

Edema caused by microvascular (alveolar) injury

Noncardiogenic pulmonary edema, acute lung injury, and diffuse alveolar damage

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Learning objectives

- Distinguish permeability-related pulmonary edema from hydrostatic edema.
- Explain endothelial and epithelial injury mechanisms in ALI/ARDS.
- Correlate hyaline membranes, organizing injury, and clinical respiratory failure.
- Interpret representative clinical scenarios using pathology mechanisms.

Pulmonary edema has more than one mechanism

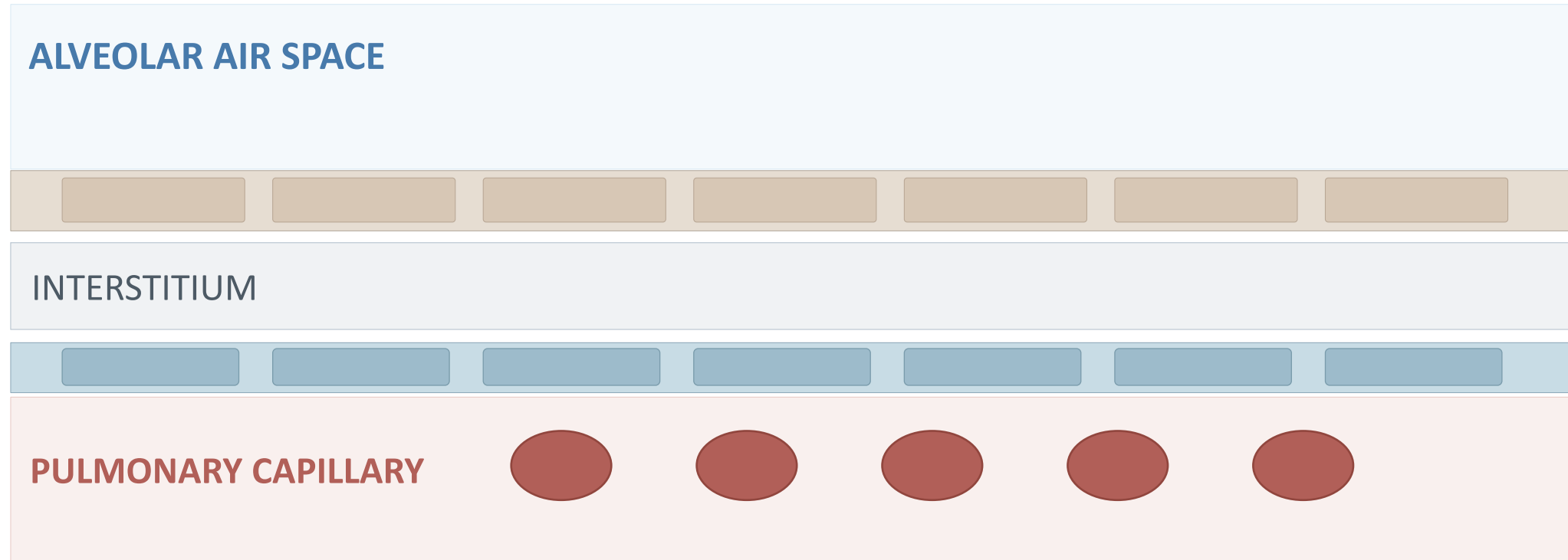
Hemodynamic edema

- Primarily increased hydrostatic pressure
- Common association: Left-sided heart failure
- Alveolar fluid is mainly transudative

Alveolar wall-injury edema

- Primary barrier injury and increased permeability
- Endothelial and/or alveolar epithelial damage
- Inflammatory, protein-rich exudate

