
Increased Vascular Permeability

(Vascular Leakage)

Acute inflammation · mechanism and clinicopathologic interpretation

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

Distinguish exudation, exudate, transudate and edema

Explain mediator-induced endothelial contraction

Contrast immediate, delayed and sustained leakage

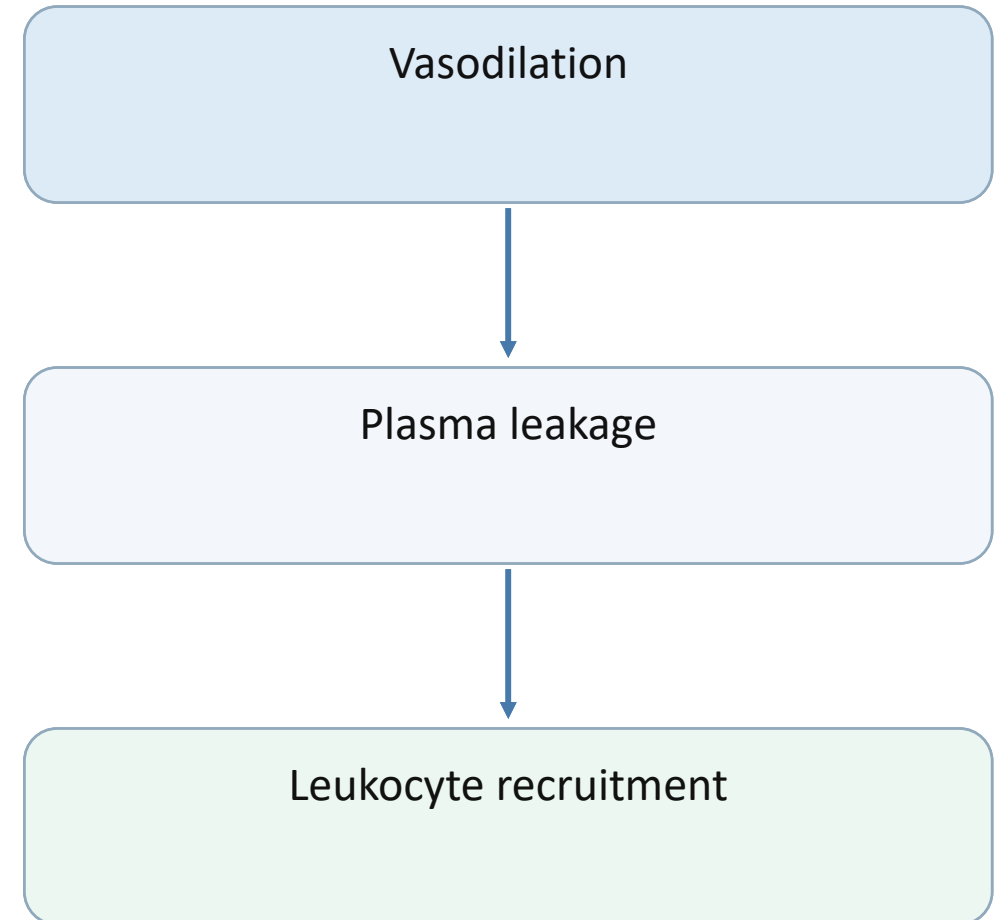
Interpret edema patterns using the vascular mechanism

Three linked components of acute inflammation

Dilation of small vessels increases local blood flow

Increased microvascular permeability permits plasma constituents to escape

Leukocytes leave the circulation and act at the injury site

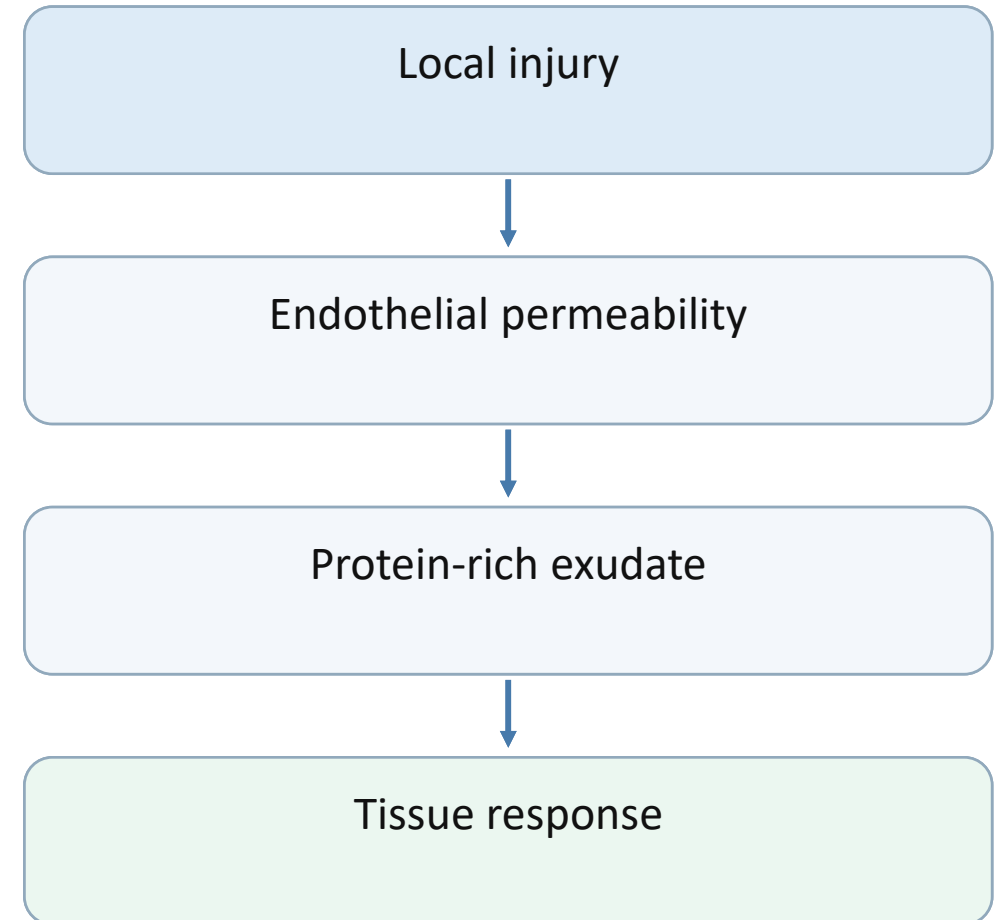


The purpose of vascular leakage

Soluble plasma components reach infected or damaged tissue

Intravascular fluid enters the extravascular compartment

Excess leakage may become harmful despite its defensive role



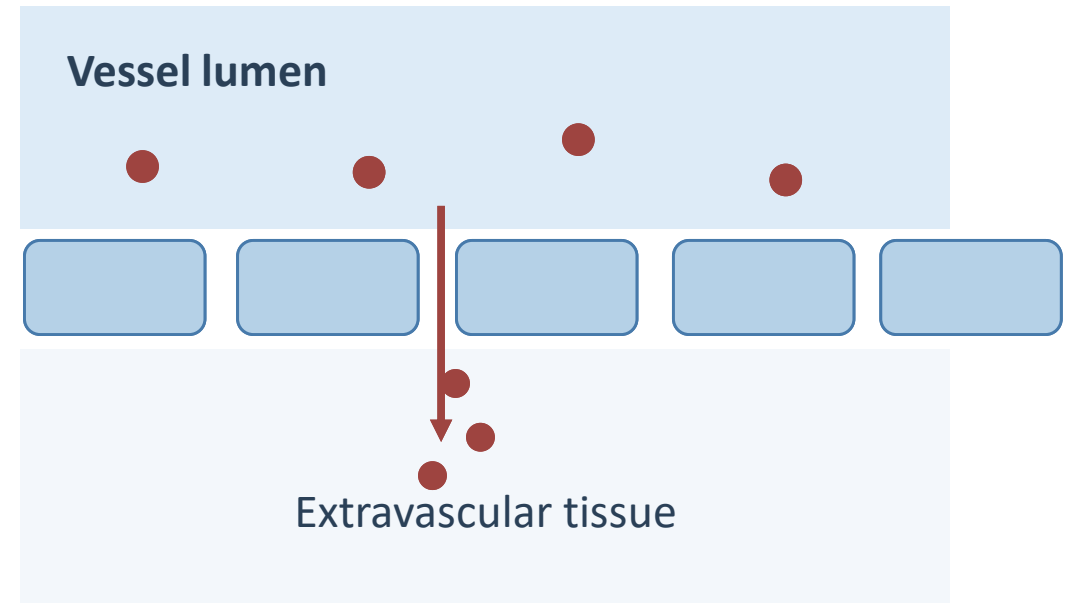
Postcapillary venules: The principal site

The main permeability change occurs in postcapillary venules

Mediator-driven gaps form between neighboring endothelial cells

Leukocyte contact can additionally damage the venular lining

Original schematic · postcapillary venule



Intercellular gap

Red dots = plasma proteins (schematic)

Vascular reactions have two dimensions

Vasodilation alters vessel caliber and blood flow

Permeability changes alter the movement of fluid and proteins

The two reactions occur together but are not synonymous

**Caliber /
flow**

Vasodilation → hyperemia

**Barrier /
permeability**

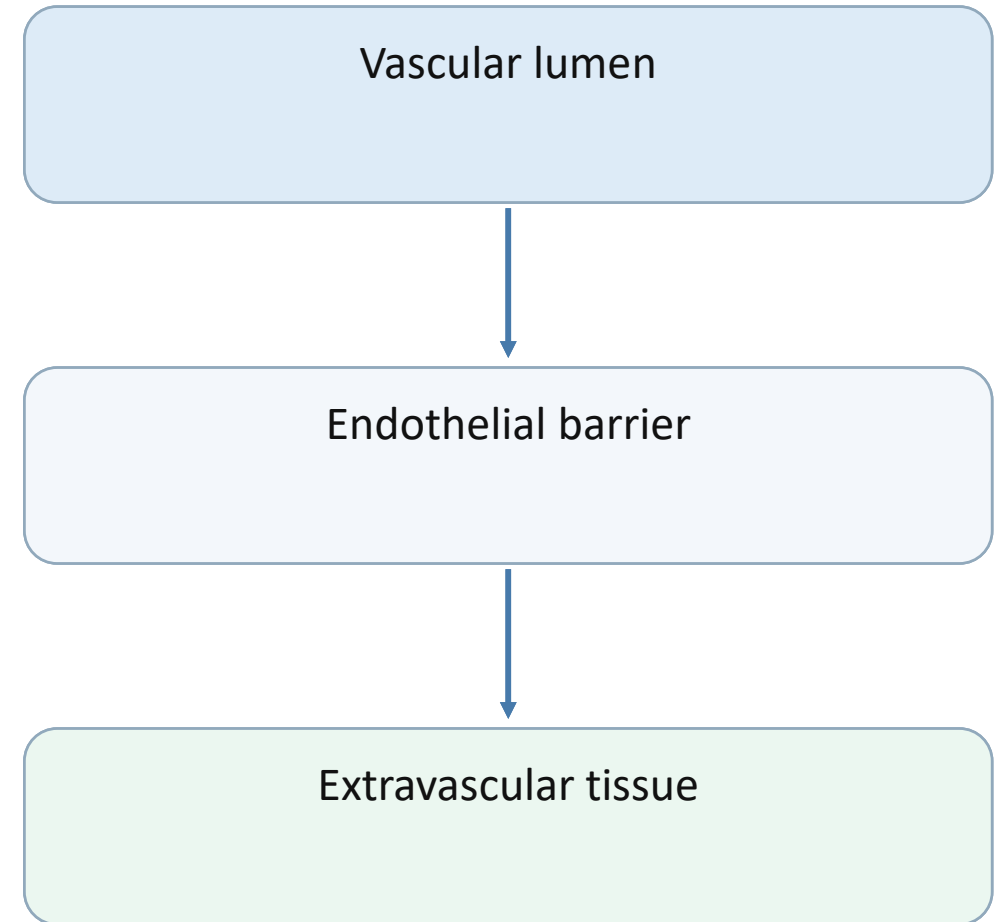
Gap formation or cell damage →
exudation

Exudation is movement out of the vascular system

Fluid, plasma proteins and sometimes cells escape from small vessels

The destination is interstitial tissue or a body cavity

Protein-rich escape is characteristic of inflammatory exudation



Edema describes location and amount of fluid

Edema is excess fluid in interstitial tissue or serous cavities

The definition alone does not specify inflammatory causation

Both exudates and transudates can contribute to edema

Edema

Excess extravascular fluid

Exudate

Inflammatory, protein rich

Transudate

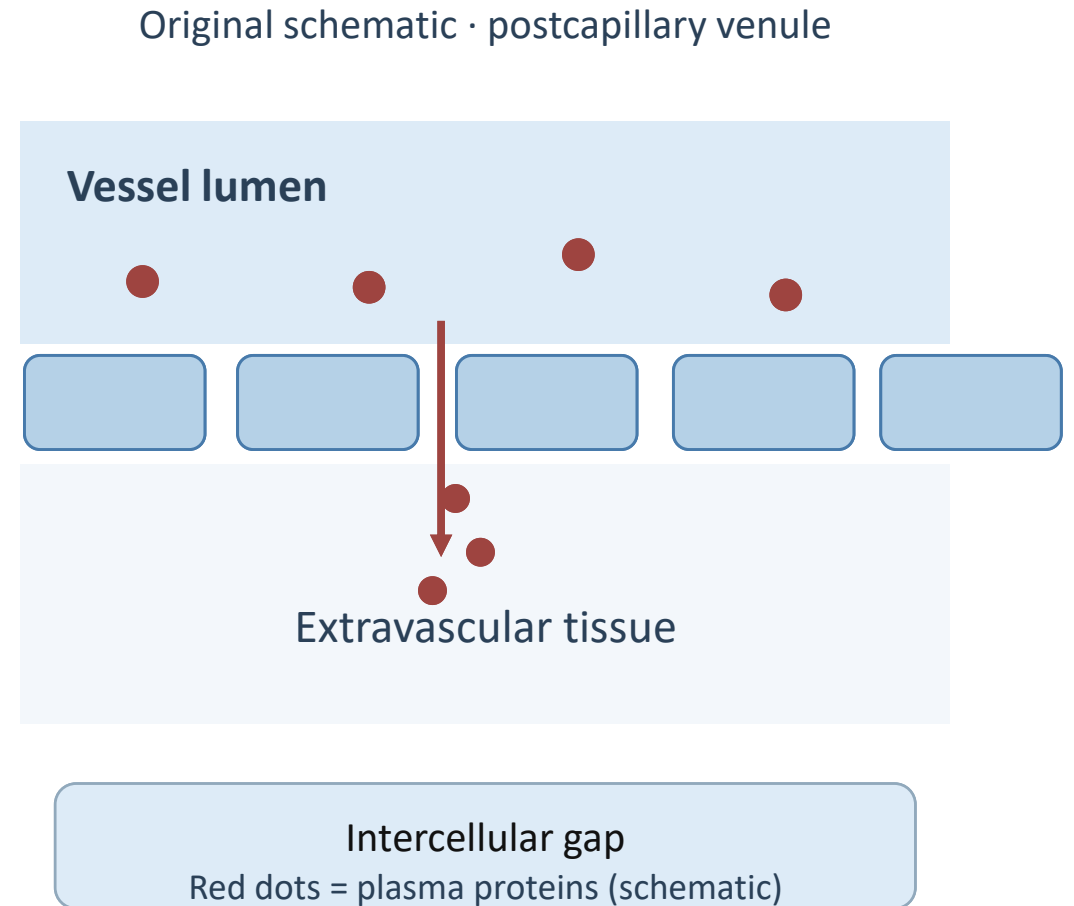
Hemodynamic, relatively protein poor

An exudate indicates altered permeability

Inflammatory exudates contain relatively high concentrations of protein

Cell debris, leukocytes or some red cells may also be present

The underlying lesion is increased permeability of small vessels



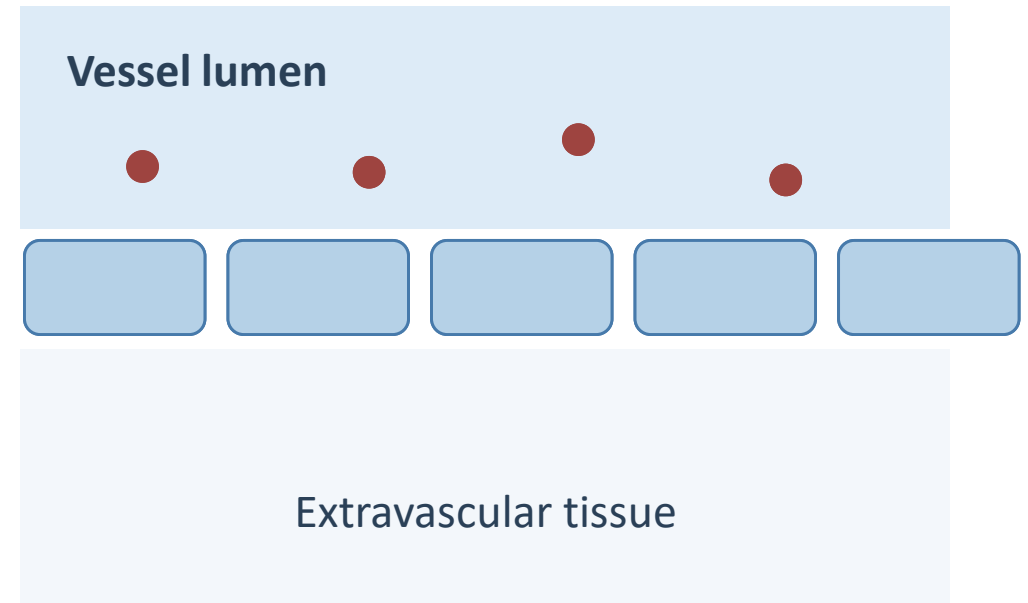
A transudate reflects a pressure imbalance

Transudates have low protein content and few or no cells

They form without a primary increase in endothelial permeability

Raised hydrostatic or reduced colloid osmotic pressure favors fluid escape

Original schematic · postcapillary venule



Continuous endothelial lining
Red dots = plasma proteins (schematic)

