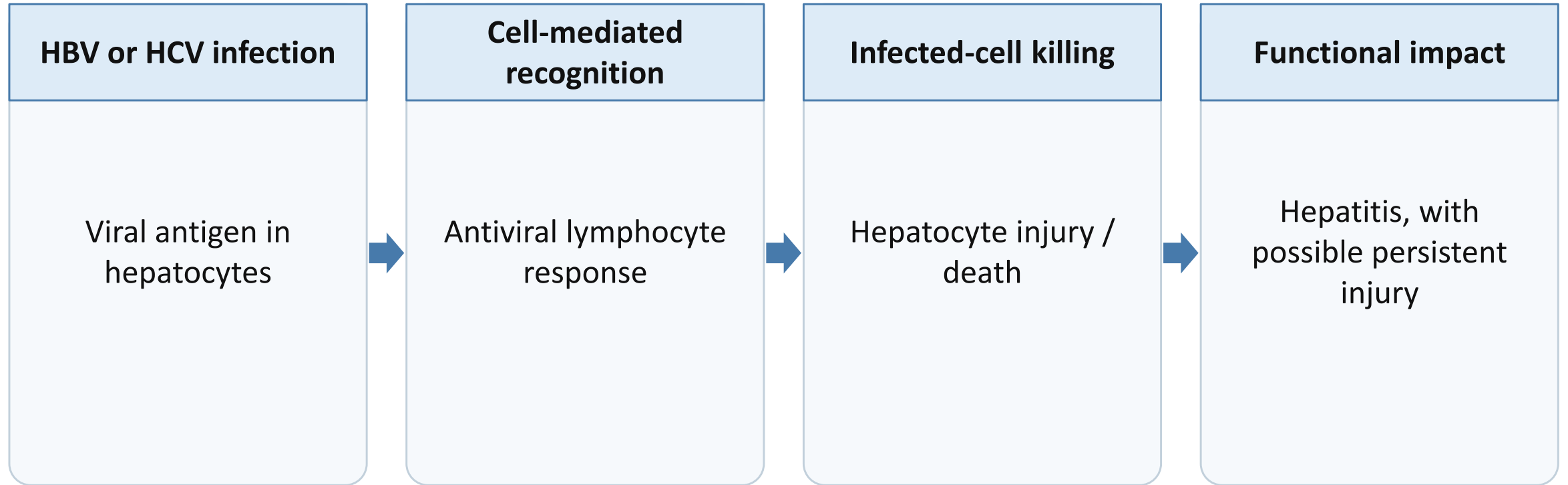
Damage

- Necrosis interrupts tissue architecture
- Fibrosis may persist after inflammation resolves
- Organ function reflects both infection and repair

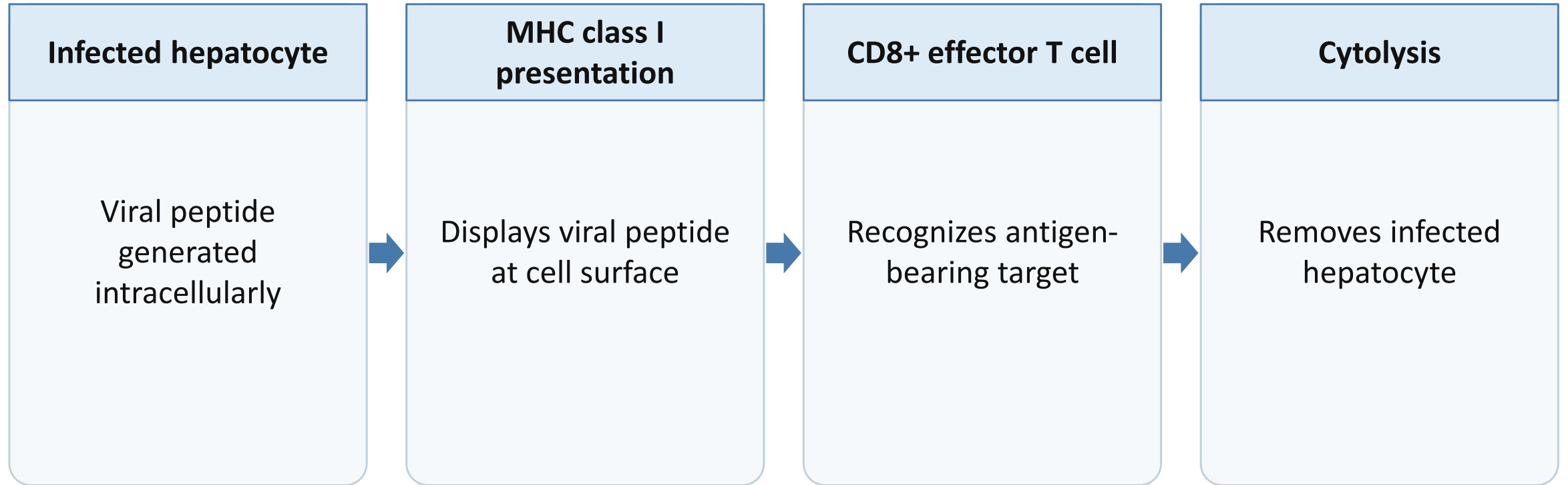
Granulomatous injury: Mechanistic synthesis



Viral hepatitis: Cytotoxic defense damages parenchyma



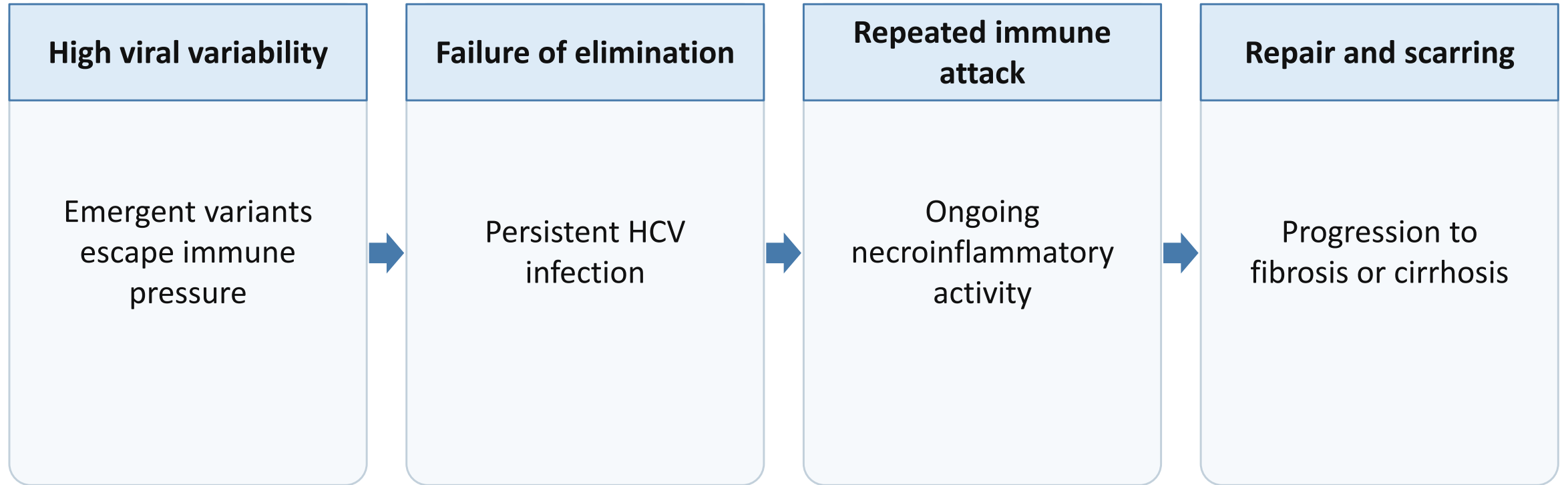
CD8+ T-cell specificity follows MHC class I