The intact alveolar–capillary barrier



Schematic · Thin alveolar epithelium, interstitium, and capillary endothelium

Two cellular layers regulate alveolar dryness

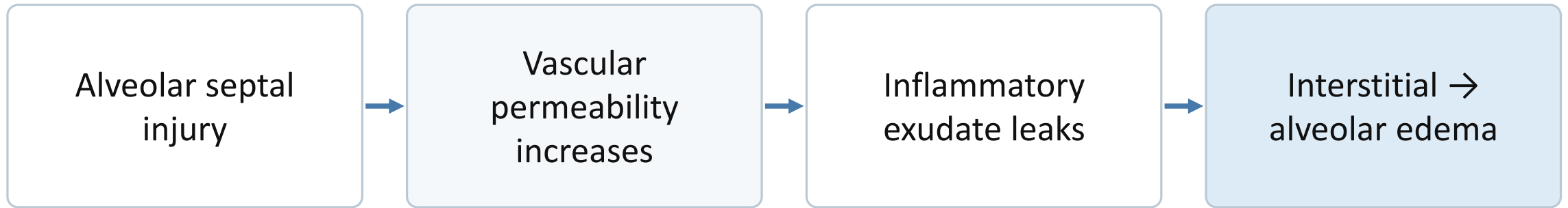
Alveolar epithelium

- Type I cells constitute thin gas-exchange lining
- Type II pneumocytes maintain surfactant
- Epithelial continuity supports edema clearance

Pulmonary capillary endothelium

- Forms vascular interface of alveolar septum
- Activation changes adhesion and permeability
- Injury permits movement of inflammatory exudate

Noncardiogenic edema begins with septal injury

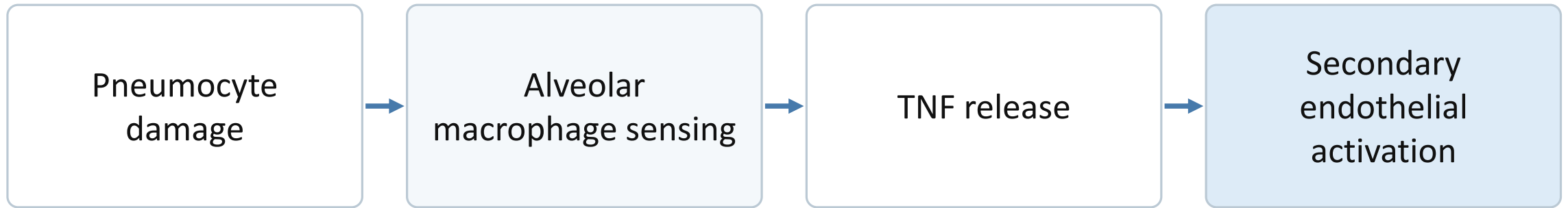


Protein leakage follows a loss of barrier integrity rather than pressure overload alone.

Primary endothelial injury: Vascular entry point

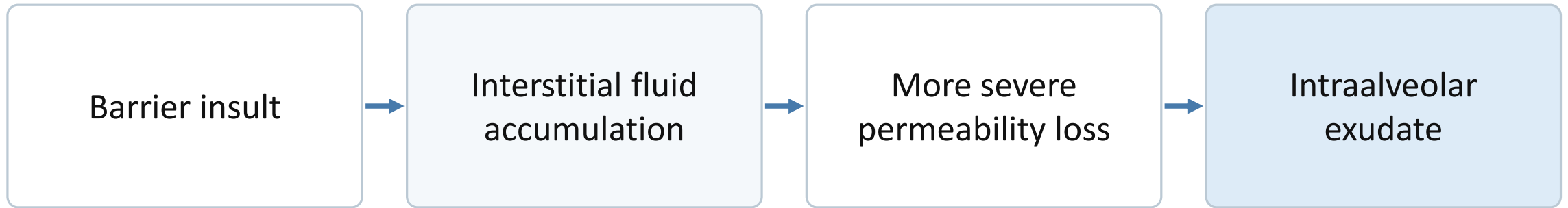
- Endothelial activation or damage may initiate permeability edema.
- Activated vessels become adhesive and proinflammatory.
- Leakage starts in the interstitium and may reach the alveolar air spaces.
- Epithelial injury often amplifies the pulmonary damage.

Primary epithelial injury: Alveolar entry point



Initial epithelial damage can trigger a secondary vascular inflammatory response.

Severity changes the compartment containing fluid



Alveolar flooding represents more advanced injury than isolated interstitial edema.