Exudate versus transudate

Composition is more informative than fluid quantity alone

Assess the underlying vascular process rather than appearance alone

Inflammation and hemodynamic imbalance are different pathways to edema

Exudate

Barrier permeability increased;
Protein rich

Transudate

Pressure imbalance; Protein poor

Both

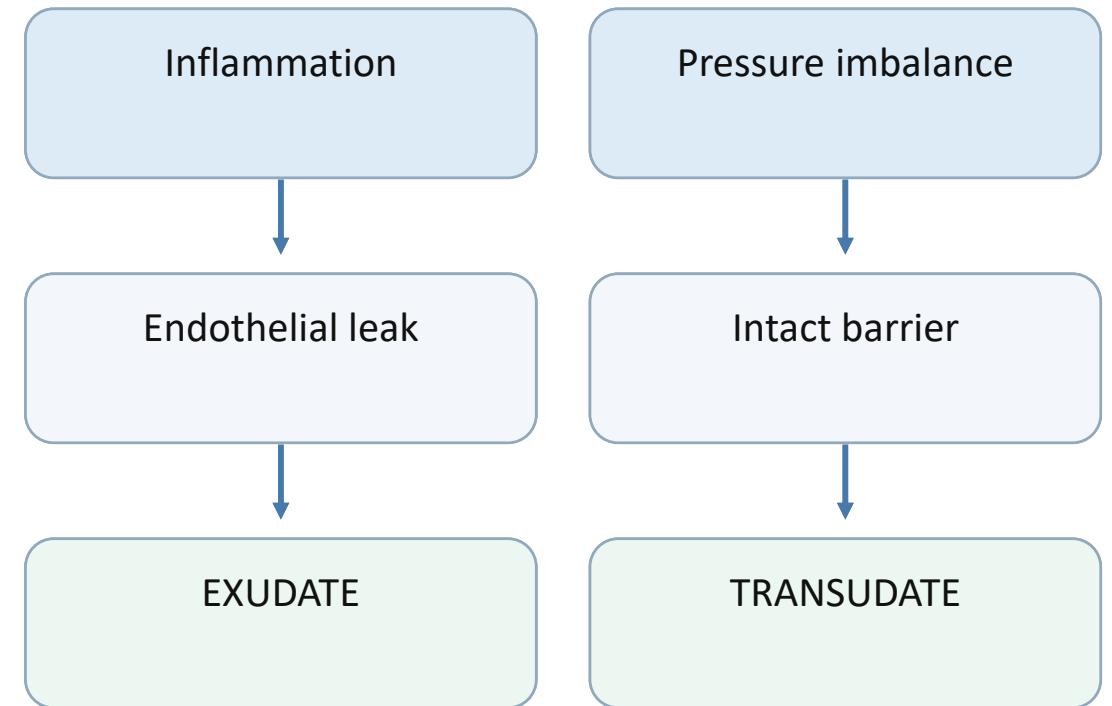
May accumulate as tissue or cavity fluid

Two pathways to extravascular fluid

Inflammation opens or damages the endothelial barrier

Hydrostatic / osmotic changes can move fluid across an intact barrier

Protein escape is the central mechanistic distinction

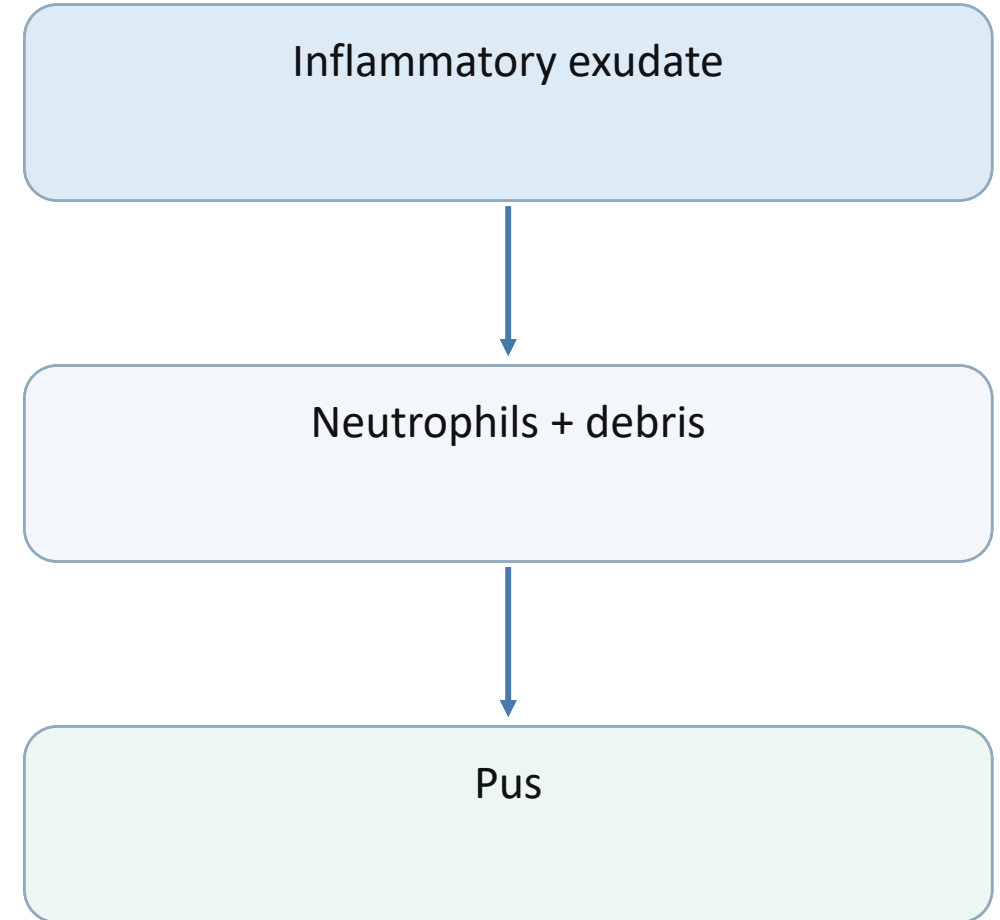


Purulent exudate: A specific inflammatory product

Pus is an inflammatory exudate rich in leukocytes

Neutrophils predominate among its cellular constituents

Dead-cell debris and, often, microbes accompany the fluid



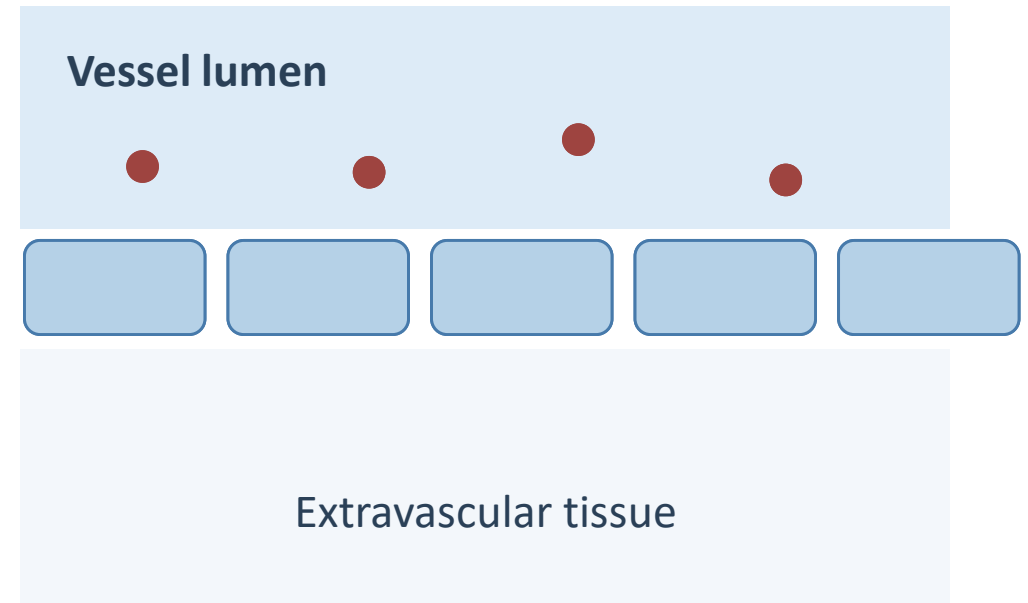
Normal endothelium restricts protein escape

Endothelial cells form a continuous interface with the blood

The normal vascular barrier limits movement of plasma proteins

The inflamed venule loses this barrier function locally

Original schematic · postcapillary venule



Continuous endothelial lining
Red dots = plasma proteins (schematic)

Permeability differs from fluid-driving pressure

Hydrostatic pressure favors fluid movement outward

Colloid osmotic pressure tends to retain fluid intravascularly

Increased permeability is a change in barrier properties, not merely pressure

**Driving
forces**

Hydrostatic and colloid osmotic pressures

**Barrier
behavior**

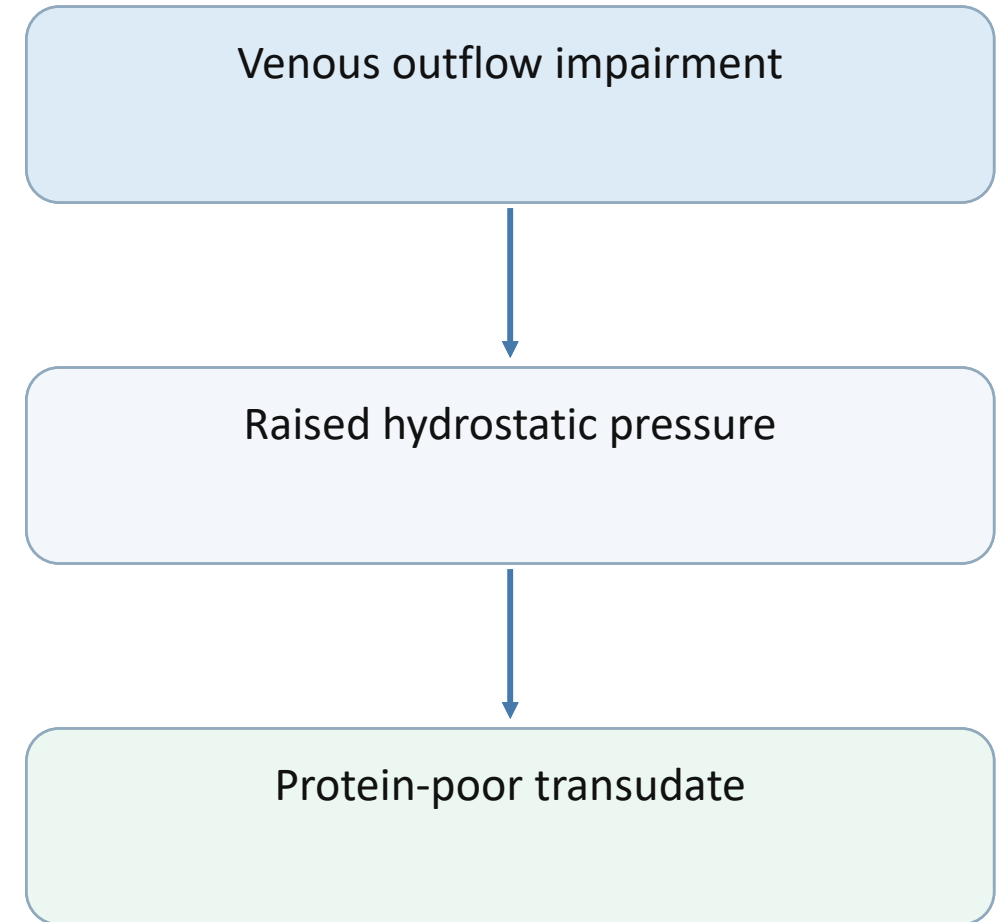
Endothelial junctions and cell integrity