HBV pathology depends strongly on host immunity

- The immune response is a major determinant of HBV outcome.
- Most hepatocyte injury results from attack by virus-specific CD8+ cells.
- Viral replication and proteins can also produce cytopathic changes.
- An effective antiviral response may clear infection but still generate acute hepatitis.

HCV persistence prolongs the inflammatory exposure



T-cell injury is not equivalent to viral cytotoxicity

Direct virus-associated change

- A virus may alter synthesis, metabolism, or viability
- Cytopathic mechanisms depend on virus and cell

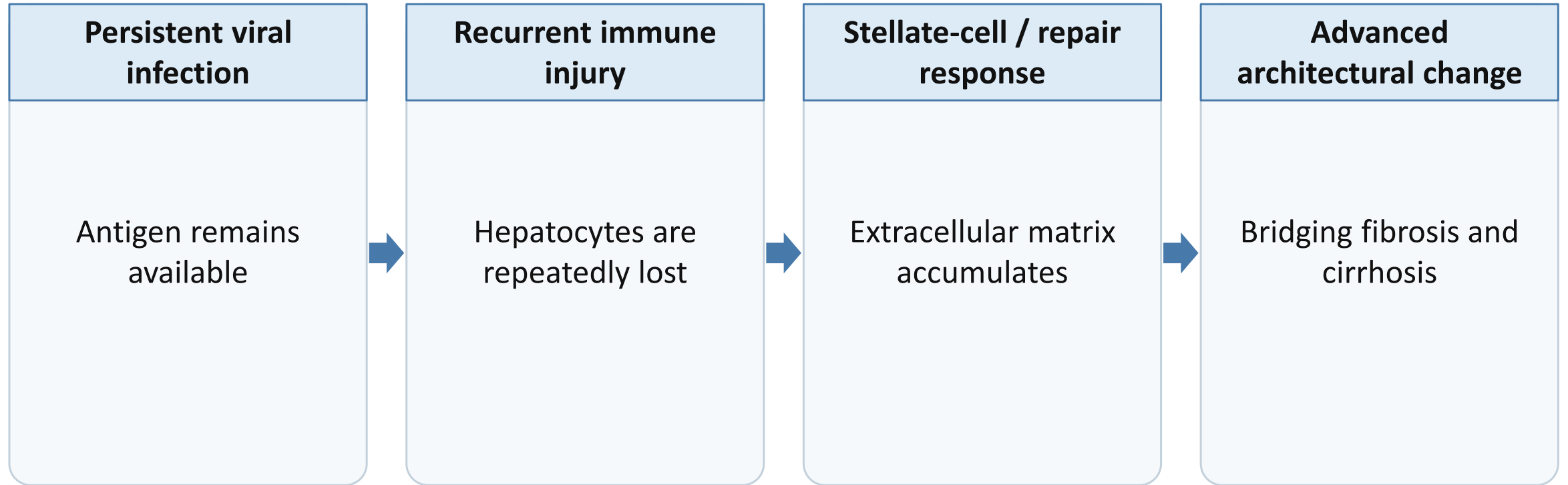
Immune-mediated hepatitis

- T cells recognize infected hepatocytes
- Cell death arises during attempted clearance
- Both processes can coexist in viral diseases

Morphology of ongoing hepatitis follows cell loss

- Hepatocellular injury occurs amid an inflammatory lymphocytic response.
- Repeated death and regeneration can distort the architecture of liver parenchyma.
- Sustained injury promotes progressive deposition of fibrous tissue.
- Advanced scarring impairs the structure and function of the liver.

Hepatitis can convert defense into chronic fibrosis



Hepatitis-related cancer reflects more than one route

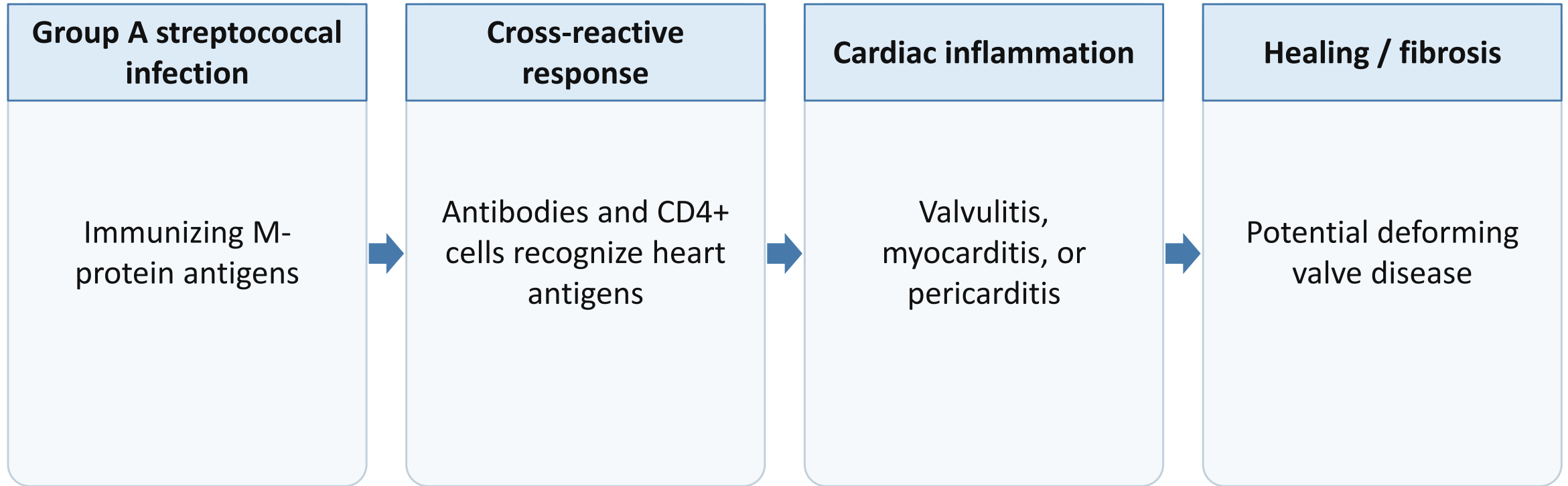
Chronic inflammatory setting

- Hepatocyte turnover and scarring accompany persistence
- HCV-related cancer often follows chronic disease