Raised hydrostatic pressure creates transudate

Venous outflow obstruction can increase
vascular hydrostatic pressure

Congestive heart failure is an example given

The endothelial barrier need not be inflamed or
disrupted

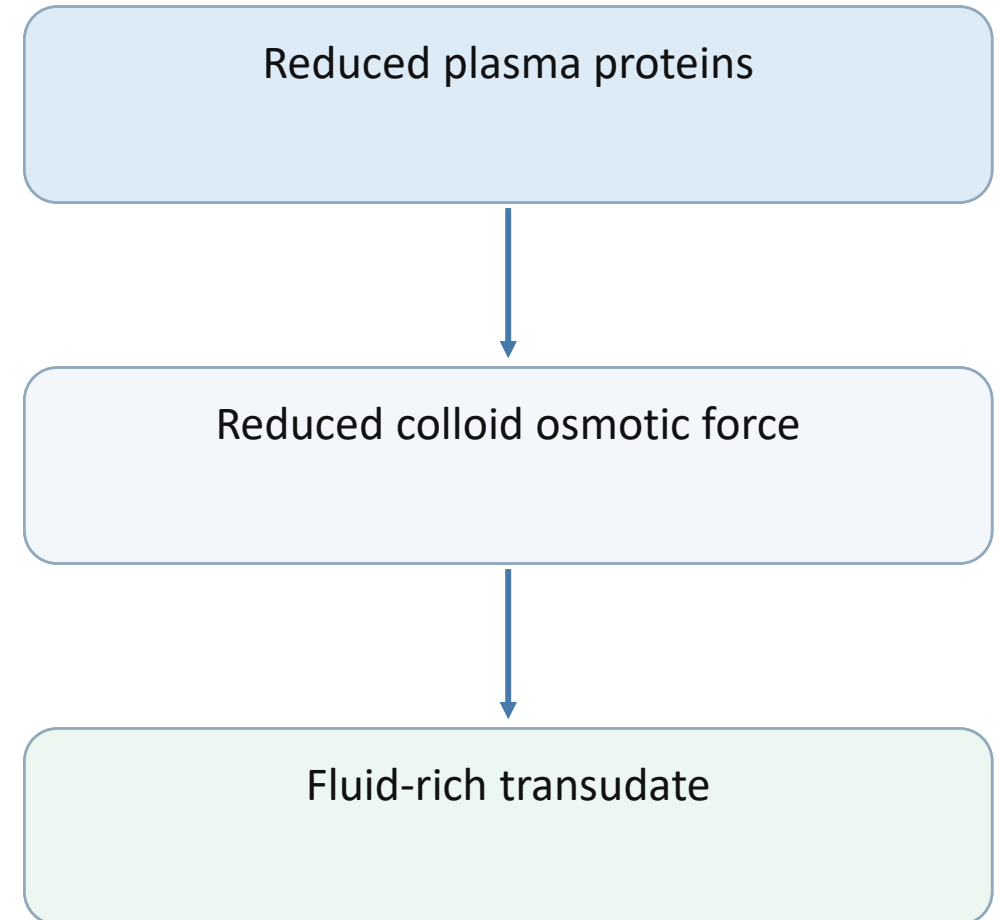


Reduced colloid osmotic pressure creates transudate

Lower plasma protein content weakens fluid-retaining forces

Liver disease may reduce protein synthesis

Renal protein loss or protein malnutrition can produce a similar imbalance

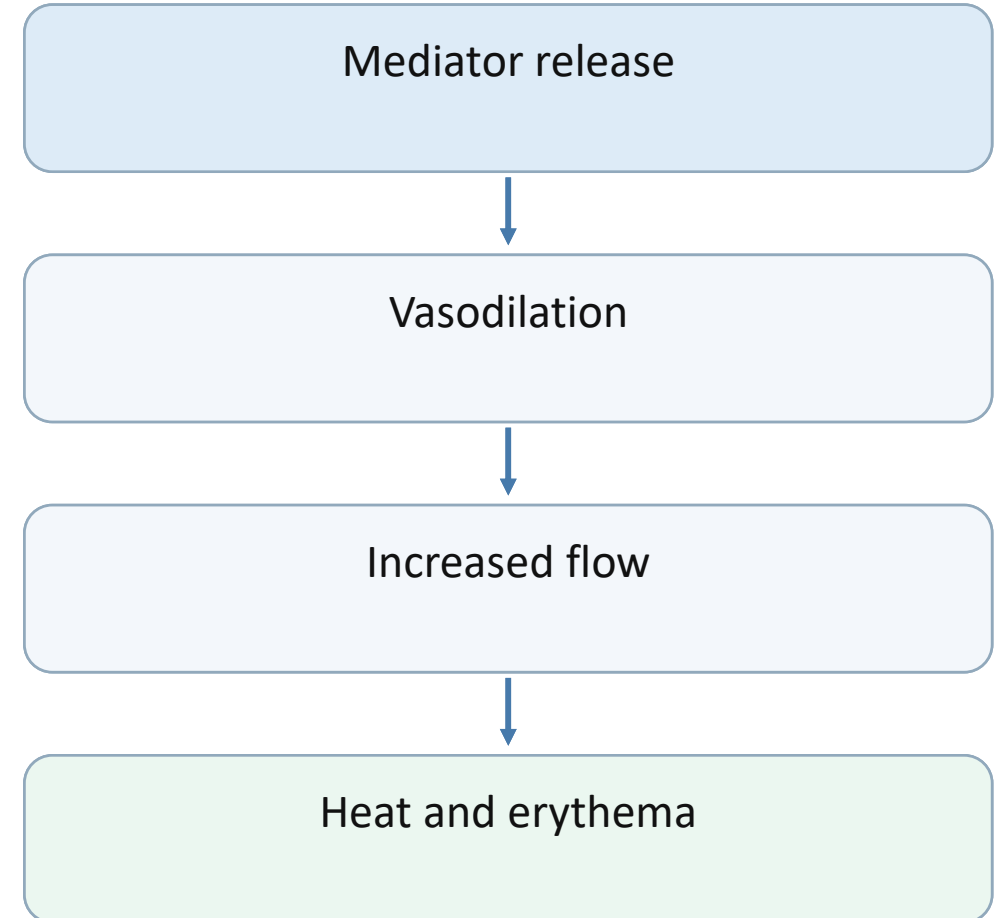


Vasodilation is an early vascular event

Histamine and other mediators relax vascular smooth muscle

Small-vessel dilation increases blood flow into the affected tissue

This process contributes to warmth and erythema



Hyperemia does not itself define exudation

Heat and redness result principally from increased local blood flow

Protein-rich escape requires a permeability change

Both processes frequently coexist in acute inflammation

Hyperemia

More blood flow → warmth / redness

Exudation

More protein/fluid escape → swelling

Leakage contributes to vascular stasis

Fluid leaves the intravascular compartment
through permeable venules

Blood becomes more concentrated as flow slows

Stasis follows fluid loss in dilated microvessels

Vasodilation + fluid loss



Hemoconcentration



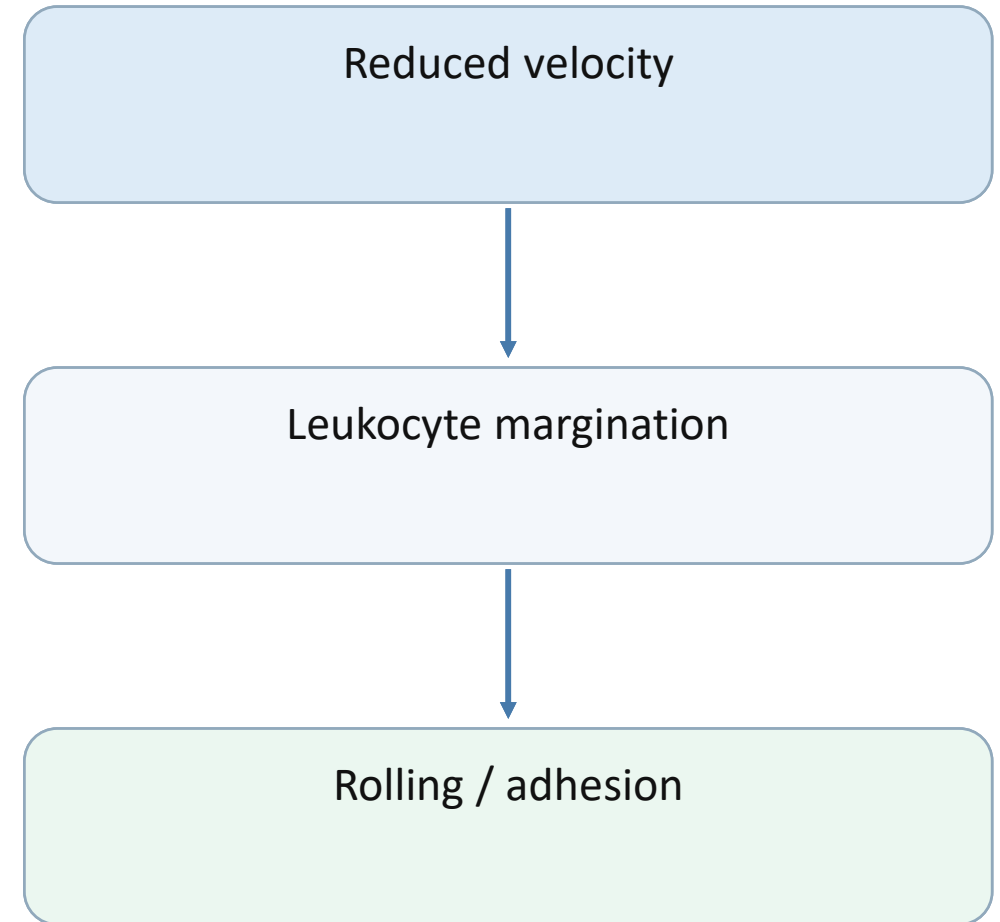
Stasis

Stasis favors leukocyte margination

Slow blood flow shifts leukocytes toward the endothelial surface

Neutrophils become positioned for rolling and adhesion

Vascular leakage therefore precedes important cellular events

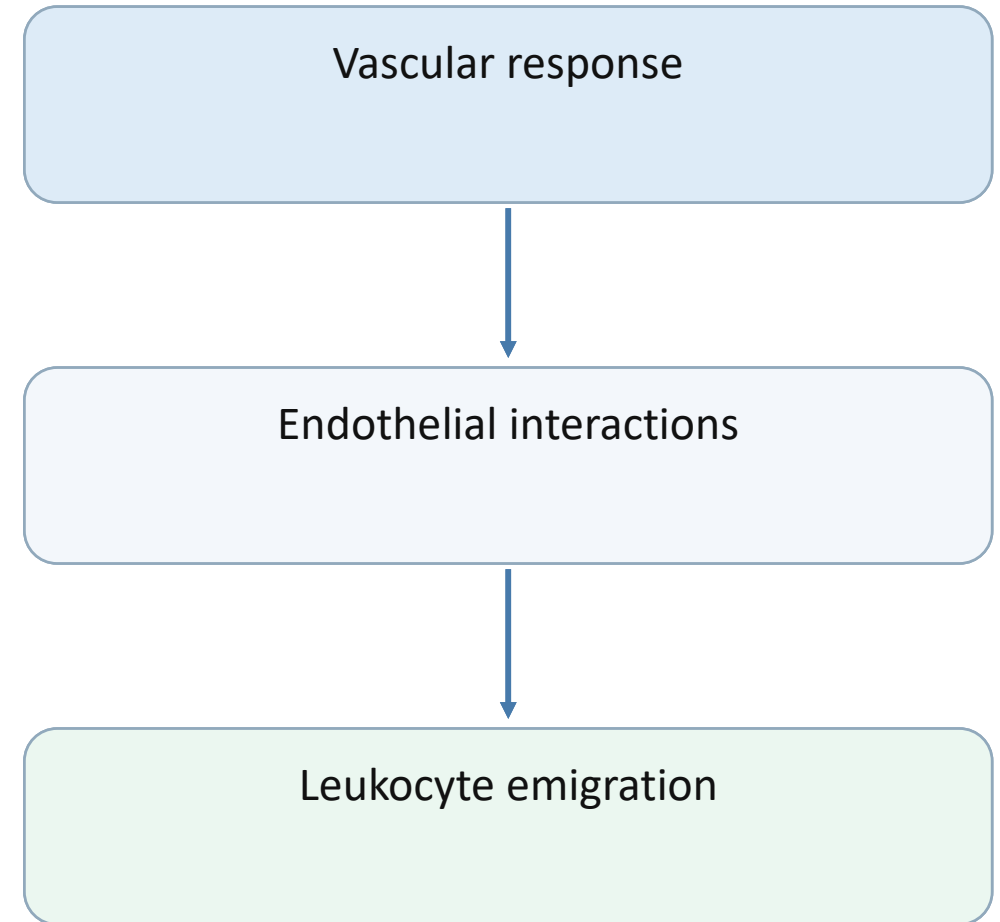


Vascular and cellular responses form a sequence

Microvascular changes deliver fluid and soluble proteins

Stasis and endothelial activation promote leukocyte adhesion

Leukocytes subsequently migrate into injured tissue

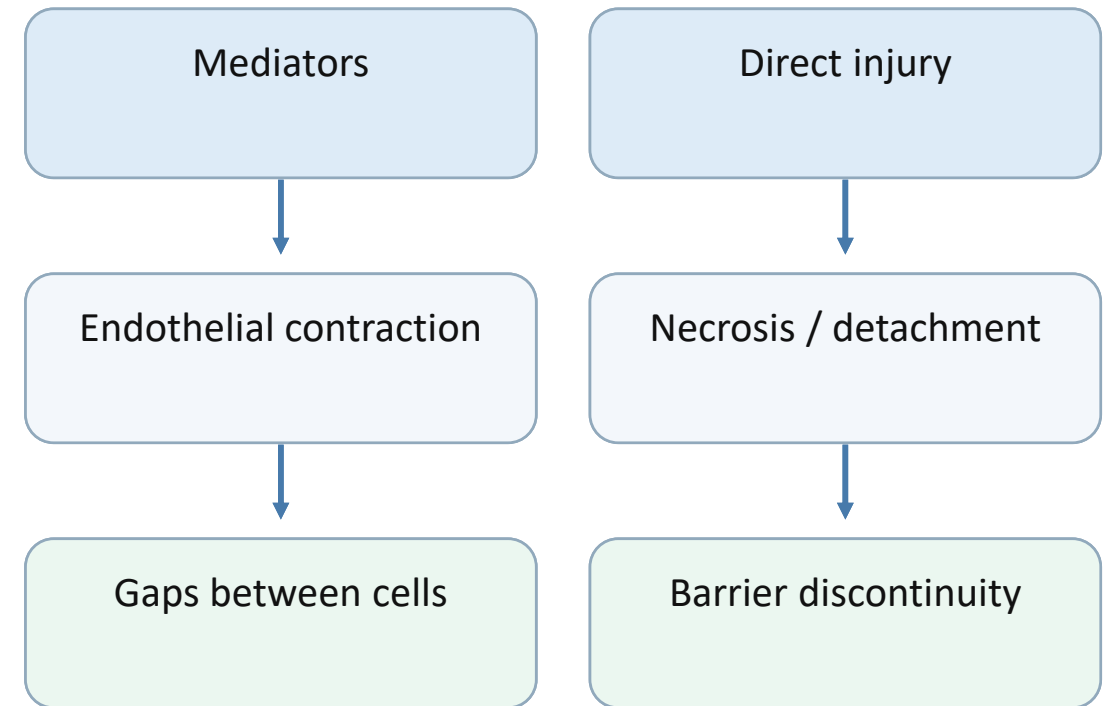


Two principal structural routes of leakage

Mediator-induced endothelial contraction
creates intercellular gaps

Direct injury causes endothelial necrosis and
detachment

The mechanisms often coexist rather than acting
in isolation



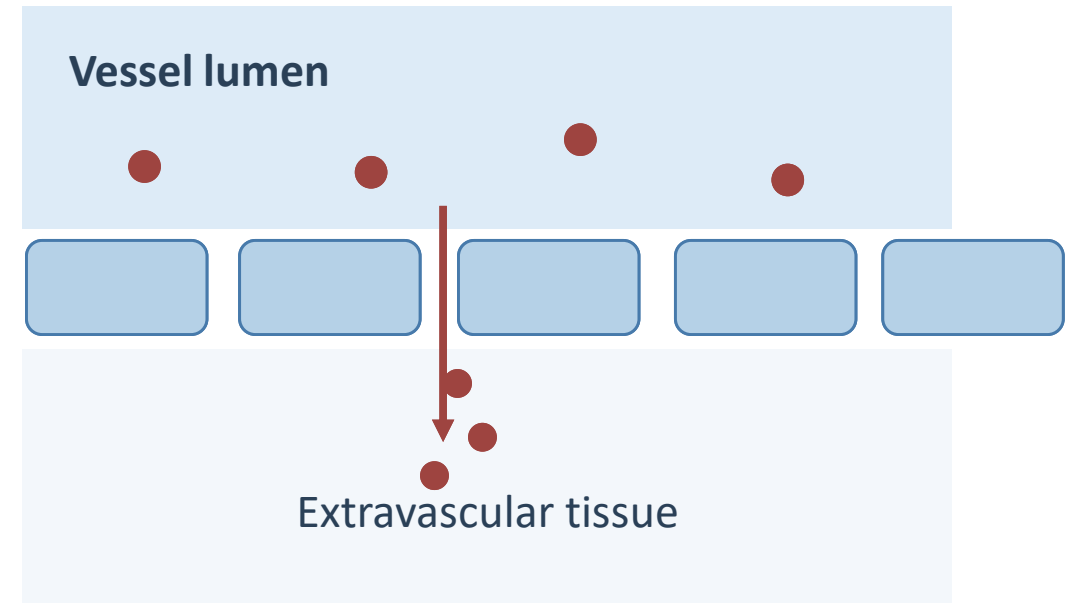
Endothelial contraction opens intercellular gaps

Neighboring endothelial cells retract from one another

The widened space permits plasma fluid and proteins to escape

This is the most common permeability mechanism in inflammation

Original schematic · postcapillary venule



Intercellular gap

Red dots = plasma proteins (schematic)

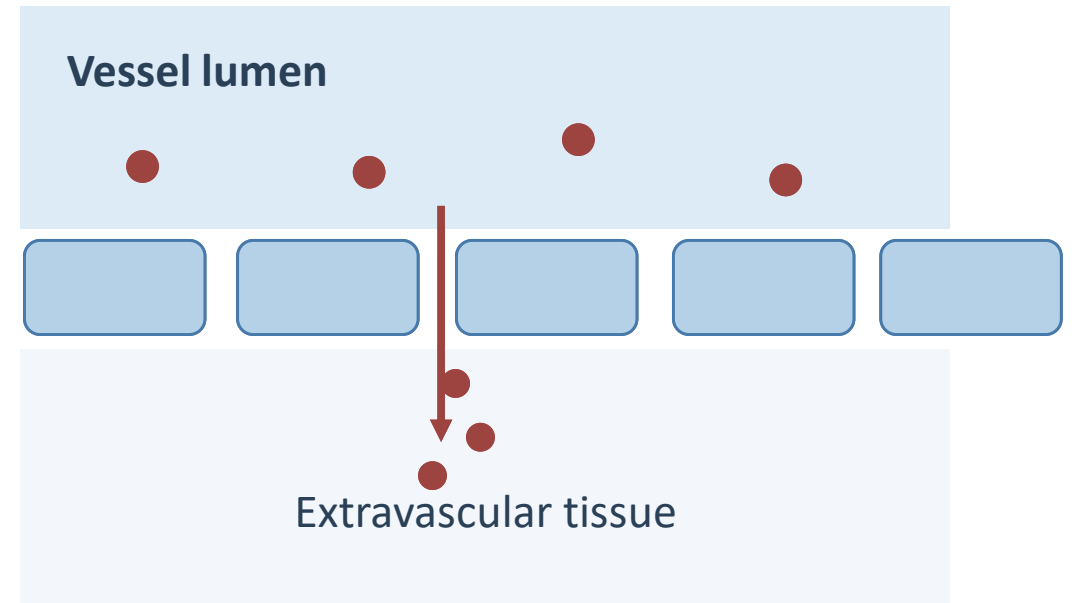
A permeability gap is not necessarily necrosis

Contracted endothelial cells can remain viable

Gaps reflect altered cell shape and junctional apposition

Do not equate every early exudate with endothelial destruction

Original schematic · postcapillary venule



Intercellular gap

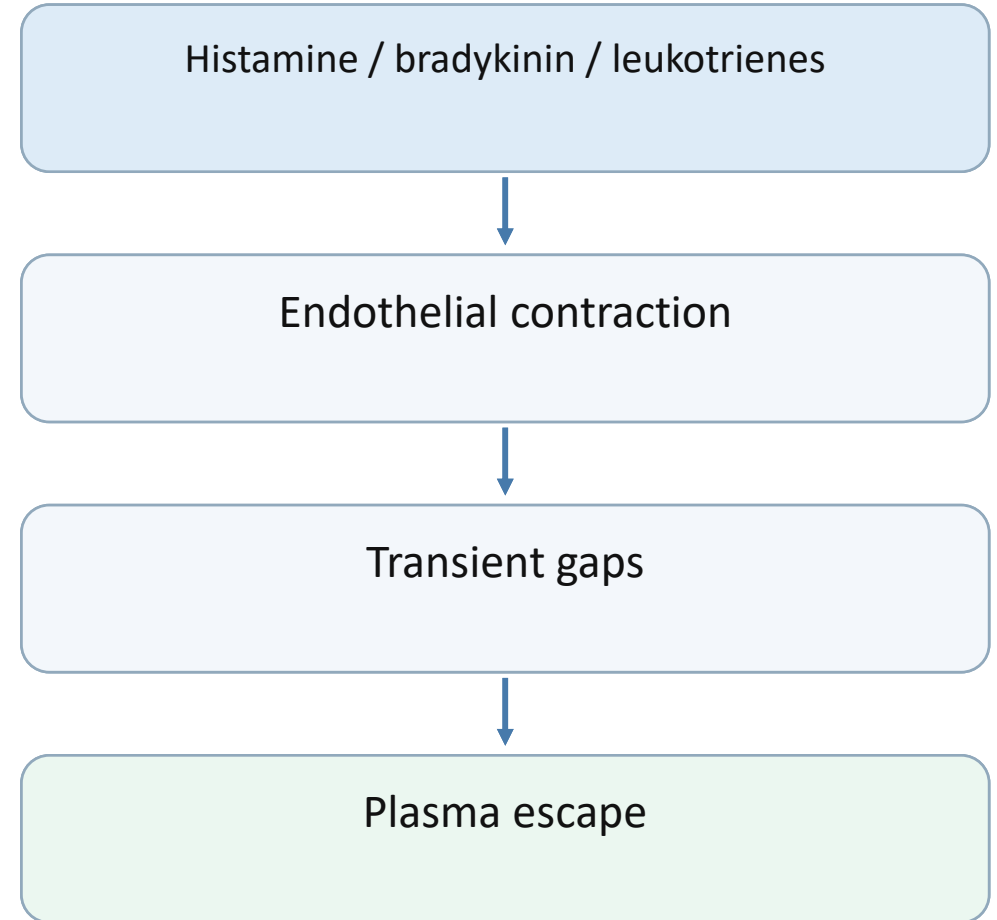
Red dots = plasma proteins (schematic)

Mediators trigger endothelial contraction

Histamine is a major immediate mediator

Bradykinin and leukotrienes are additional triggers

Their effects converge on opening endothelial gaps

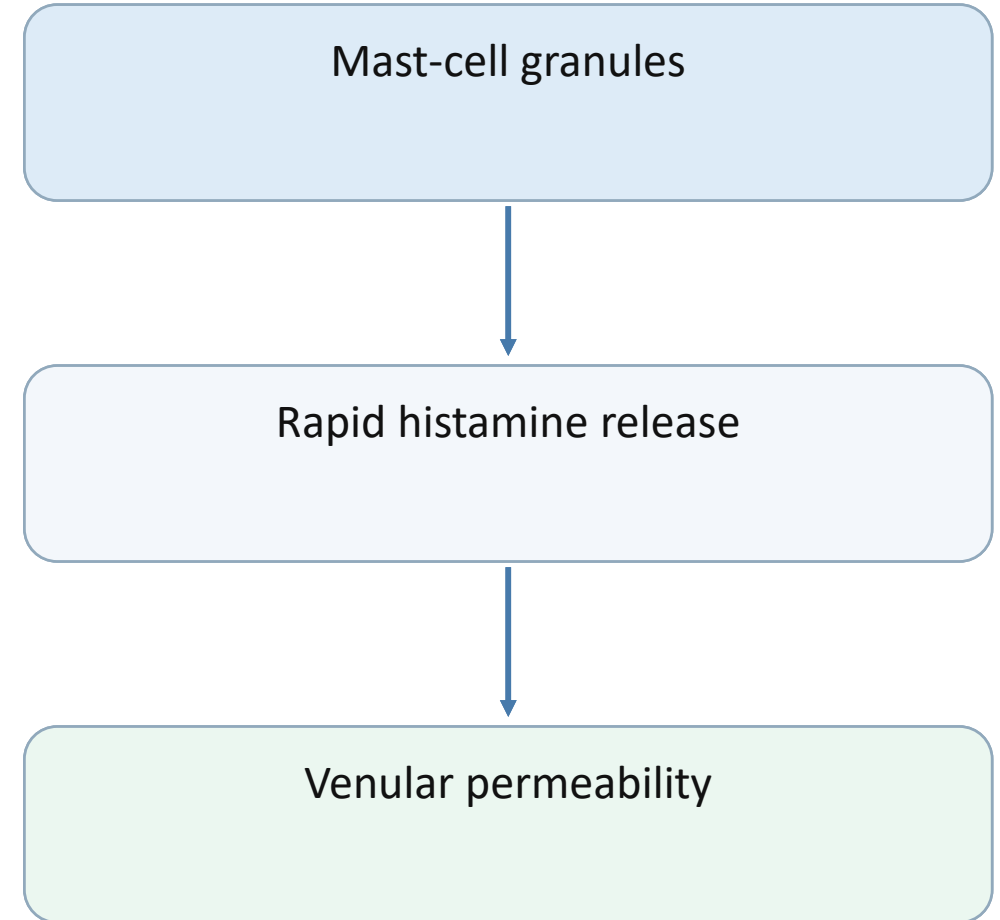


Histamine is a preformed vasoactive mediator

Mast cells near vessels are a major source

Basophils and platelets also contain histamine

Preformed stores permit a rapid response after stimulation

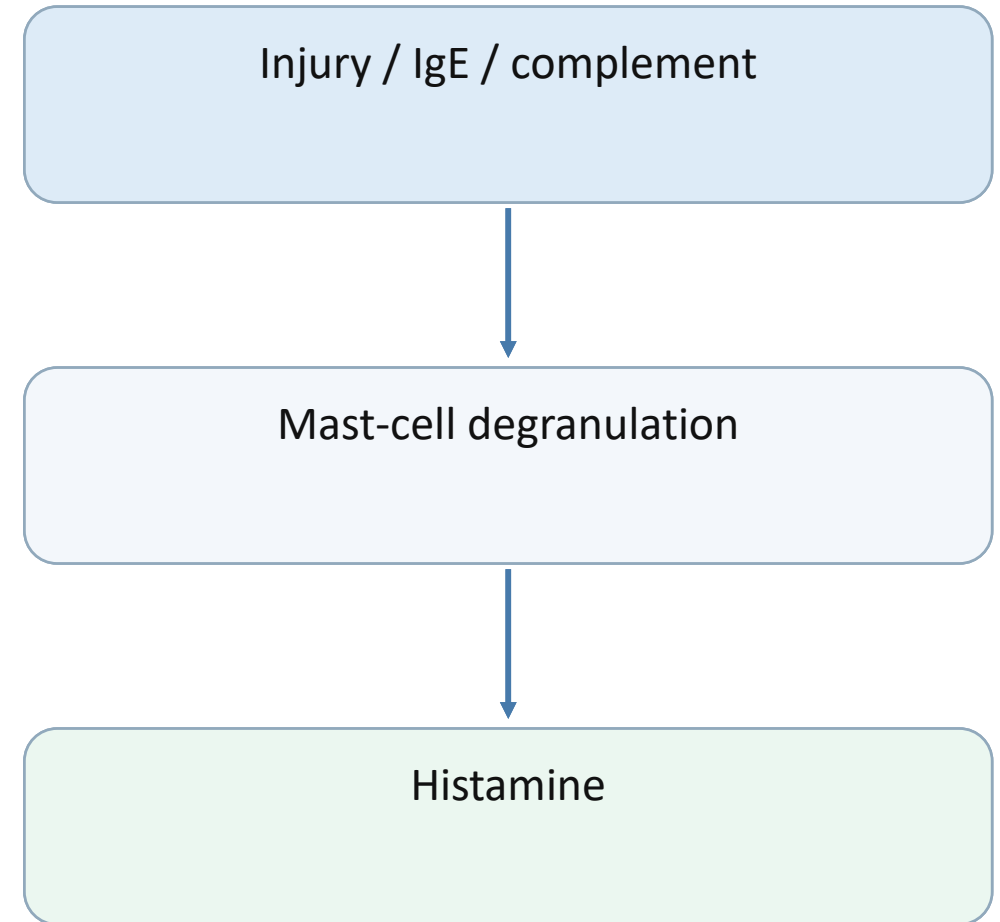


Mast-cell degranulation can be triggered rapidly

Physical injury and thermal stimuli may trigger mediator release

Antigen binding to mast-cell IgE supports immediate hypersensitivity

Complement fragments C3a and C5a can also promote degranulation

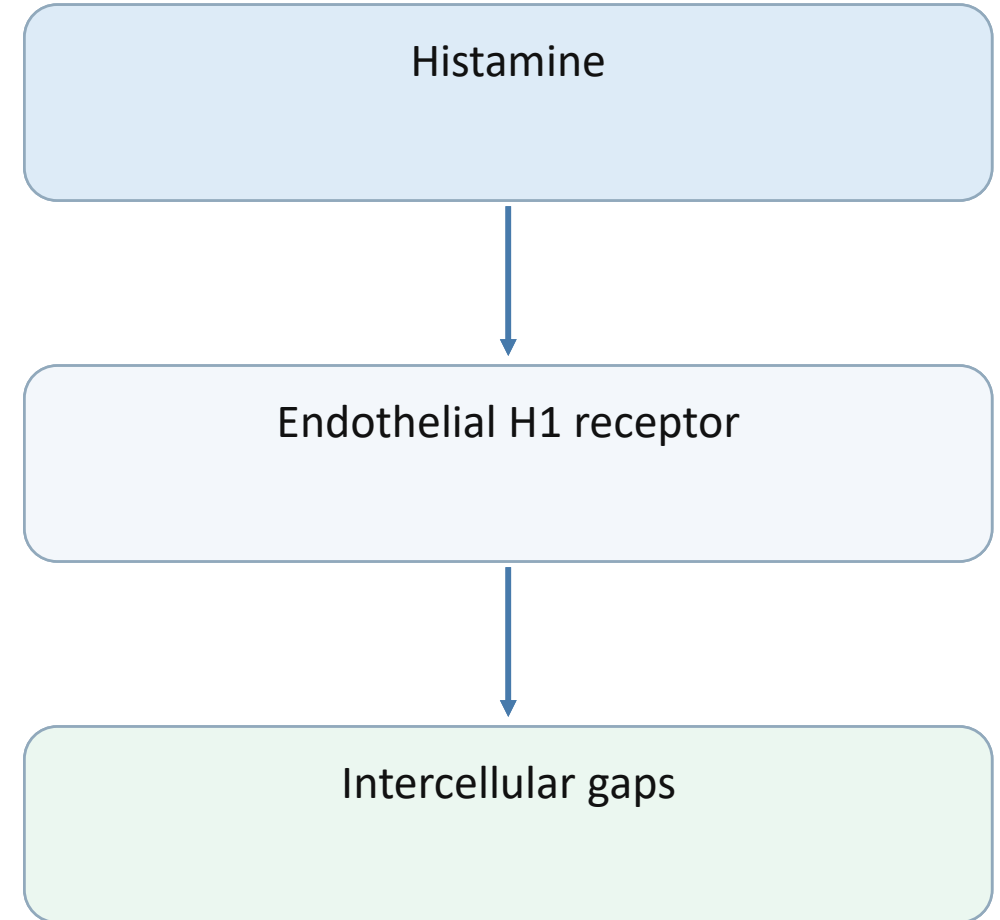


Histamine acts on microvascular endothelium

Histamine causes arteriolar dilation and venular permeability

Its vasoactive effect is mediated mainly through endothelial H1 receptors

The permeability response features gaps in postcapillary venules

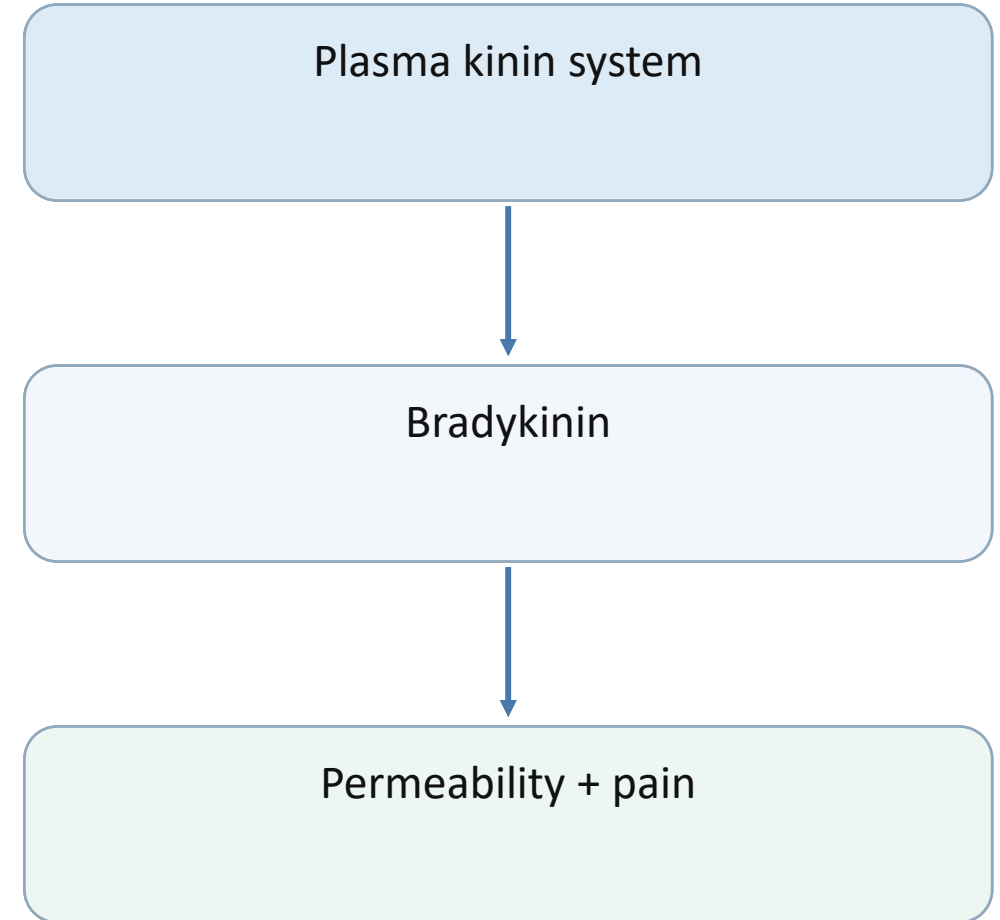


Bradykinin promotes inflammatory leakage

Bradykinin belongs to the plasma-derived kinin system

Kinins increase vascular permeability and also cause pain

They provide a non-histamine route to endothelial gap formation

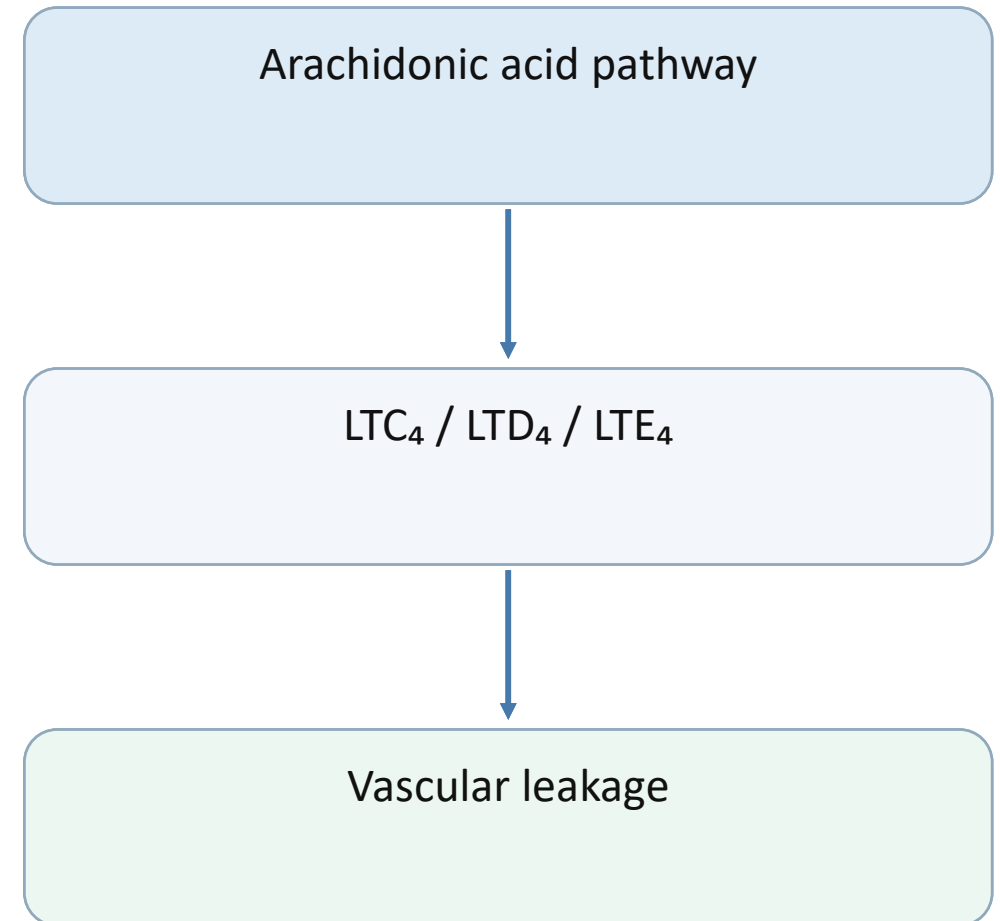


Cysteinyl leukotrienes increase permeability

Leukotrienes are lipid mediators derived from arachidonic acid

LTC₄, LTD₄ and LTE₄ are linked to vascular permeability

Their actions supplement histamine- and kinin-mediated responses



Inflammatory mediators have overlapping effects

Histamine: Vasodilation and rapid venular permeability

Kinins: Permeability, vasodilation and pain

Leukotrienes: Permeability plus other inflammatory effects

Histamine

Rapid venular gaps; Vasodilation

Kinins

Permeability; Pain

**LTC₄ / LTD₄ /
LTE₄**

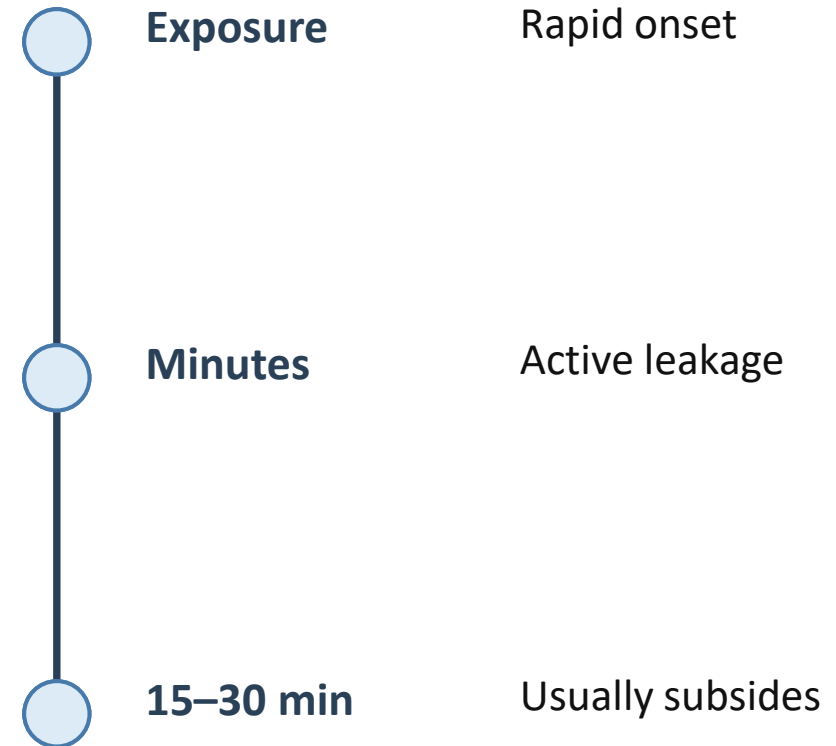
Increased permeability

The immediate transient response

Begins rapidly after exposure to the responsible mediators

Usually lasts approximately 15–30 minutes

Typically reflects mediator-induced endothelial contraction



The word “transient” refers to duration

A short-lived response can nevertheless produce protein-rich exudate

Timing provides a clue to mechanism, not proof on its own

Persistent leak should raise consideration of prolonged injury or other mechanisms