Viral contribution beyond inflammation

- HBV proteins, including HBx, are implicated in cancer
- Direct and indirect mechanisms should not be conflated

Rheumatic heart disease: An immune response without bacteria in lesions



Molecular mimicry explains the target mismatch

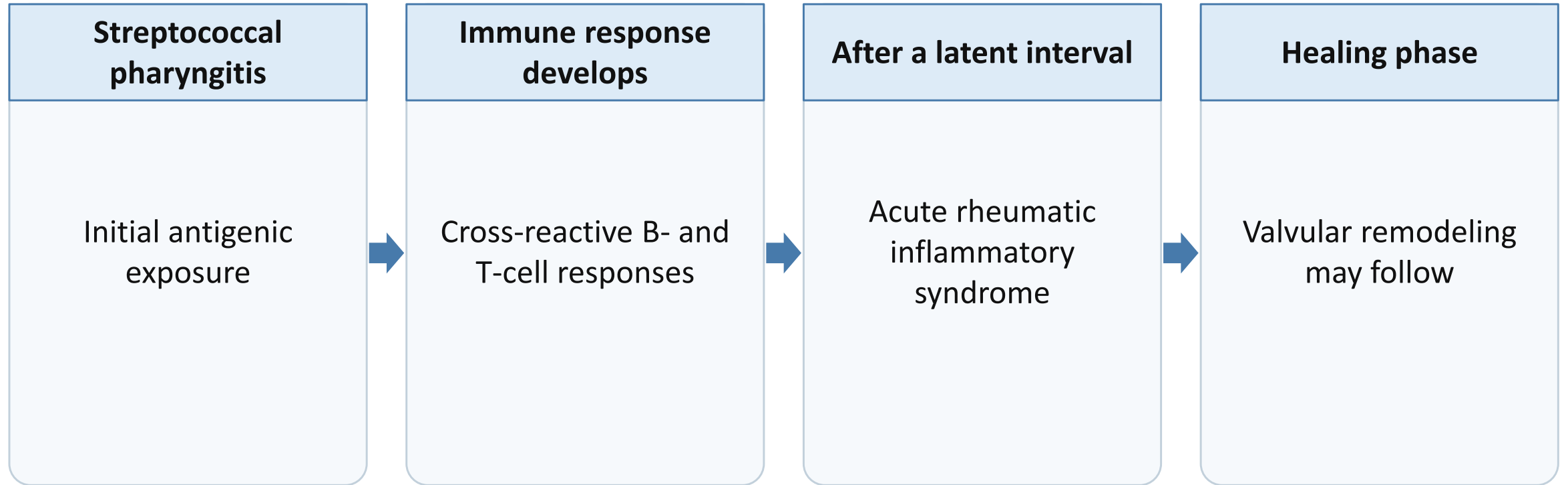
Intended recognition

- Antibody generated against streptococcal M protein
- Immune response directed at microbial material

Unintended recognition

- Cross-reactive determinants on host tissues
- Heart is injured even when bacteria are absent in lesions

The postinfectious delay is mechanistically important



Rheumatic carditis combines immune effectors

Antibody

Cross-reactivity with
cardiac antigens

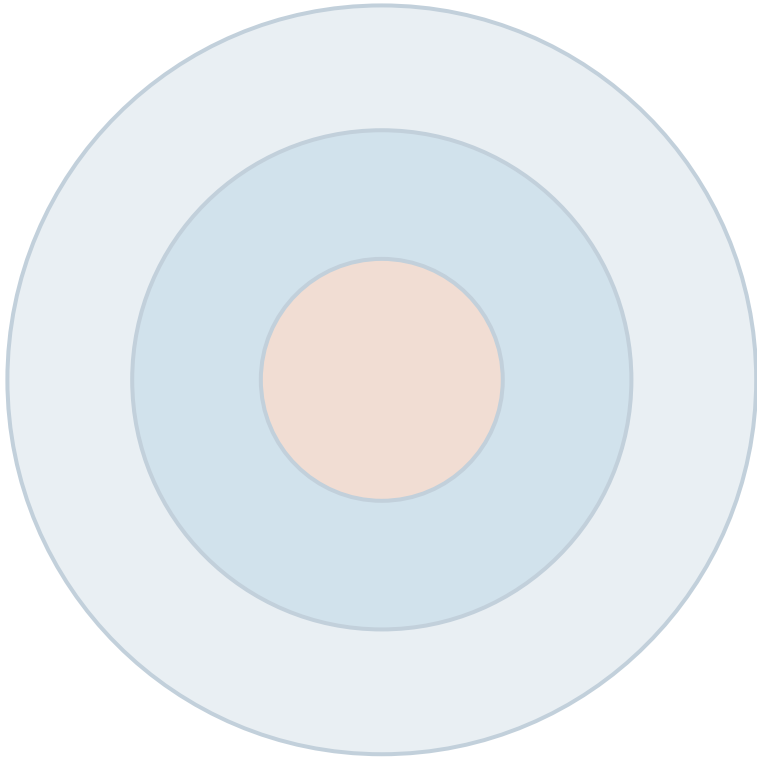
Complement / Fc cells

Inflammation after
antibody binding

CD4+ T cells

Cytokines activate
macrophages in lesions

Acute rheumatic carditis has a distinctive lesion



Schematic — cellular organization, not histology

Aschoff body

Focal inflammatory nodule

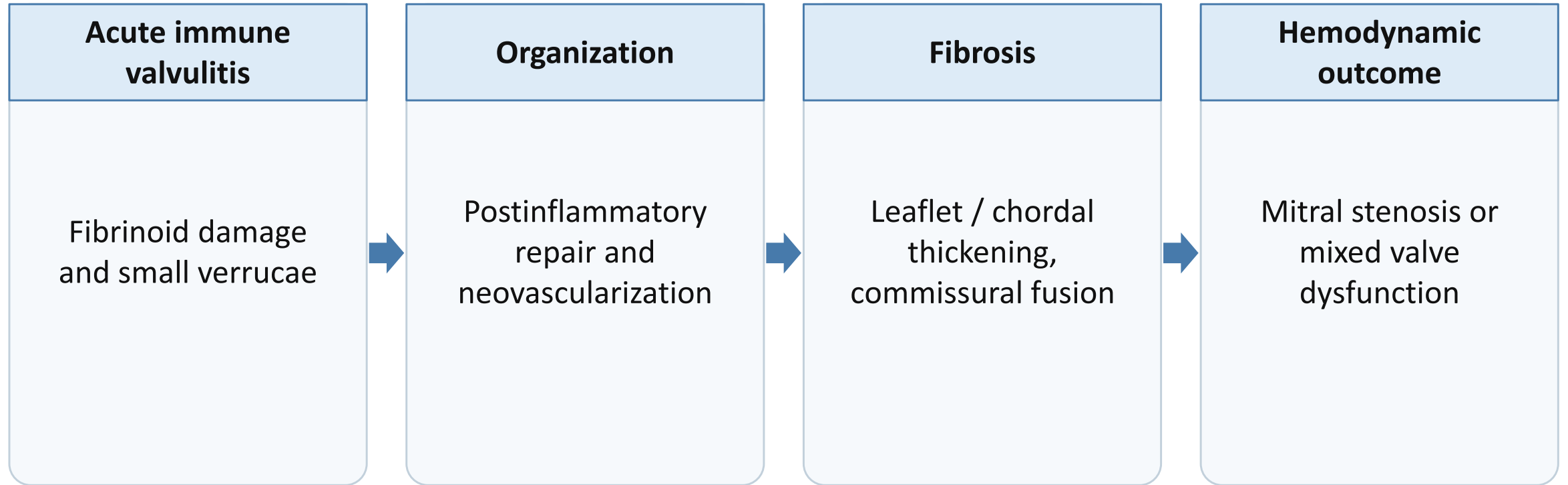
Cellular composition

T cells, plasma cells, activated macrophages

Anitschkow cells

Macrophages with wavy nuclear chromatin

Chronic rheumatic injury deforms the valve



Rheumatic valvulitis is not infective endocarditis

Rheumatic inflammatory lesion

- Poststreptococcal immune pathogenesis
- Bacteria absent from characteristic cardiac lesions
- Small verrucae along closure lines

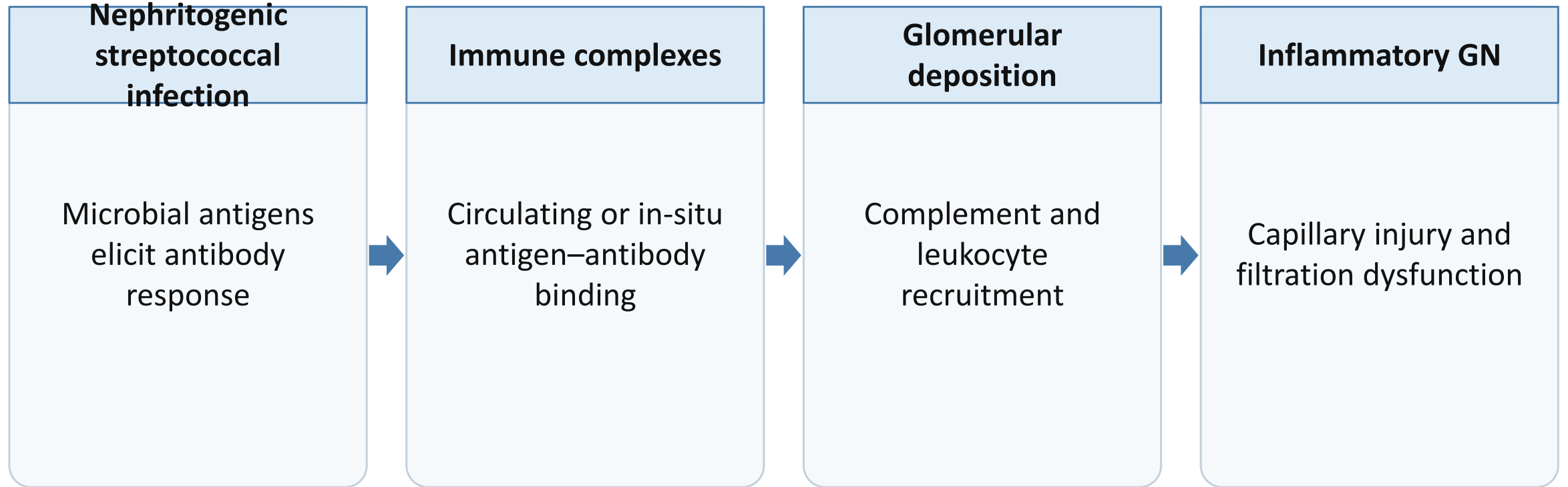
Infective endocarditis

- Organism-driven infection of endocardial surface
- Vegetations contain microbial infection
- Distinct clinical and microbiologic work-up

Cardiac sequelae may outlast the trigger

- The streptococcal episode may have resolved before the cardiac lesion is apparent.
- Repeated or healed inflammation can result in leaflet and commissural fibrosis.
- The chronic valve defect expresses accumulated tissue remodeling, not ongoing streptococcal infection.
- Clinical assessment must distinguish active inflammation from fixed stenotic disease.

Poststreptococcal nephritis: Immune complexes localize injury



An infection may be gone when nephritis appears

- Poststreptococcal glomerulonephritis often follows pharyngeal or skin infection.
- The latent interval is consistent with antibody development and complex formation.
- Renal pathology is not the result of local invasive streptococcal growth.
- Immunologic evidence of antecedent infection informs diagnosis.

Circulating and in-situ complexes converge

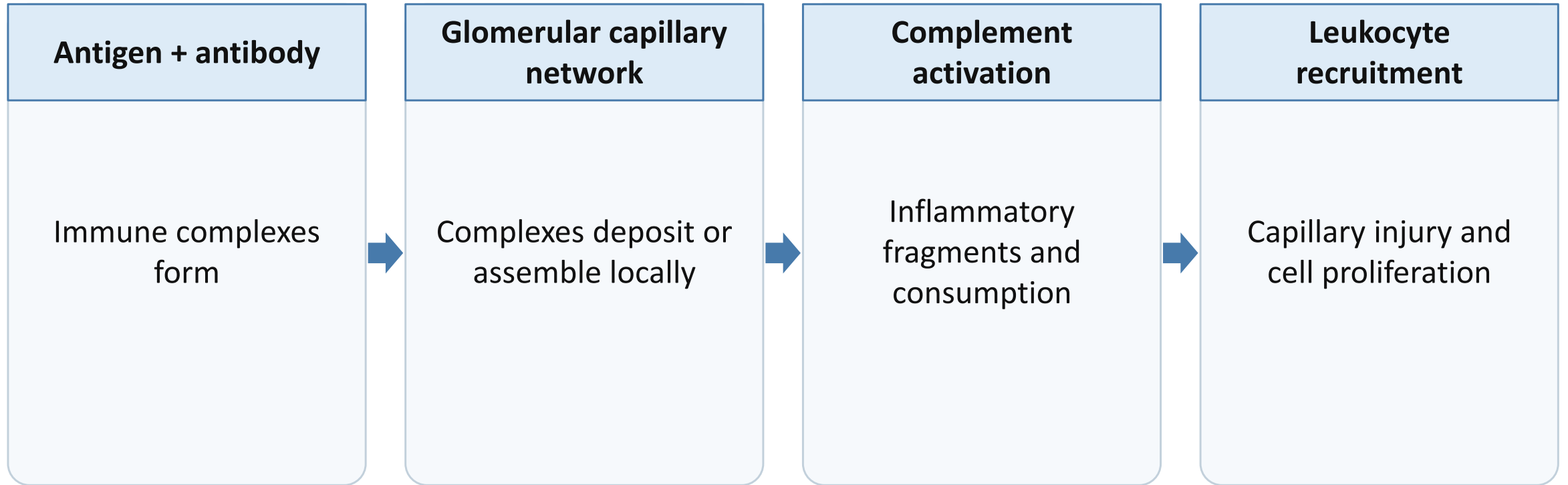
Preformed circulating complex

- Antigen and antibody associate before deposition
- Circulating complexes lodge in receptive tissue