Early and brief

Mediator-driven contraction commonly

Long-lasting

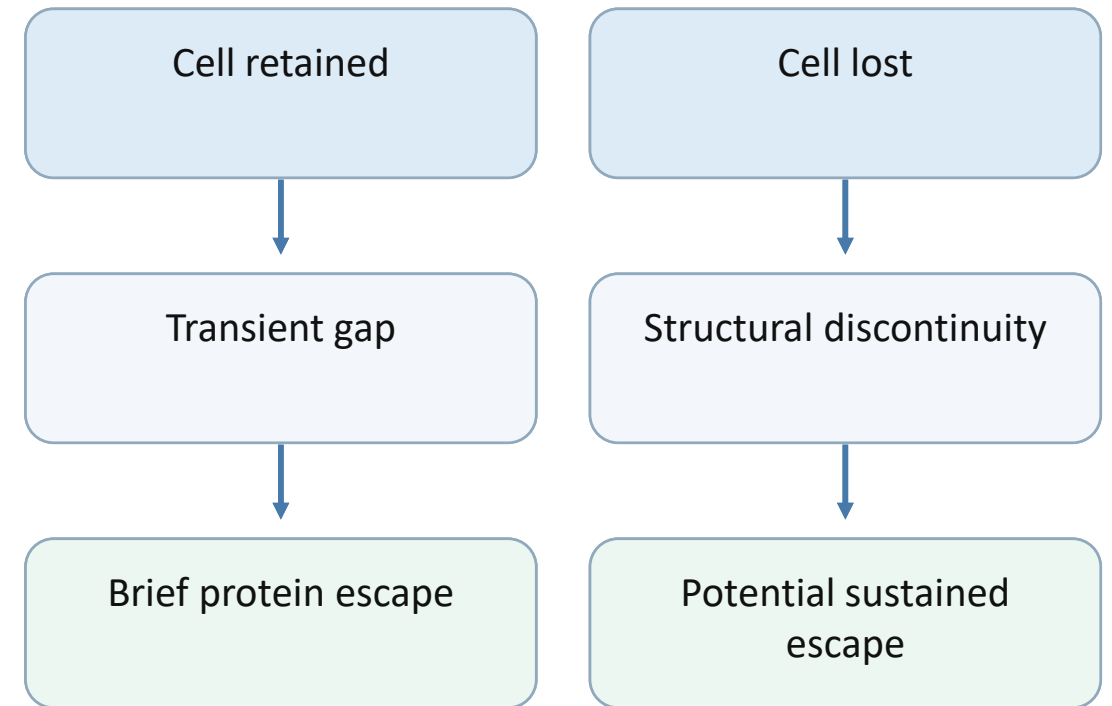
Endothelial damage or delayed response possible

Immediate leakage can be functionally reversible

Contraction creates gaps without requiring cell detachment

Brief exposure to a vasoactive mediator may produce a short response

This contrasts with structural endothelial loss after severe injury

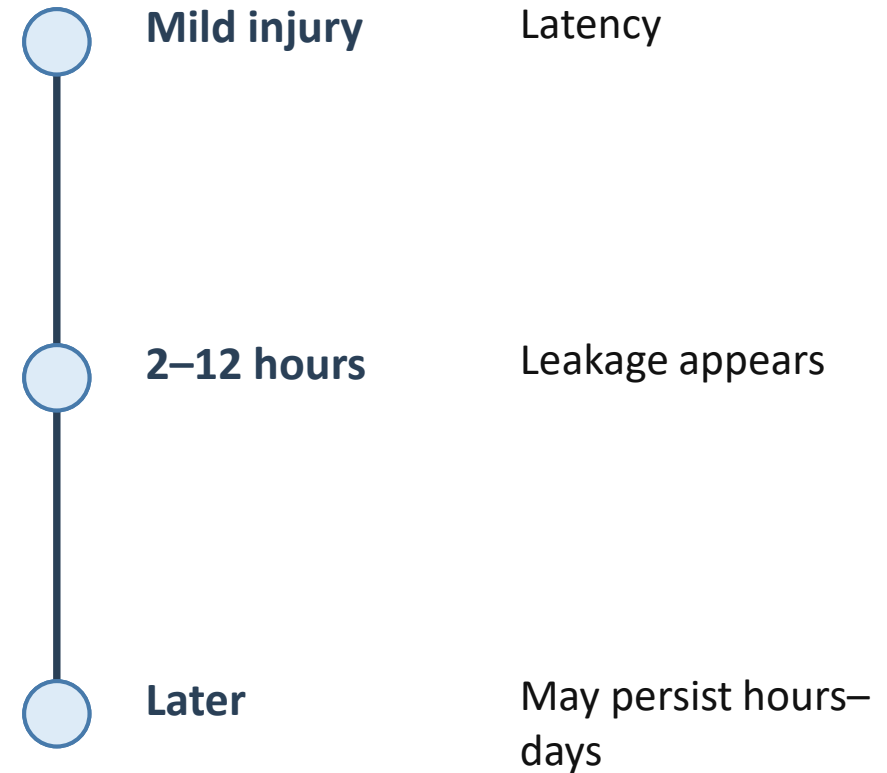


Delayed prolonged leakage has later onset

Leakage may begin 2–12 hours after some mild injuries

It can continue for several hours or even days

Contraction or mild endothelial damage may underlie this pattern

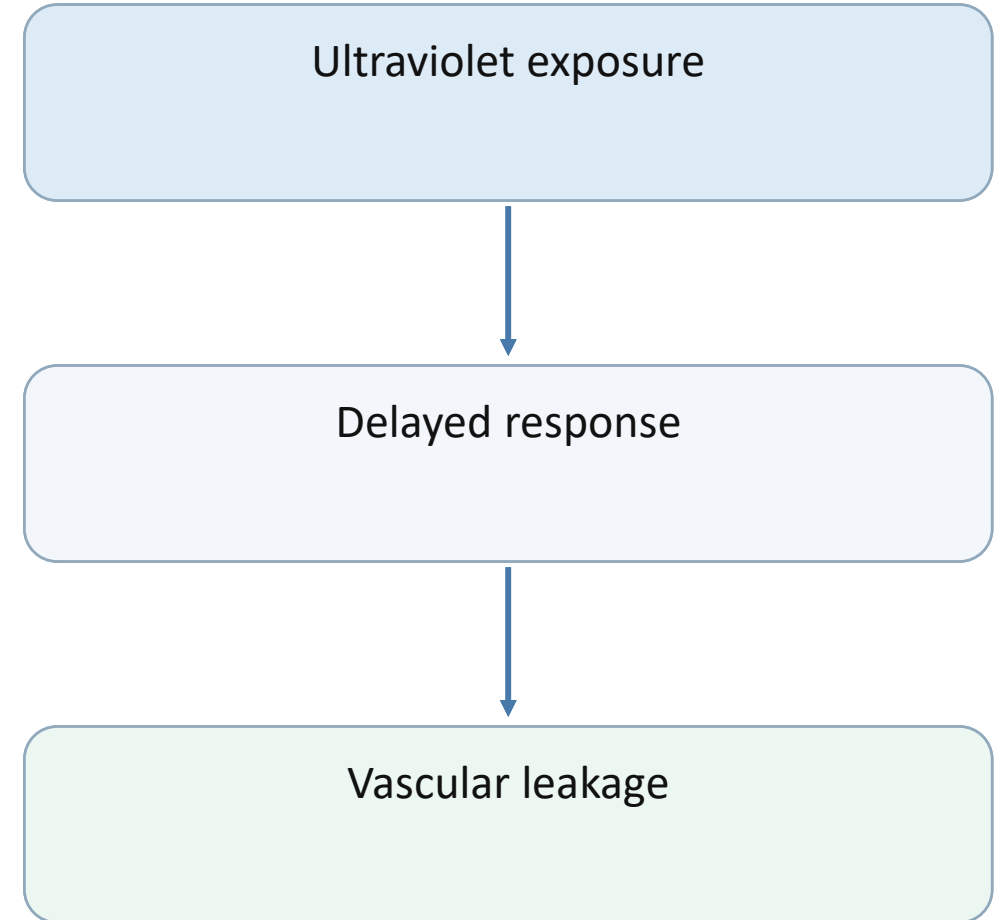


Sunburn illustrates delayed leakage

Ultraviolet exposure can precede a delayed permeability response

The swelling need not begin at the moment of exposure

Sunburn as a classic delayed-leakage example



Other settings of delayed leakage

Mild thermal injury may produce a late response

Irradiation and certain bacterial toxins are also described triggers

Delayed onset does not exclude endothelial involvement

Mild burns

Delayed leakage may occur

**Irradiation /
UV**

Delayed leak may occur

**Selected
bacterial
toxins**

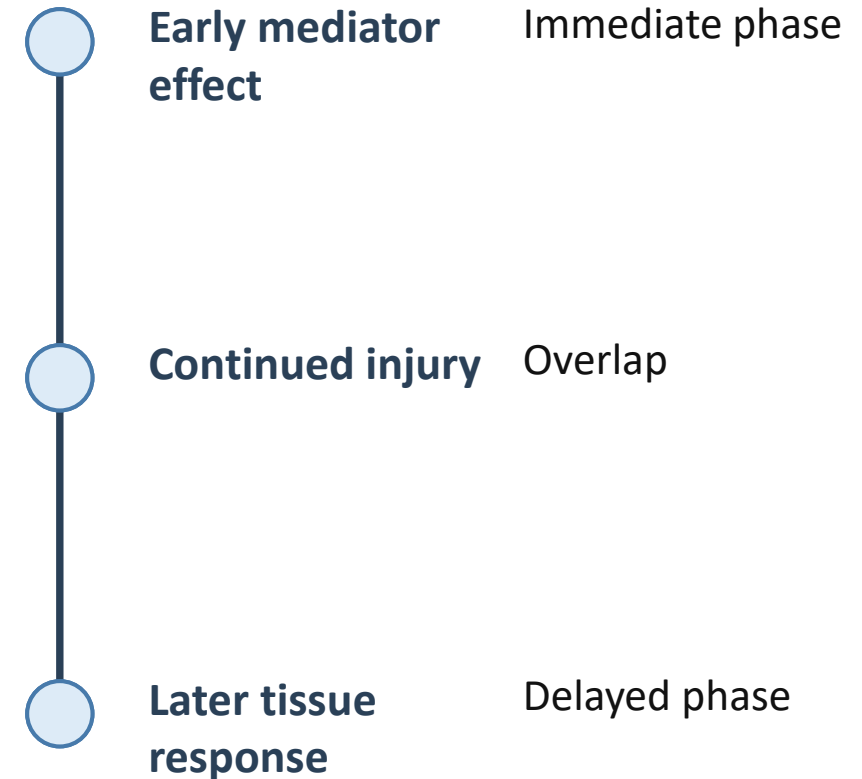
Delayed leak may occur

Immediate and delayed phases may overlap

The two response patterns are not always sharply separated

Mediator effects and mild cellular injury may evolve together

A continuous clinical course can combine early and late leakage



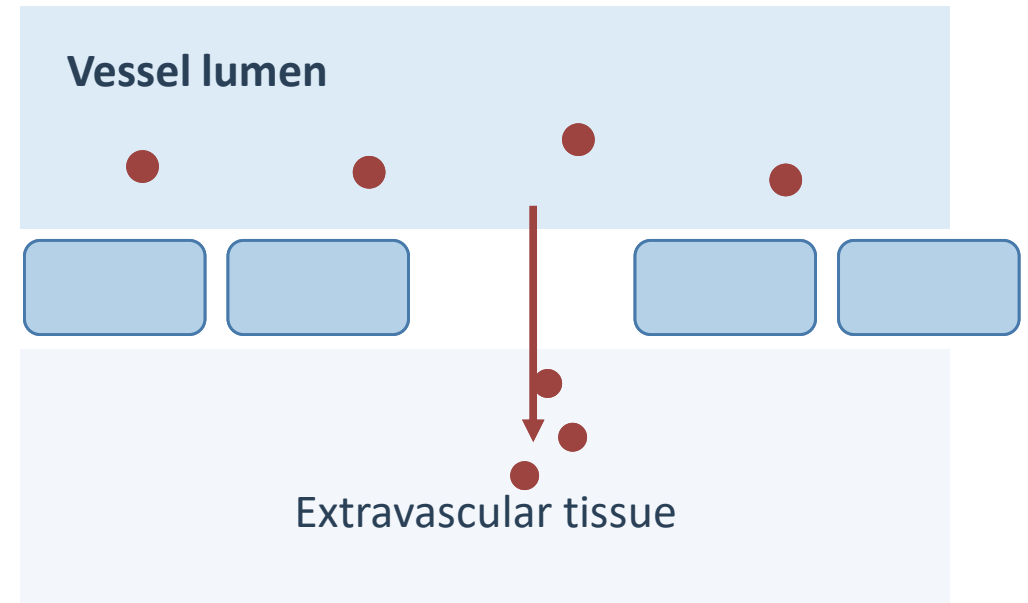
Direct endothelial injury disrupts the lining

Physical or microbial insults may injure endothelial cells directly

Severe injury can produce endothelial necrosis and detachment

Loss of intact cells creates a more persistent vascular defect

Original schematic · postcapillary venule



Injured / absent endothelium
Red dots = plasma proteins (schematic)

Necrosis and detachment differ from contraction

Necrosis means endothelial cell death

Detachment removes cells from the vascular lining

Both disrupt integrity more severely than a short-lived junctional gap

Contraction

Viable cells; Intercellular gap

Necrosis

Endothelial cell death

Detachment

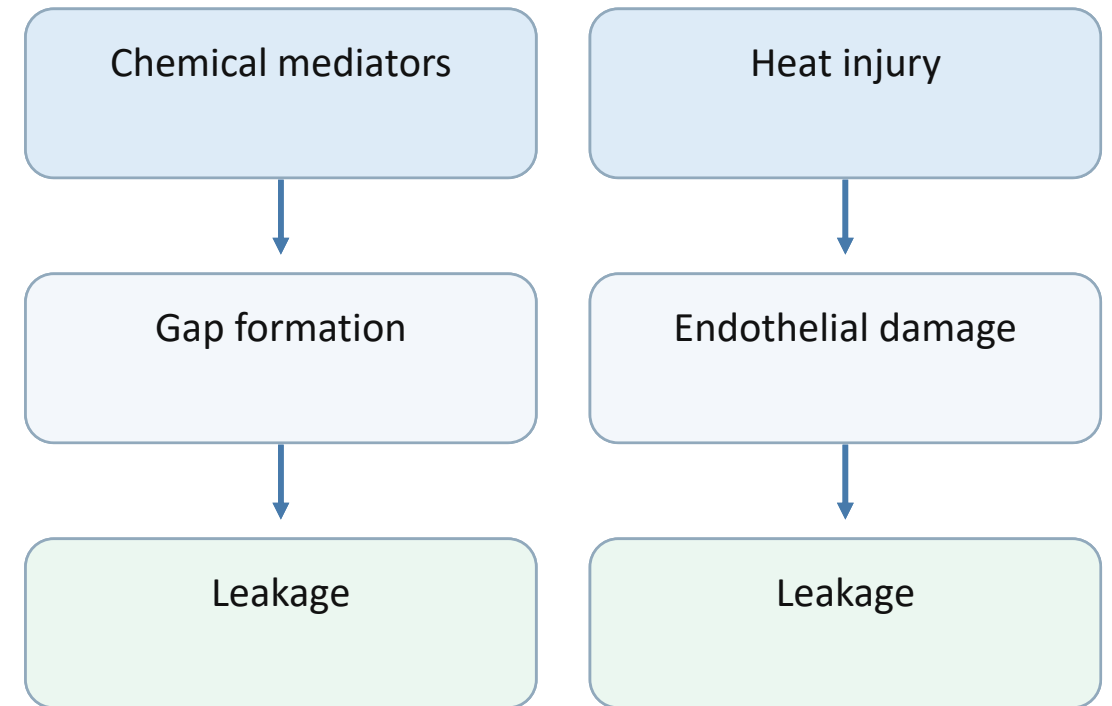
Loss of lining continuity

Severe thermal injury can damage endothelium

Major burns may produce direct physical vascular injury

Mediator-dependent contraction can occur at the same time

Combined injury can lead to extensive fluid and protein escape

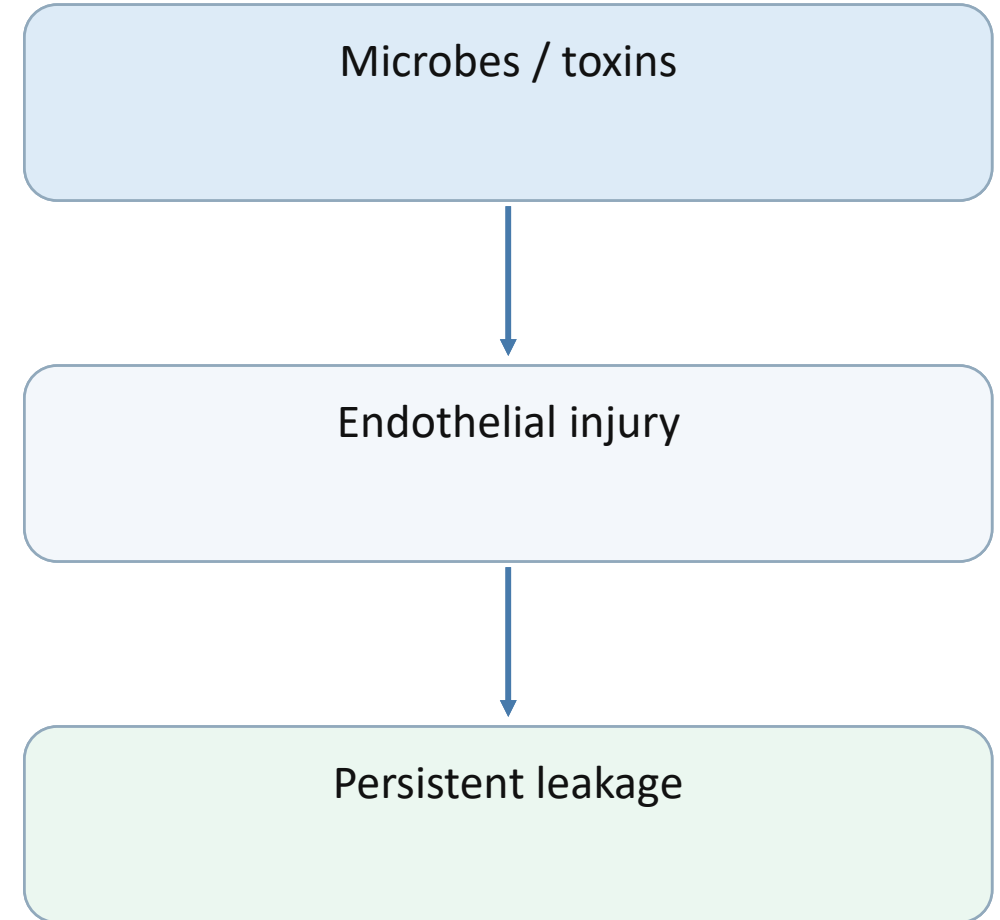


Microbes and toxins can cause direct injury

Microbial products can damage the endothelial lining

Direct injury permits fluid and proteins to escape

The resulting permeability change may persist while vessels remain damaged

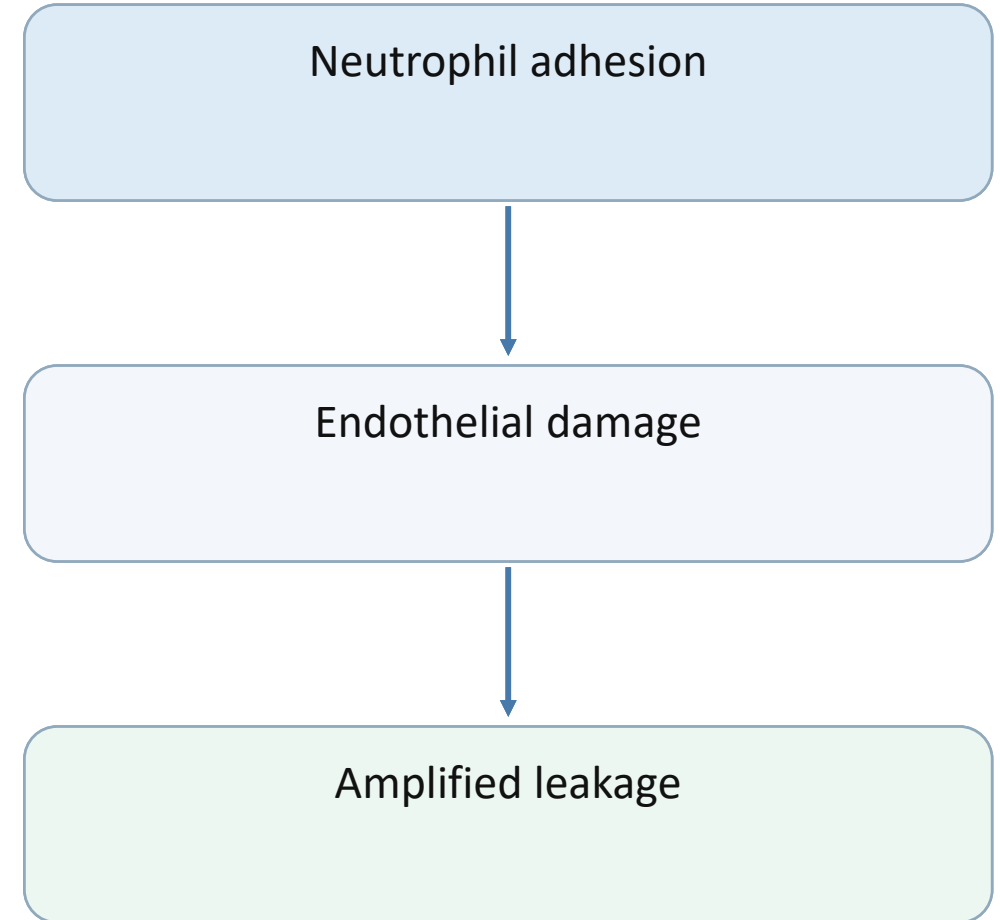


Adherent neutrophils can amplify leakage

Neutrophils adhere to endothelium during inflammation

Their interaction can injure endothelial cells

Leukocyte-dependent injury increases the permeability response

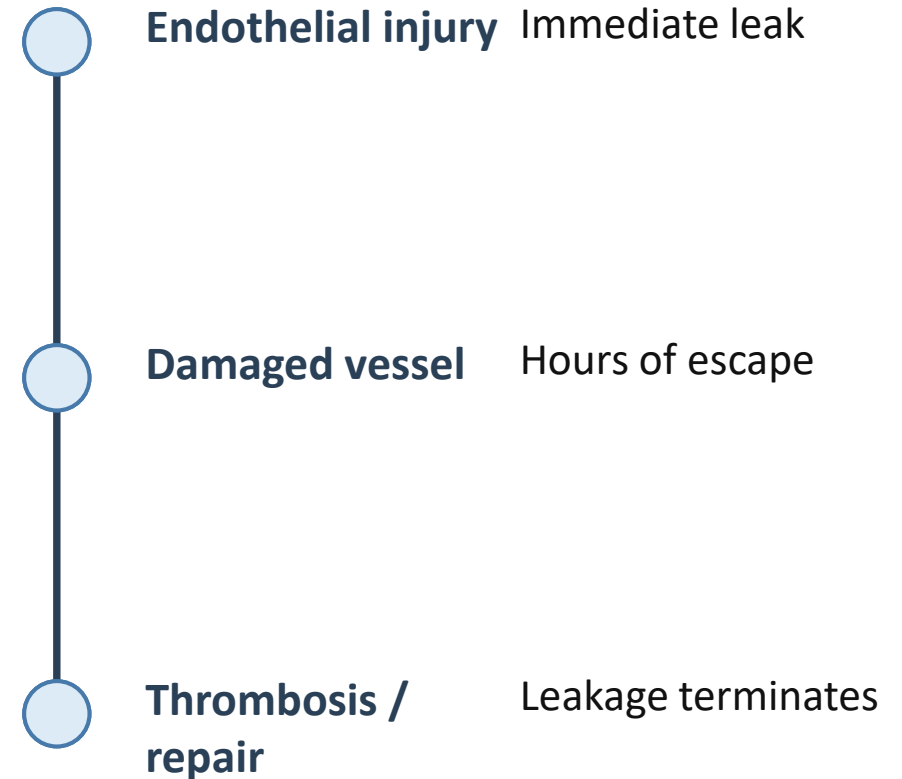


Injury-associated leakage is often sustained

In many direct-injury settings, leakage begins immediately

The defect may persist for several hours

Leakage continues until vessels undergo thrombosis or repair

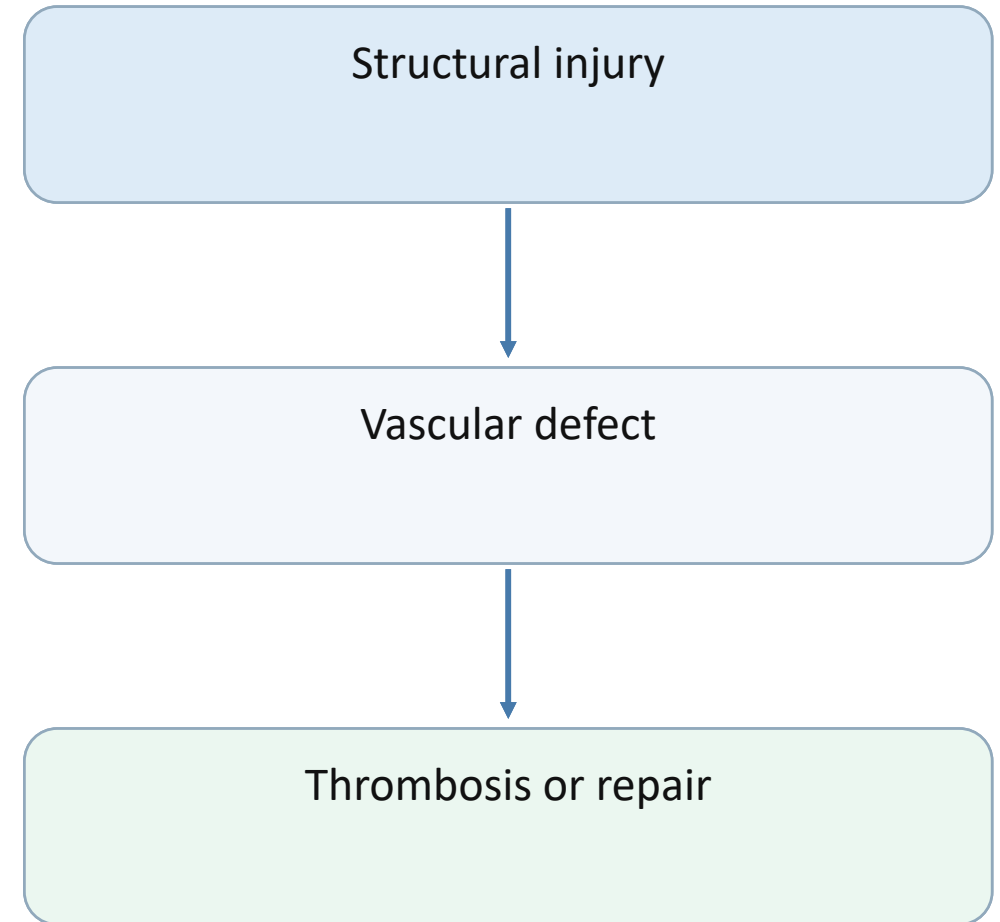


Thrombosis and repair can terminate leakage

Thrombosis can seal a severely damaged vascular segment

Repair can restore continuity of the vascular lining

The duration of exudation depends partly on resolution of the defect



Timing distinguishes common patterns

Immediate transient: Rapid, typically 15–30 minutes

Delayed prolonged: Onset after 2–12 hours; May last much longer

Direct injury: Often immediate and sustained for hours

**Immediate
transient**

Rapid; Usually 15–30 min

**Delayed
prolonged**

Onset 2–12 h; Lasts hours–days

Direct injury

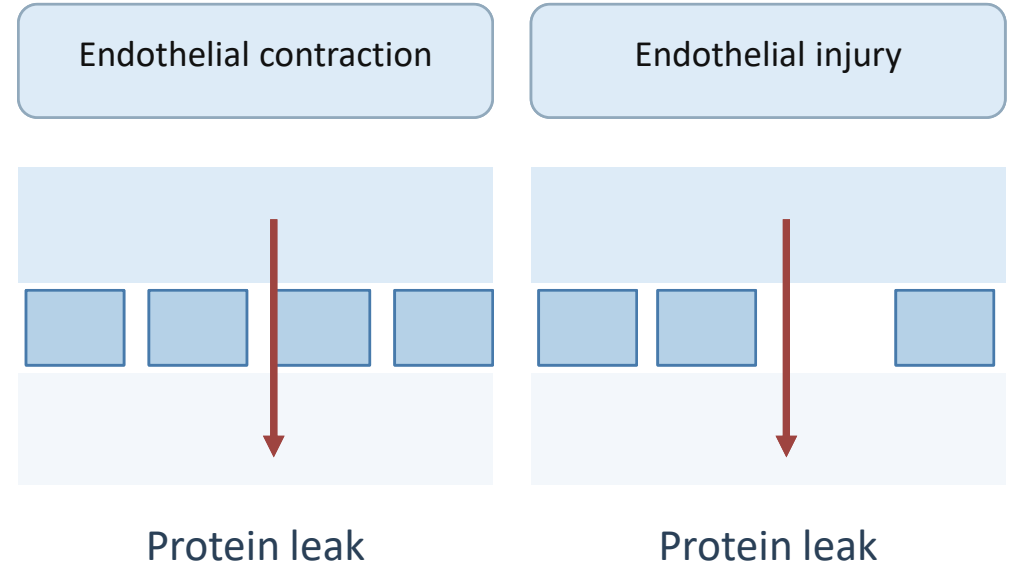
Immediate; Can last hours

Morphology of endothelial disruption

Contraction enlarges gaps between otherwise retained cells

Injury leaves damaged or missing endothelial segments

Both permit plasma proteins to cross the venular wall



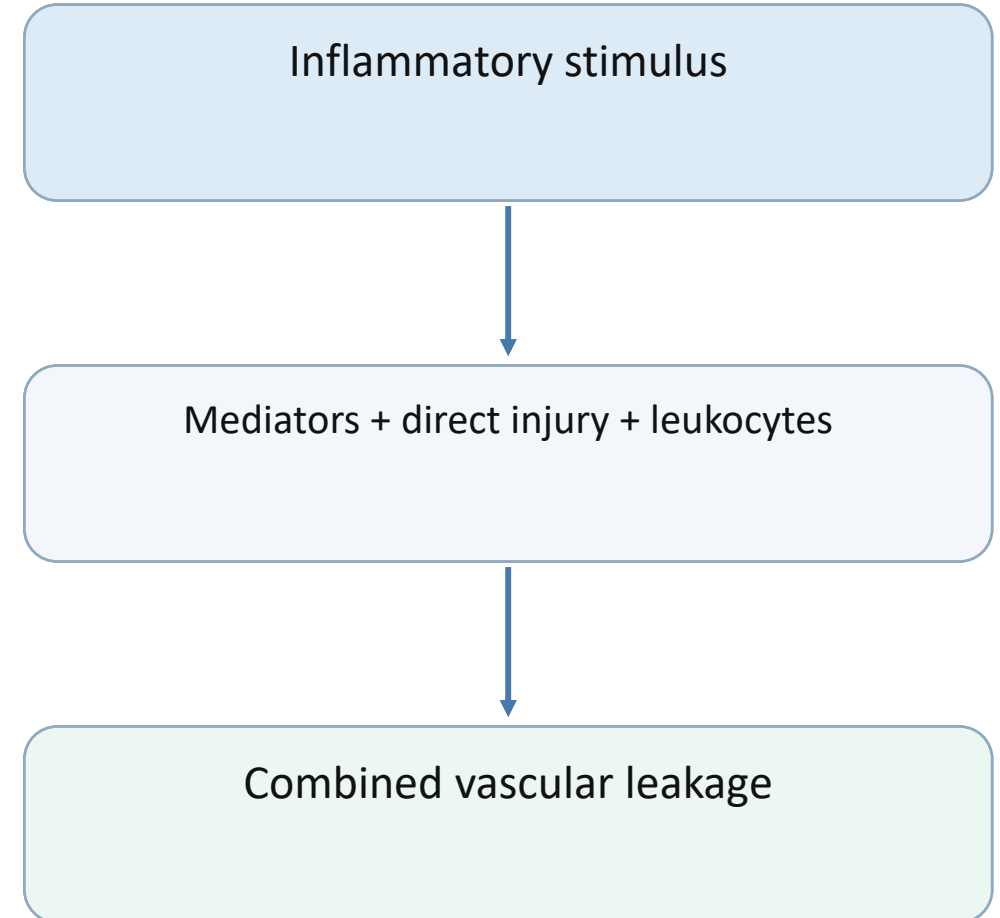
Schematic · intact cells with gaps versus structural cell loss