In-situ immune complex

- Antigen becomes localized in glomerulus first
- Antibody binds the deposited microbial antigen
- Both pathways elicit inflammatory injury

Glomeruli are vulnerable to immune-complex injury



Postinfectious glomerulonephritis has a pattern triad

Light microscopy

Diffuse endocapillary hypercellularity with leukocytes

Immunofluorescence

Granular deposits of immunoglobulin and complement

Electron microscopy

Characteristic subepithelial humplike deposits

Granular versus linear immunofluorescence matters

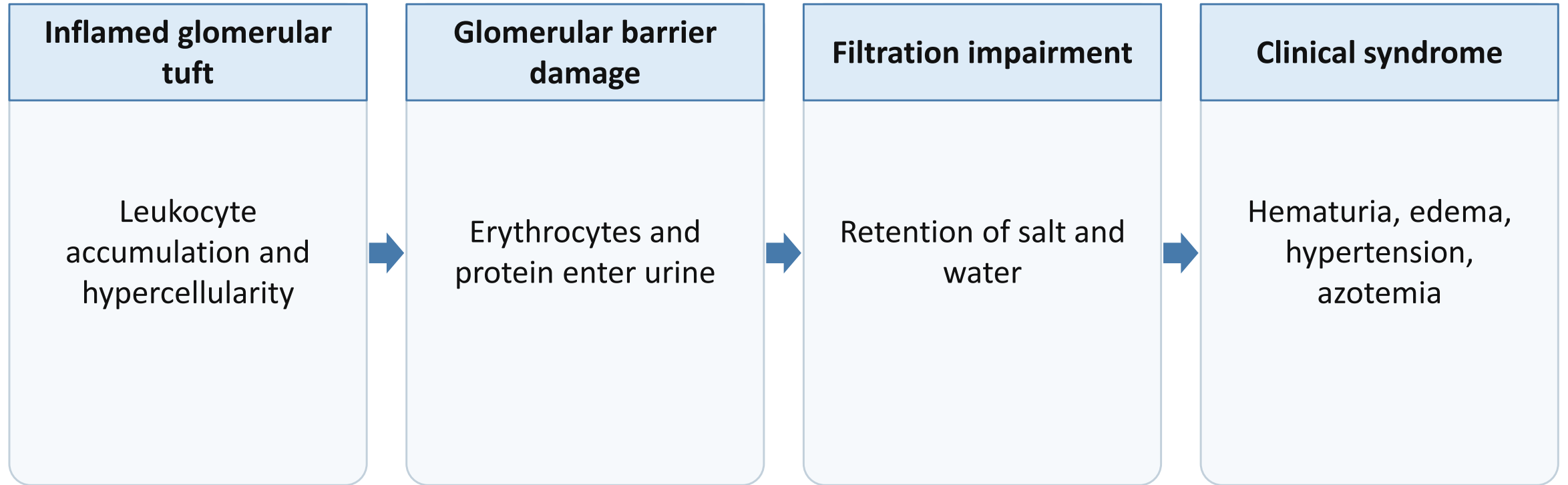
Immune-complex GN

- Granular staining corresponds to immune deposits
- Postinfectious GN is an example

Anti-GBM nephritis

- Linear staining follows binding along GBM
- Different immune mechanism and disease context

Why immune nephritis produces nephritic syndrome



Evidence should triangulate immune pathogenesis

- Clinical timing and preceding streptococcal infection support the context.
- Complement consumption can be reflected in reduced serum C3.
- Granular glomerular deposits argue for immune-complex injury.
- Morphology and microbiologic evidence must be reconciled before attributing causality.

Antibody cross-reactivity is not immune-complex nephritis

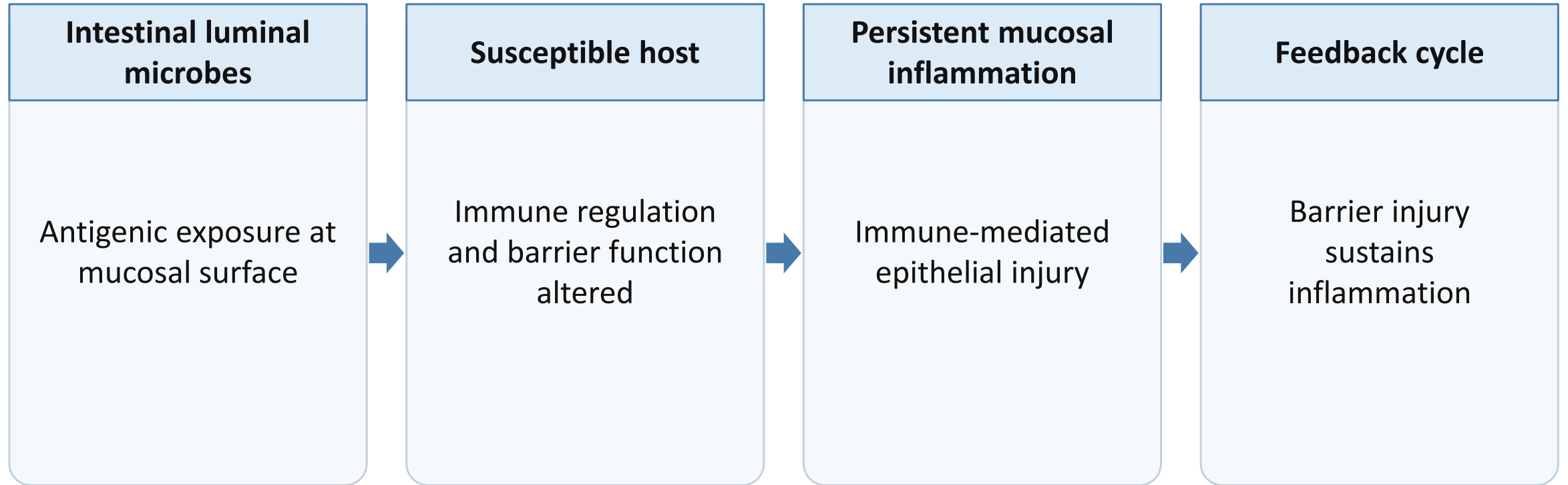
Rheumatic fever

- Molecular mimicry redirects response at cardiac antigens
- Antibody binding and T cells cause cardiac inflammation

Poststreptococcal GN

- Microbial antigen and antibody form complexes
- Glomerular deposition activates complement and leukocytes

Inflammatory bowel disease: Disturbed host–microbe dialogue



IBD is not simply infection by one organism

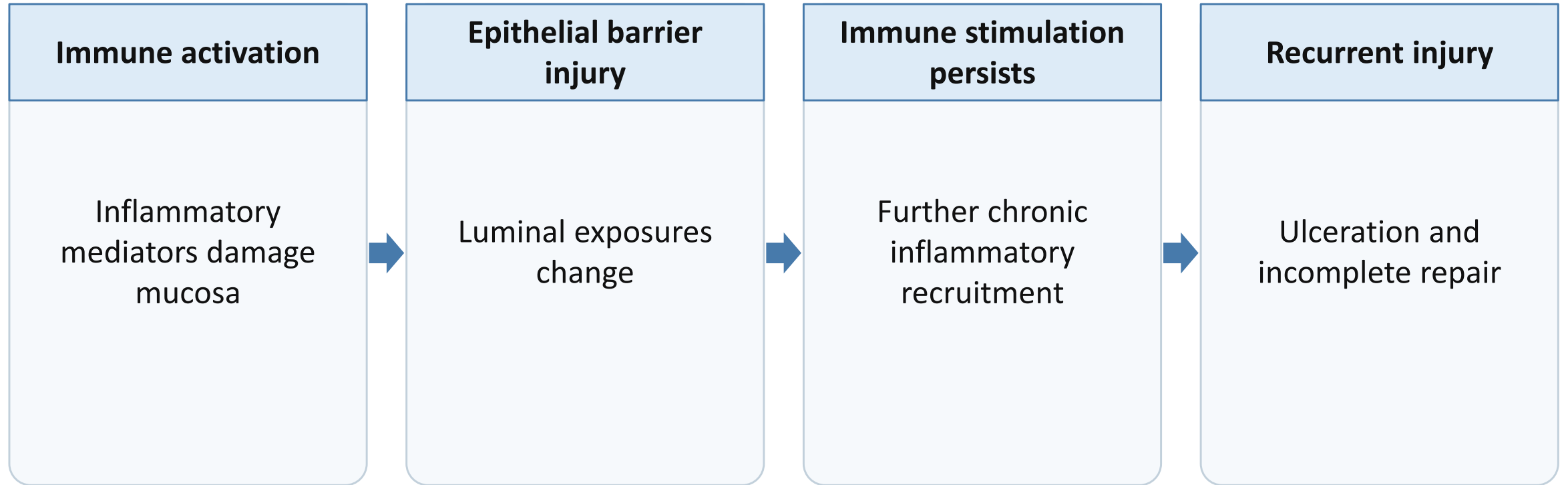
Conventional infection

- A defined invasive or toxin-producing pathogen
- Direct microbial cause may be demonstrated

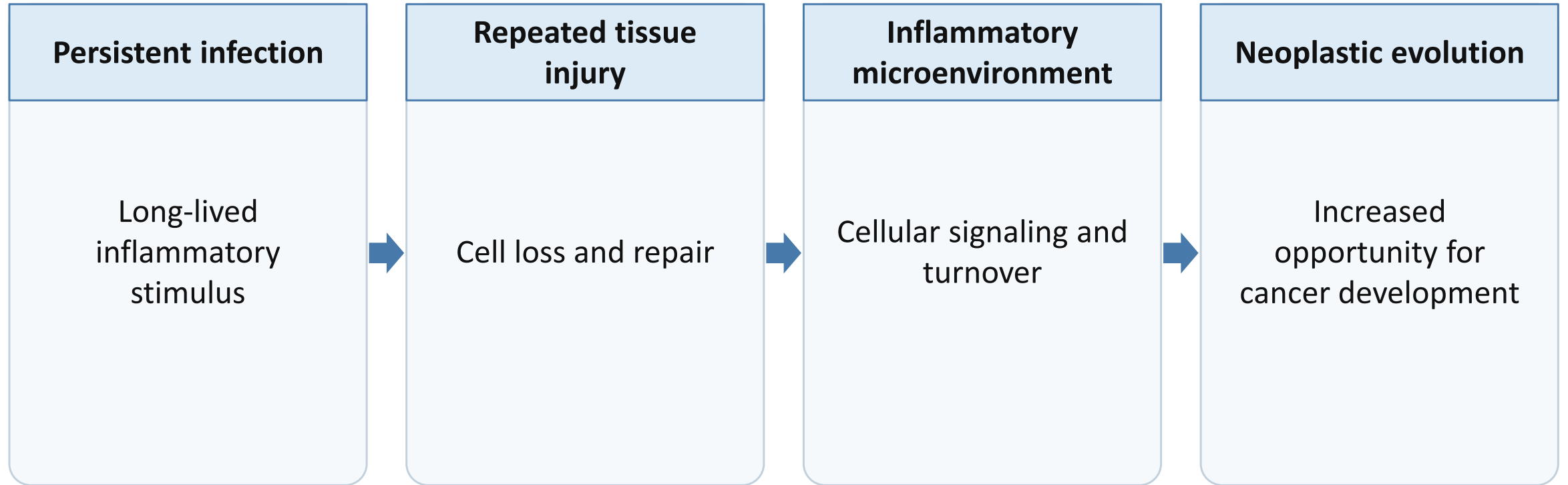
IBD host–microbe dysregulation

- Microbiota contribute within a susceptible host
- Immune regulation and epithelium are also implicated
- Avoid claiming a single causative infectious agent

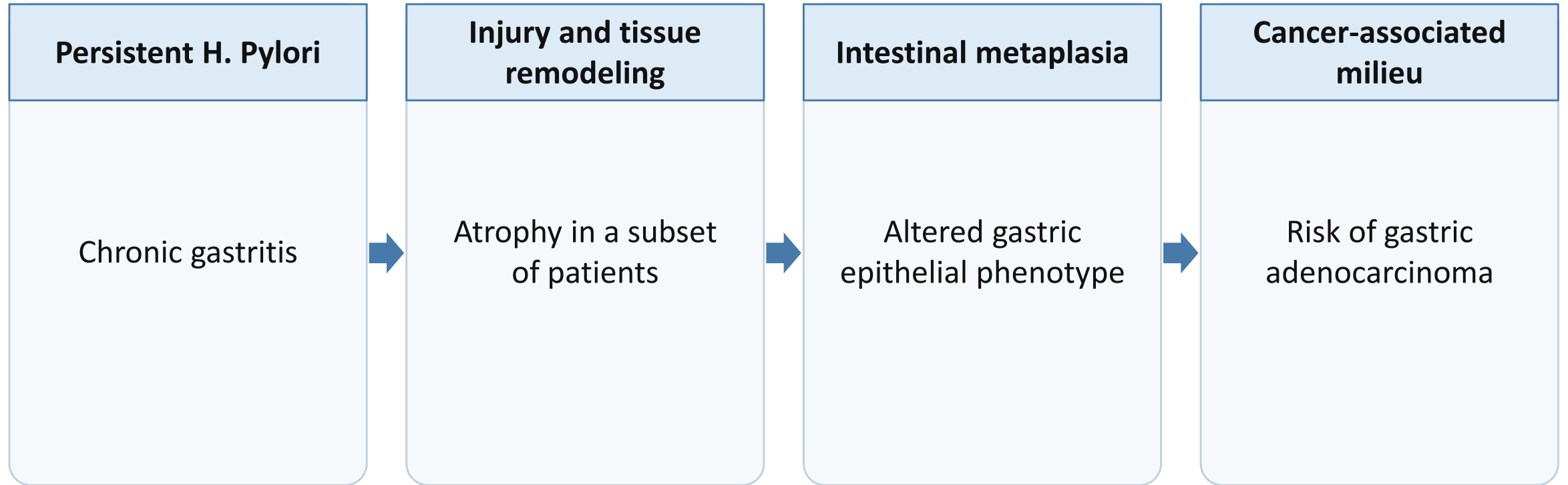
Epithelial injury can amplify mucosal inflammation