Real inflammatory lesions use mixed pathways

Mechanisms are described separately to clarify causation

Most inflammatory stimuli probably activate several pathways

The relative contributions vary with stimulus and time

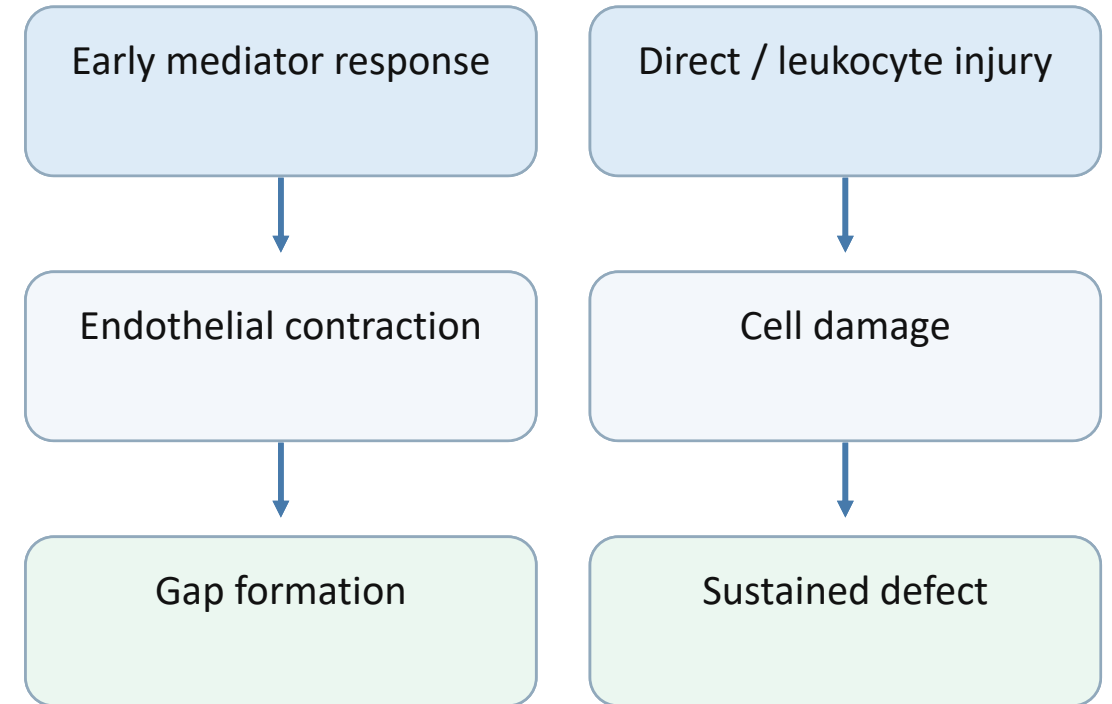


Thermal burns exemplify mixed mechanisms

Chemical mediators can induce endothelial contraction

Direct heat and recruited leukocytes can injure the lining

Different stages of one burn can show different leakage mechanisms

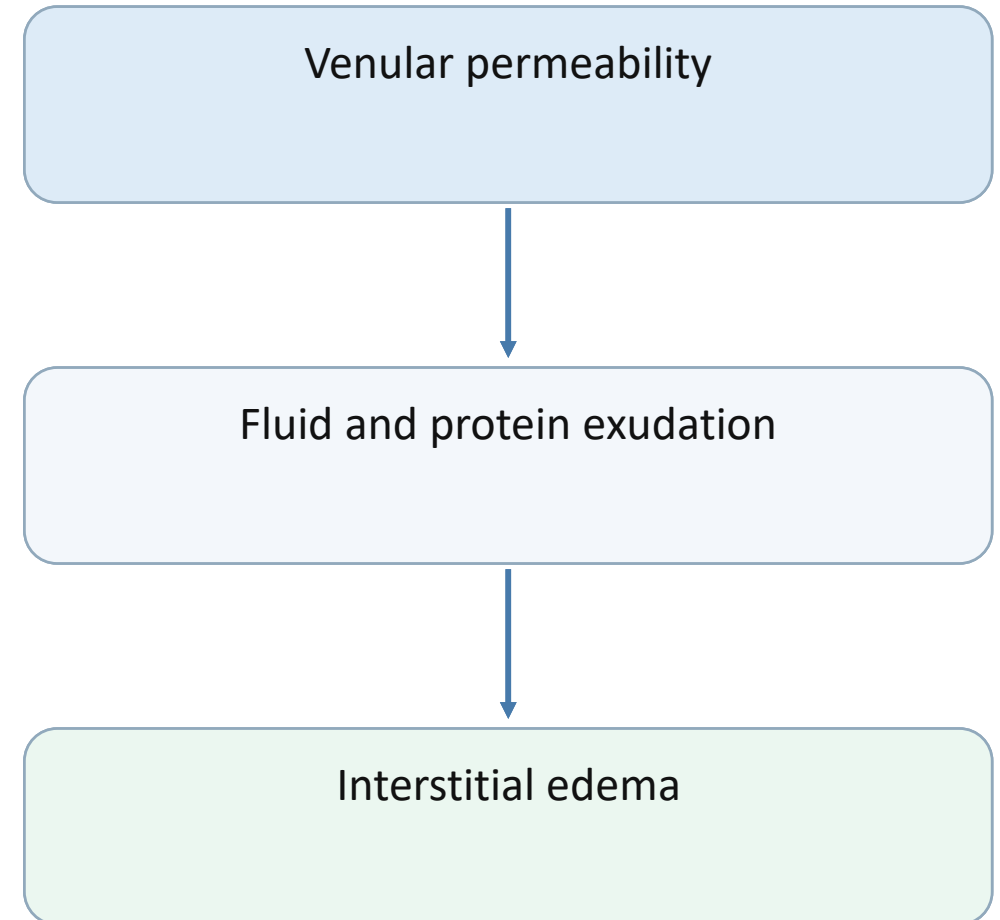


Why leakage produces tissue swelling

Fluid leaving blood vessels accumulates outside the circulation

Protein-rich fluid also enters the interstitial compartment

The excess extravascular fluid is clinically recognized as edema

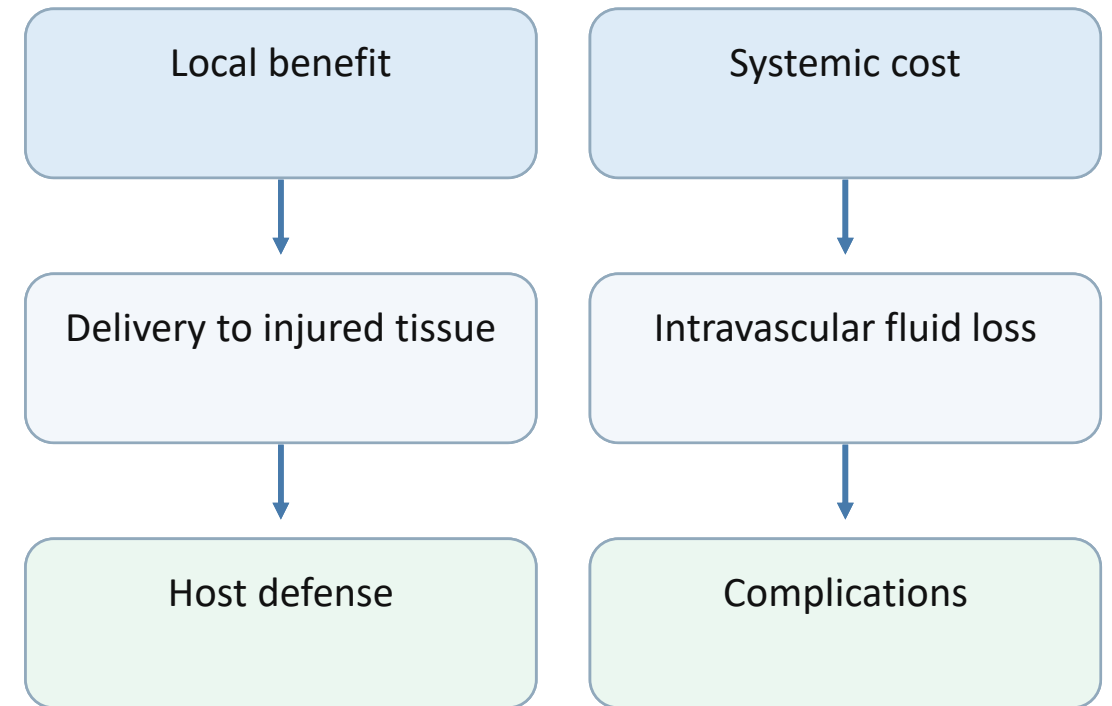


Inflammatory edema is not always harmless

Exudate can carry protective plasma constituents to injured tissue

The same process removes fluid from the circulating compartment

When severe, the cost of extensive leakage may exceed local benefit

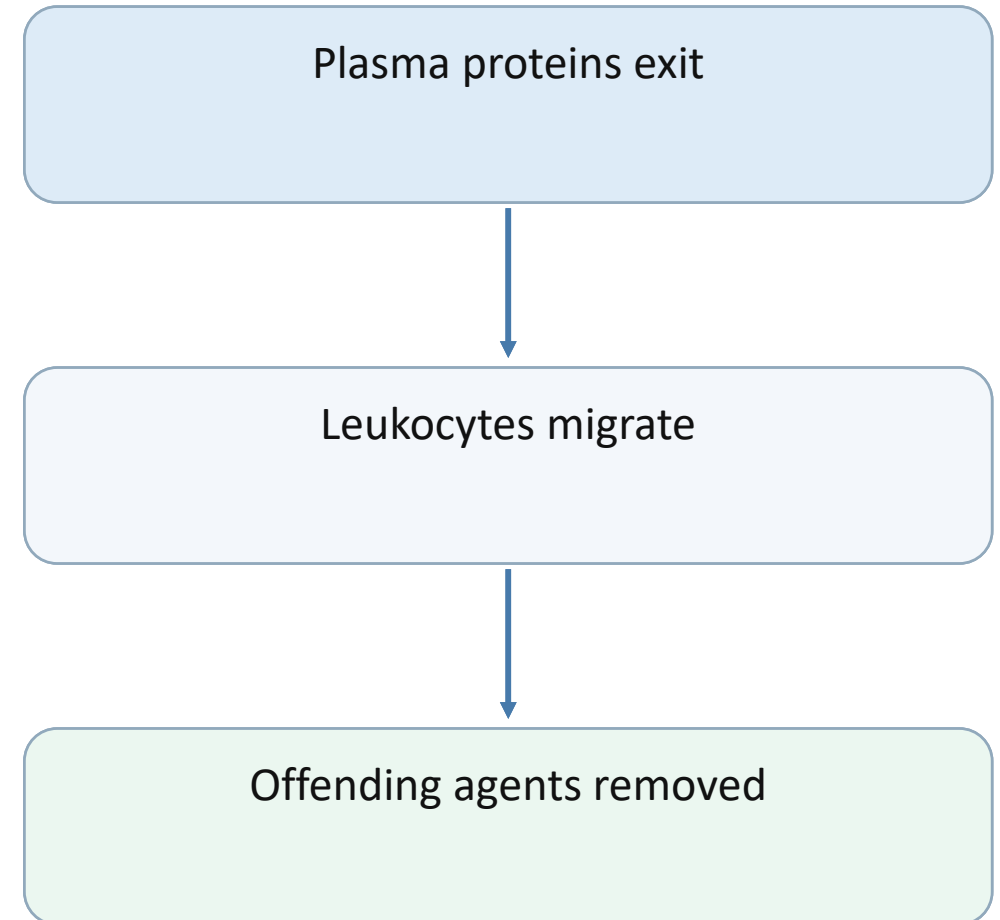


Leakage supports delivery of host-defense components

The vascular response brings plasma proteins into affected tissues

Recruitment of leukocytes follows the vascular changes

These mechanisms support removal of microbes and damaged cells

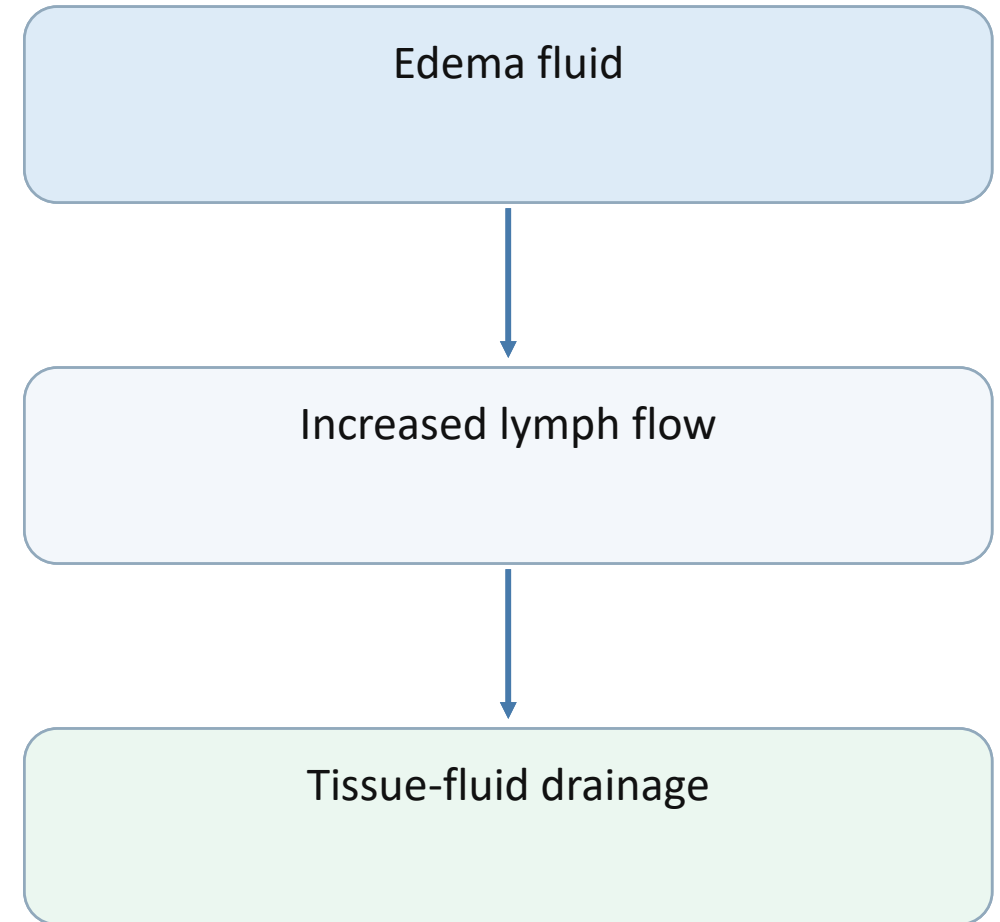


Lymphatics help clear excess interstitial fluid

Normal lymphatics drain the small baseline tissue-fluid escape

Inflammation increases lymph flow as edema fluid accumulates

Lymphatic clearance partially counters increased vascular filtration

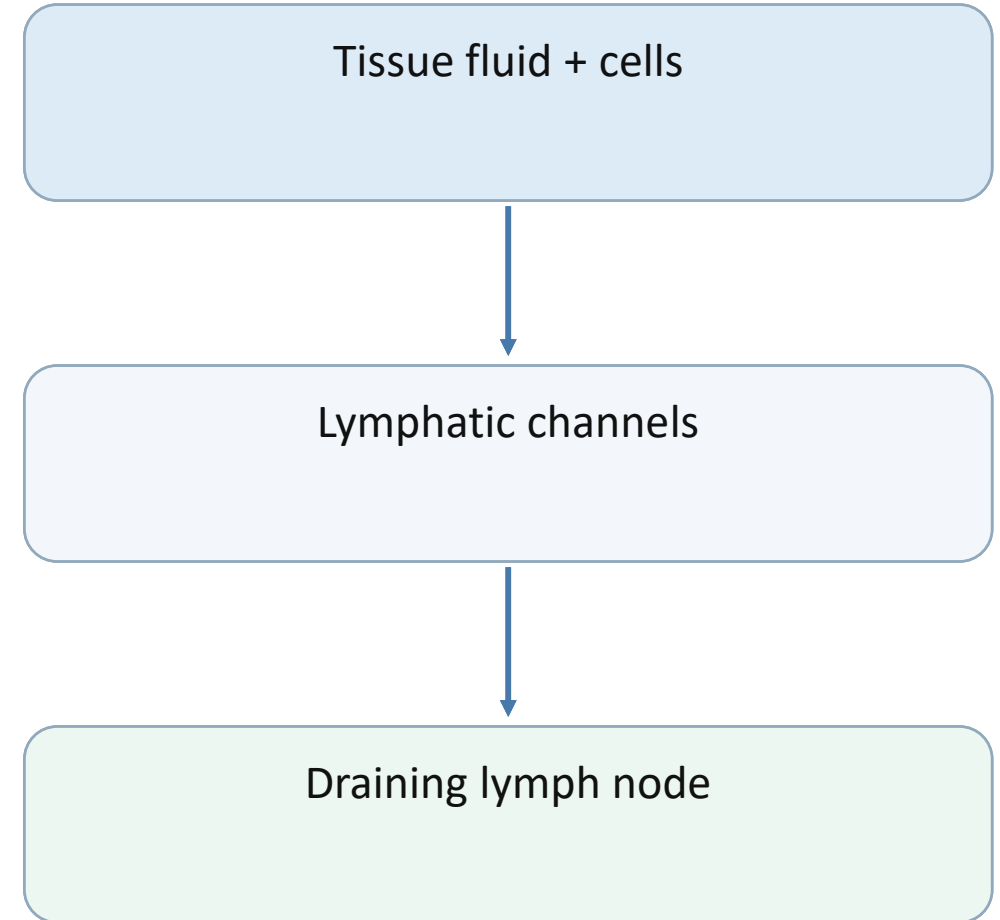


Lymphatics also transport inflammatory material

Leukocytes, cellular debris and microbes may enter lymph

Draining lymph nodes filter the lymphatic contents

Reactive enlargement may accompany the inflammatory response

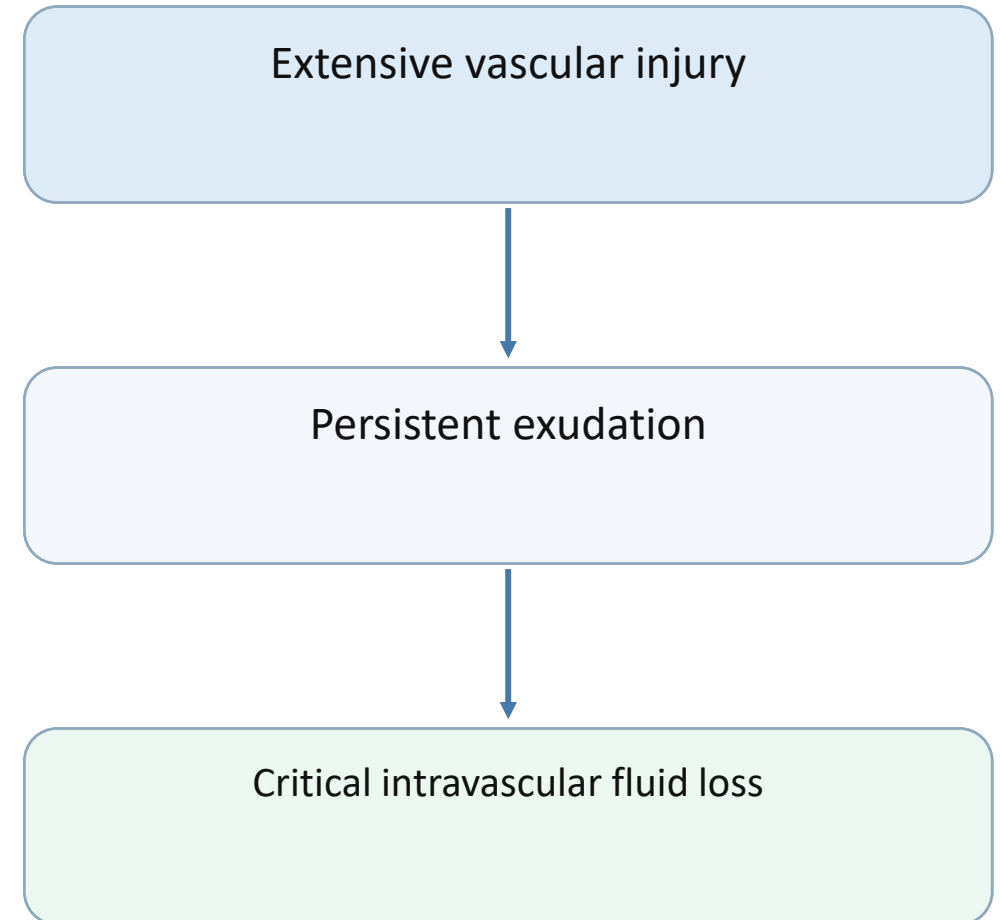


Severe burns can cause dangerous fluid loss

Extensive injured microvasculature leaks fluid and proteins

The vascular effect can be prolonged and multifactorial

Potentially life-threatening fluid loss in severe burns

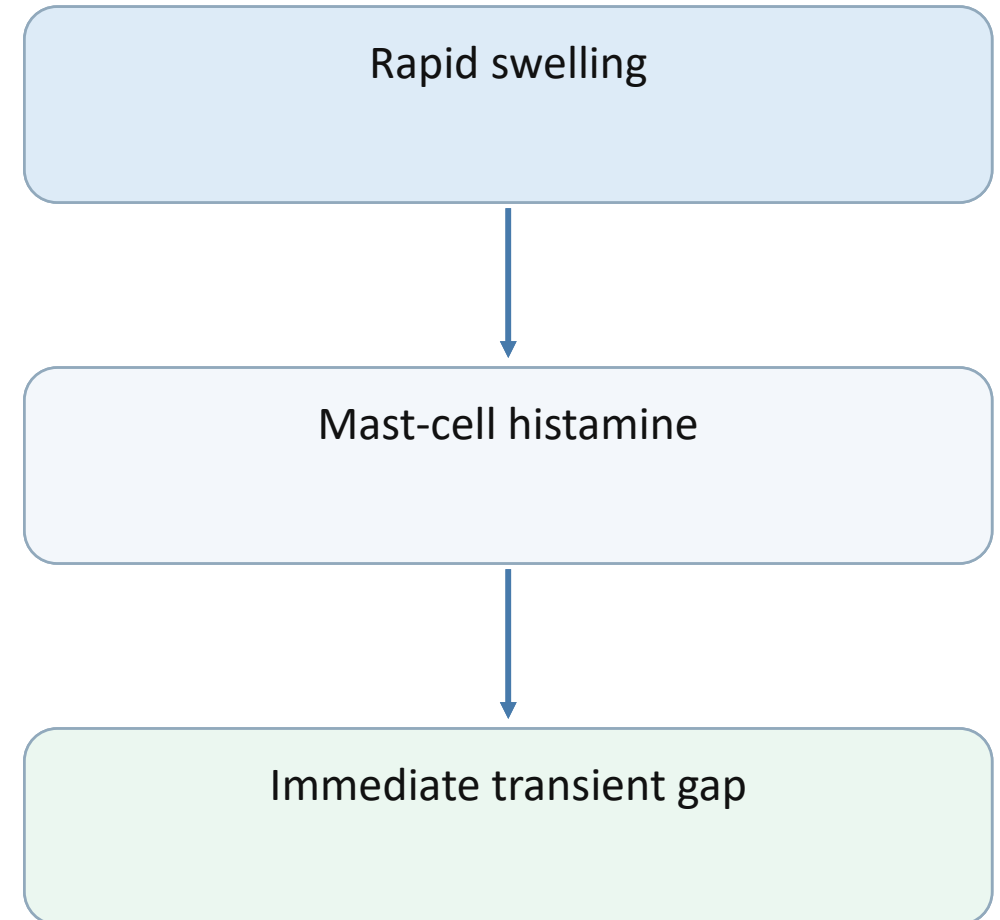


Clinical reasoning: Rapid allergic swelling

A localized reaction begins rapidly after antigen exposure

IgE-linked mast-cell activation can promptly release histamine

Expected vessel mechanism: Brief interendothelial gap formation

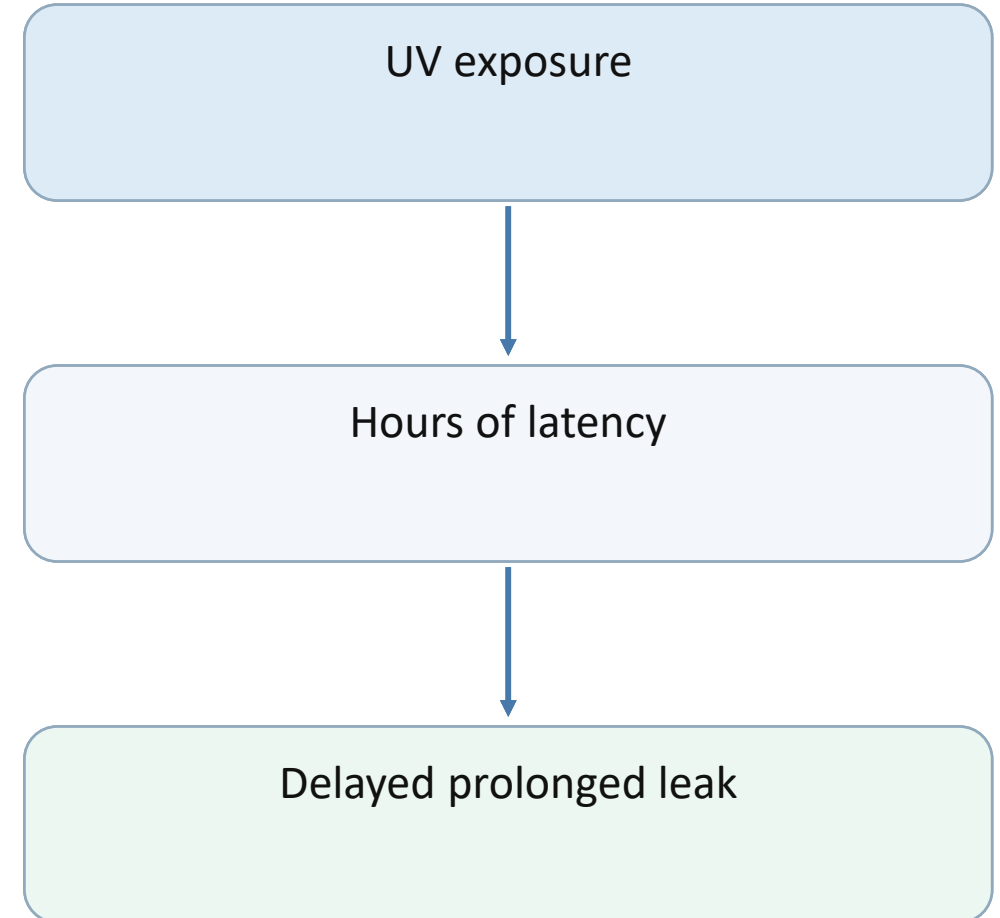


Clinical reasoning: Swelling after sun exposure

A patient notices edema hours after intense ultraviolet exposure

The latency is compatible with delayed prolonged permeability