Chronic inflammation provides a carcinogenic setting



H. Pylori: Inflammation modifies gastric cancer risk



Infection-related oncogenesis needs causal precision

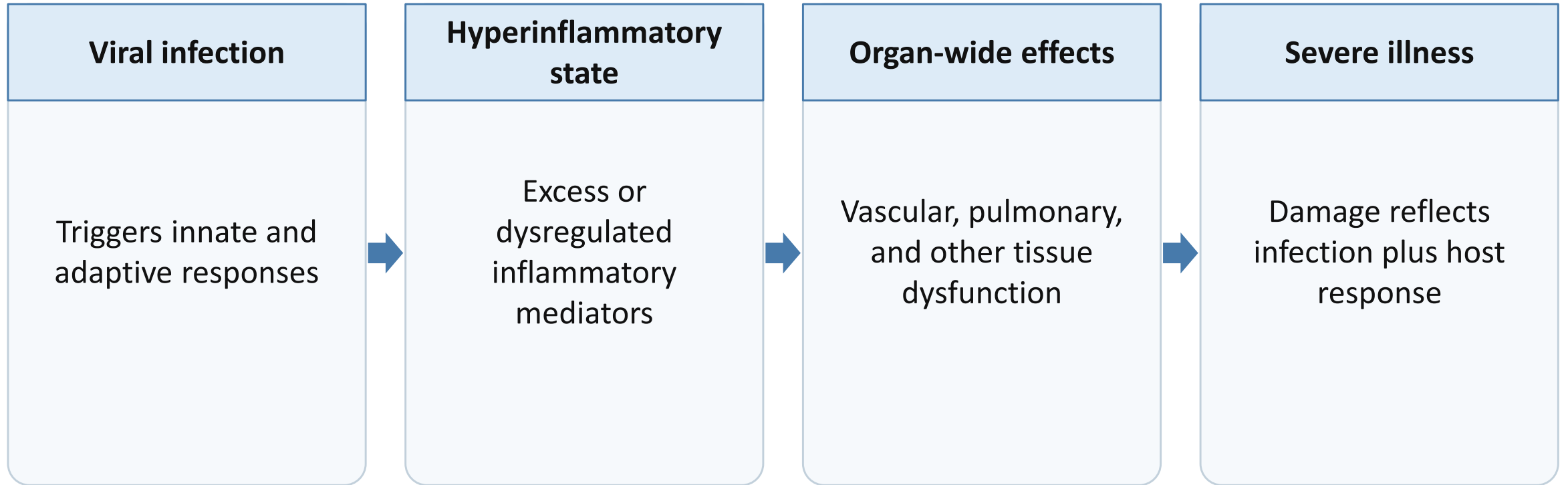
Cancer-promoting inflammatory environment

- H. Pylori gastritis and chronic viral hepatitis
- Long-term repair, cell turnover, and inflammation

Direct microbial oncogenic contribution

- Some viruses encode transforming or regulatory proteins
- HBV-associated cancer may involve HBx
- Do not assert all infection-associated cancers share one mechanism

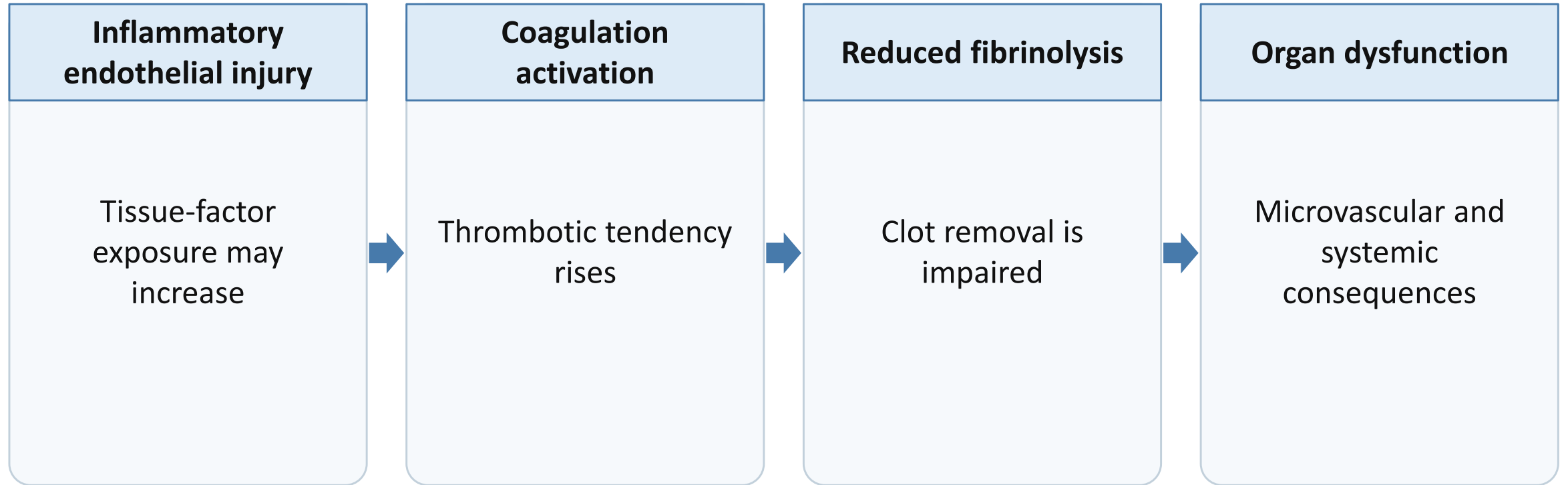
Severe viral illness can become systemic immunopathology



COVID-19 illustrates cytokine-associated injury

- Severe COVID-19 may involve a hyperinflammatory response.
- Increased cytokines, including TNF and IL-6.
- Abnormal myeloid-cell responses and lymphopenia accompany immune dysregulation.
- These observations support host-response injury but do not exclude direct viral effects.

Inflammation and coagulopathy can reinforce harm



Local inflammatory control versus systemic spillover

Locally focused response

- Antigen and effector cells concentrated in tissue
- Potential containment of microbes
- Risk of focal necrosis and fibrosis

Systemic dysregulation

- Cytokines and vascular effects extend beyond the focus
- Multiorgan dysfunction and coagulopathy possible
- Requires clinicopathologic attribution

Match tissue target to immune mechanism

Liver

Infected hepatocyte killed
by antiviral T cells

Heart

Cross-reactive immune
response after streptococci

Kidney

Glomerular immune
complexes activate
inflammation

Tissue timing is diagnostic information

During persistent infection

- Tuberculous granulomas
- Chronic viral hepatitis
- H. Pylori–related inflammation

Following microbial exposure

- Acute rheumatic fever after streptococci
- Poststreptococcal immune-complex nephritis
- Immune damage may persist after organism clearance

Do not infer the infectious agent from pattern alone

- A granuloma identifies an inflammatory pattern—not uniquely tuberculosis.
- Granular immunofluorescence indicates immune deposits—not uniquely streptococci.
- Lymphocyte-rich hepatitis establishes a reaction pattern—not viral type.
- Etiologic attribution requires appropriate organism-specific testing and context.

Case: Necrotizing granulomatous lung lesion

Clinical reasoning exercise

- A lung biopsy shows a macrophage-rich granuloma with central necrosis.
- Which host effector is most closely related to its architecture?
- Why is the lesion both protective and destructive?
- What test category is needed before assigning tuberculosis?

Case analysis: Cell-mediated containment

Mechanistic answer

- Th1-derived IFN- γ activates macrophages
- Organized reaction can contain resistant bacilli

Interpretive caution

- Granulomatous inflammation itself damages parenchyma
- Seek acid-fast stain, microbiologic culture, or molecular identification

Case: Nephritis after sore throat

Clinical reasoning exercise

- A child develops hematuria and edema after a recent sore throat.
- Glomerular findings include hypercellularity and granular immune staining.
- Identify the principal immune mechanism.
- Predict the role of complement in producing the lesion.

Case analysis: Immune complexes in glomeruli

Mechanistic answer

- Streptococcal antigen and antibody associate
- Immune deposits recruit complement and leukocytes

Expected corroboration

- A preceding infection with an appropriate interval
- Possible serum C3 consumption
- Granular deposits and subepithelial humps

Case: Mitral disease after streptococci

Clinical reasoning exercise

- A patient develops inflammatory carditis weeks after group A streptococcal illness.
- No organisms are found in the characteristic cardiac lesion.
- What explains the tissue specificity?
- How can the disease later produce fixed mitral stenosis?

Case analysis: Mimicry followed by scar

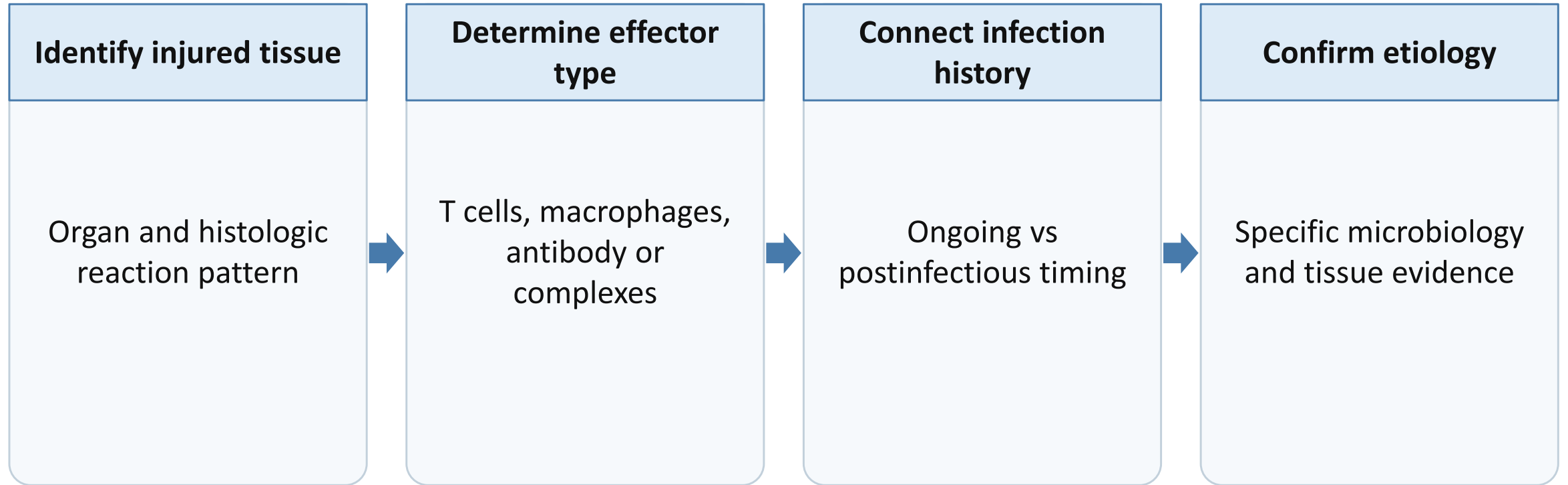
Acute mechanism

- Cross-reactive antibodies and CD4+ T cells
- Inflammation and macrophage activation in heart

Chronic consequence

- Repair replaces inflamed valvular tissue with fibrosis
- Leaflet thickening and commissural fusion
- Persistent dysfunction without active organisms

Mechanism-based diagnosis: A compact decision path



Comparative synthesis: Five injury pathways

Containment injury

TB: Granuloma → necrosis
/ fibrosis

Specific cell killing

HBV/HCV: Antiviral T cells
→ hepatitis

Misidentification

Rheumatic fever:
Molecular mimicry →
carditis

Five statements to retain

- Defense may contain microbes yet injure the tissue containing them.
- CD8+ cytotoxicity is central to much viral hepatitis-related hepatocyte loss.
- Rheumatic carditis and poststreptococcal GN are immunologically different.
- Persistent inflammation can cause scarring and favor cancer development.
- Clinical interpretation must integrate morphologic pattern and pathogen evidence.

References and source boundaries

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. Ch. 8, p. 308 (primary assigned passage).
- Mechanistic context: Ch. 3 (inflammation); Ch. 6 (hypersensitivity).
- Organ-specific context: Ch. 12 (rheumatic heart disease); Ch. 18 (hepatitis); Ch. 20 (glomerulonephritis).
- Additional context: Ch. 17 (IBD and H. pylori); Ch. 7 (cancer); Ch. 8 (COVID-19).
- All mechanism and morphology graphics are editable, original PowerPoint schematics; no textbook figure is reproduced.