The vignette does not require immediate endothelial necrosis

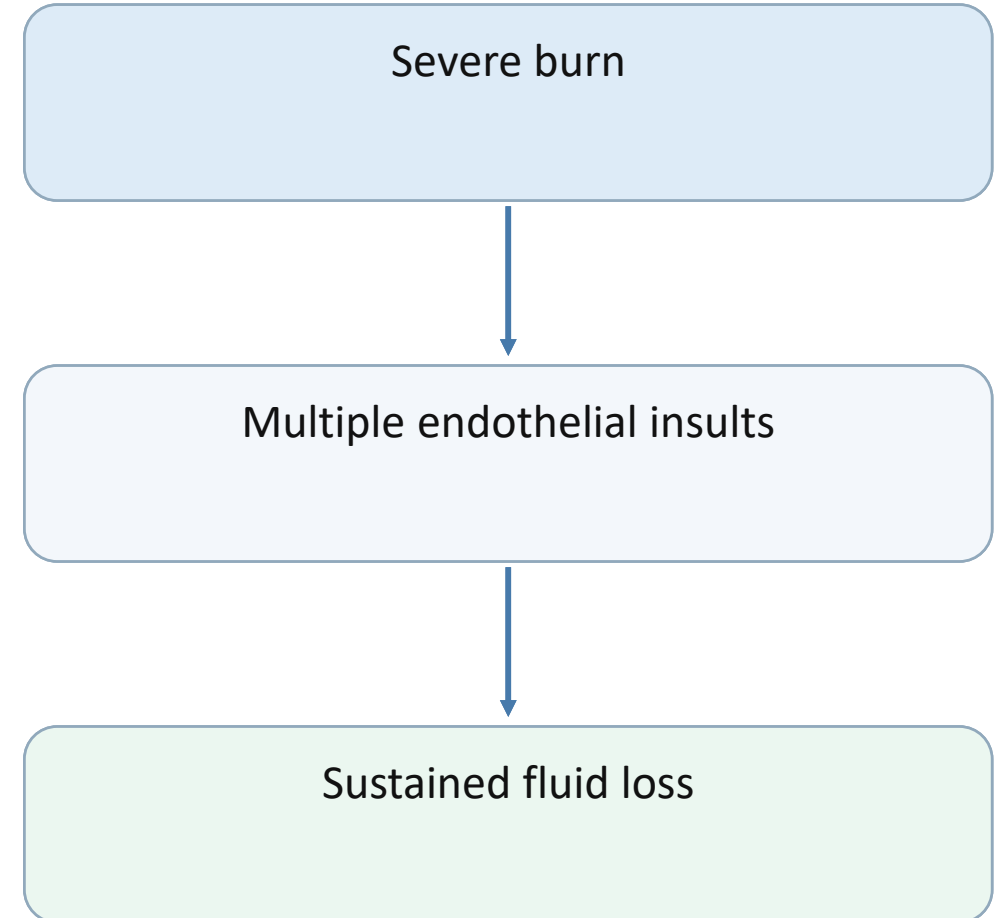


Clinical reasoning: Major thermal burn

A severe burn produces early and persistent fluid escape

Direct endothelial injury and mediator action may coexist

Neutrophil-dependent injury can further amplify vascular leakage



Clinical reasoning: Cardiac versus inflammatory edema

Heart-failure-associated venous pressure favors transudation

Inflamed venules release protein-rich exudate through permeability defects

Correct classification requires identifying the mechanism

Heart failure Hydrostatic imbalance → transudate

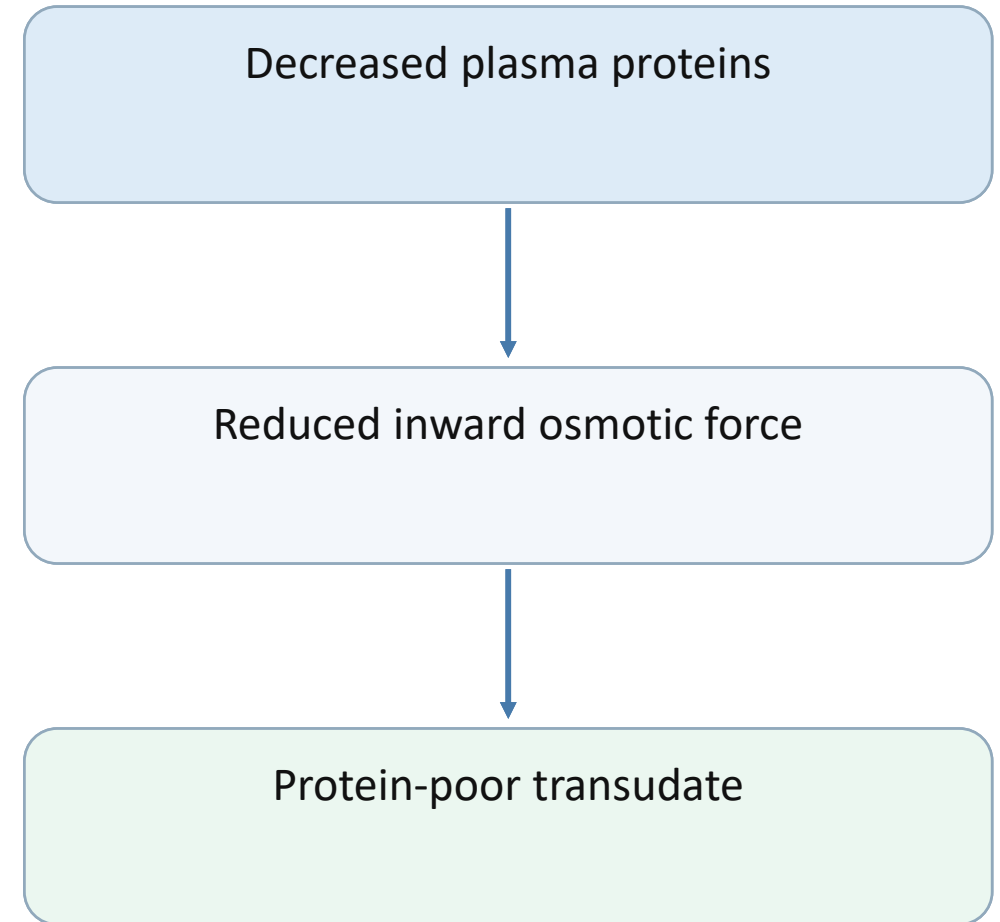
**Acute
inflammation** Permeability change → exudate

Clinical reasoning: Low plasma protein states

Liver disease may lower albumin synthesis

Renal protein loss and severe malnutrition may reduce oncotic pressure

The consequent transudate need not imply endothelial inflammation

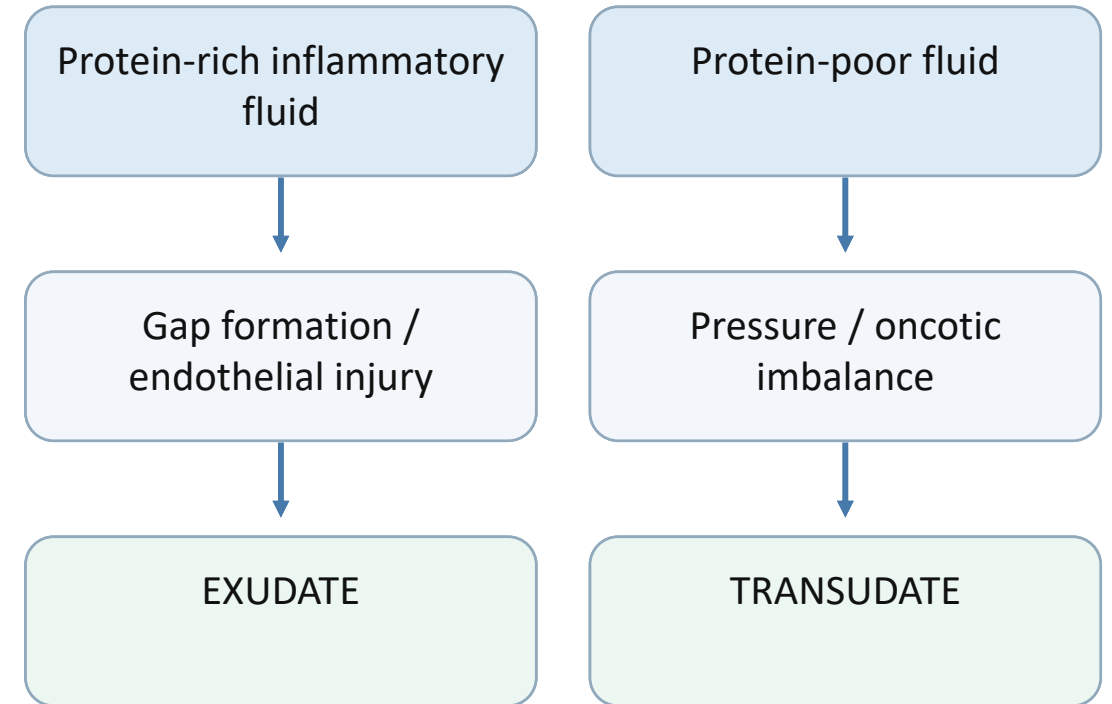


A mechanistic diagnostic decision path

First: Determine whether fluid accumulation reflects inflammation

Next: Assess whether vessel permeability or pressure forces are primary

Finally: Interpret onset and duration to refine the leakage mechanism



Common conceptual errors

Edema is not automatically an exudate

Vasodilation is not the same event as permeability increase

Endothelial contraction does not necessarily imply cell death

Immediate and delayed leakage need not be separate episodes

Timing exercise: Identify the mechanism

Leakage within minutes, resolving quickly → mediator-driven gap likely

Leakage after hours of sun exposure → delayed prolonged pattern

Immediate persistent leakage after severe heat injury → endothelial damage likely

**Minutes →
brief**

Immediate transient response

**Hours to
onset**

Delayed prolonged response

**Immediately
→ sustained**

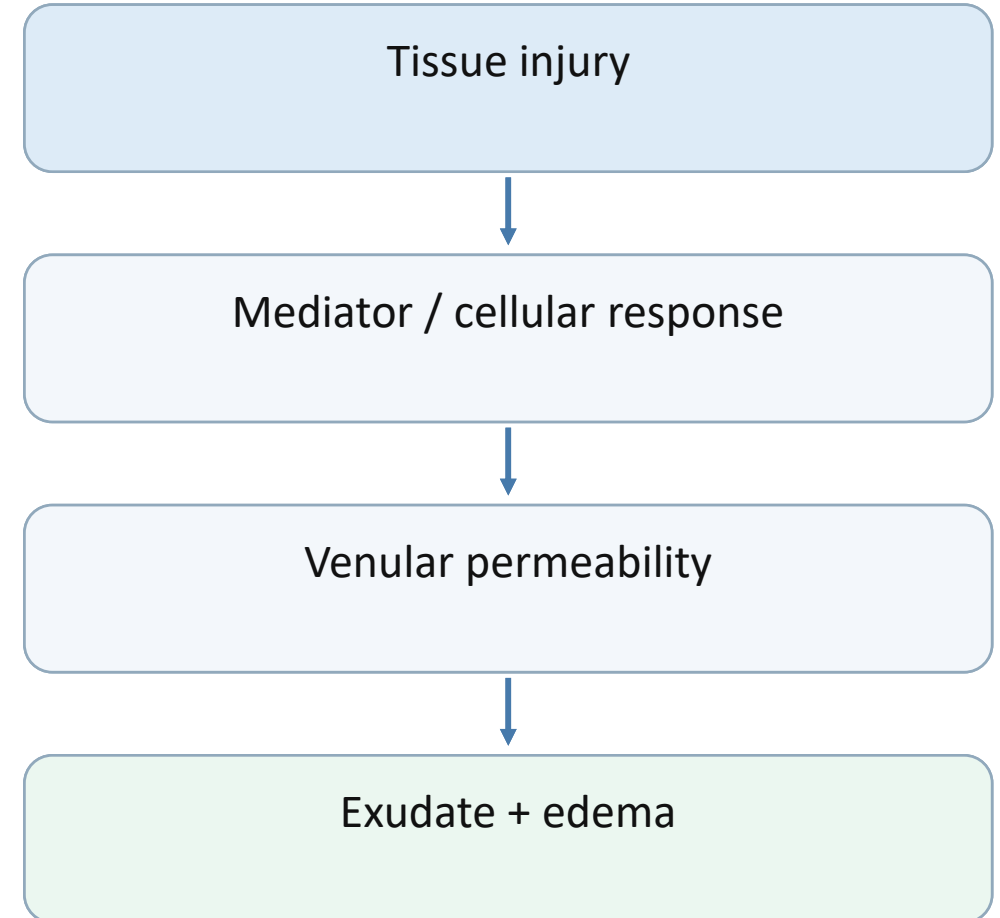
Direct injury often involved

Integrated mechanism of inflammatory exudation

Injury stimulates soluble mediators and cellular reactions

Venules develop gaps, structural injury or both

Plasma proteins and fluid enter tissue; Stasis and edema follow



High-yield synthesis

Postcapillary venules are the main site of inflammatory leakage

Endothelial contraction is common and usually rapidly transient

Necrosis/detachment and leukocyte injury prolong leakage

Exudate is protein rich; Transudate reflects pressure imbalance

Primary reference

Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition (2026), chapter “Inflammation and Repair”

Mechanisms, vascular reactions and inflammatory mediators

Figures 3.2 and 3.3 informed original editable schematics