What the edema fluid signifies

Hemodynamic mechanism

- Raised hydrostatic pressure
- Transudate: Pale intraalveolar material
- Often associated with vascular congestion

Inflammatory permeability mechanism

- Endothelial or epithelial damage
- Exudate: Protein-rich edema fluid
- Fibrin and epithelial debris may form hyaline membranes

Direct and indirect causes converge on the lung

Direct injury to the lung

Infection Bacterial or diffuse pneumonia

Aspiration Gastric contents or near-drowning

Inhalation Oxygen toxicity; Smoke; Irritant gases

Tissue injury Contusion, trauma, radiation

Indirect / systemic injury

Systemic Sepsis; Burns; Pancreatitis; Trauma

Transfusion Transfusion-associated lung injury

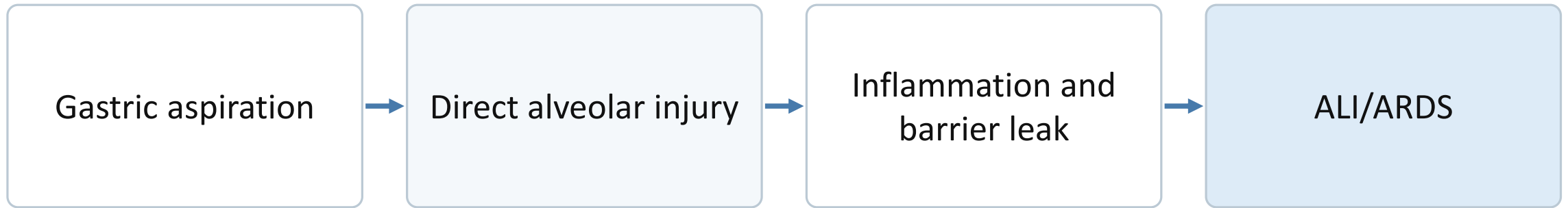
**Drugs /
chemicals** Listed medications and toxins

Other contexts DIC, uremia, cardiopulmonary bypass

Pulmonary infection is an important direct insult

- Diffuse pulmonary infection is one of the principal associations with ARDS.
- Textbook examples include viral, Mycoplasma, pneumocystis, and miliary tuberculosis.
- Bacterial pneumonia can directly injure the alveolar wall.
- Local epithelial injury can provoke macrophage-dependent inflammation.

Aspiration exposes alveoli to damaging material



The initiating insult occurs directly at the alveolar surface.

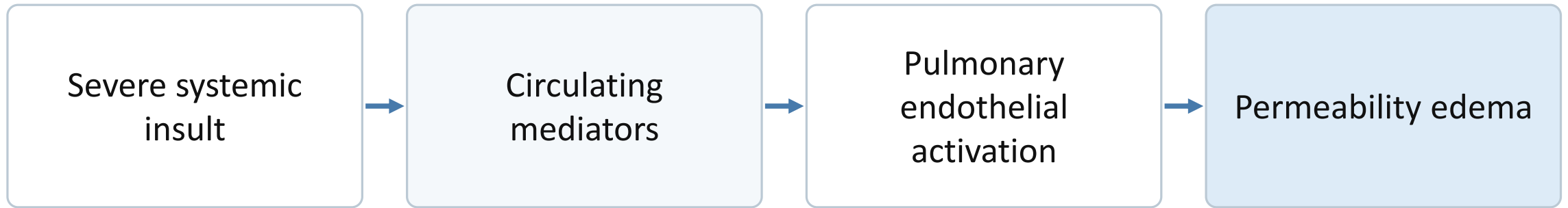
Inhaled agents can injure the alveolar septum

- High oxygen concentrations may produce oxygen toxicity.
- Smoke and irritant gases are recognized inhalational triggers.
- These are lung-directed injuries rather than isolated elevation of venous pressure.
- Clinical context identifies the injurious exposure.

Physical and environmental lung injury

- Pulmonary contusion follows direct thoracic injury.
- Near-drowning introduces liquid-associated lung injury.
- Radiation and severe burns are among listed injury contexts.
- Major mechanical trauma, including head injury, is associated with ARDS.

Systemic inflammation can initiate lung injury



A distant source of inflammation can damage the alveolar–capillary interface.

Sepsis is a major associated trigger

- Circulating inflammatory signals can activate pulmonary capillary endothelium directly.
- Endothelial changes recruit neutrophils and favor barrier dysfunction.
- Sepsis can coexist with other injuries, intensifying pulmonary damage.
- Sepsis among the prominent ARDS-associated conditions.

Transfusion and hematologic associations

- Transfusion-associated lung injury appears in the list of ARDS associations.
- Disseminated intravascular coagulation is another listed hematologic context.
- Systemic and hematologic insults can converge on pulmonary endothelial injury.
- Association alone does not specify a unique histologic pattern.

Drugs and chemicals are heterogeneous triggers

Examples

- Heroin or methadone overdose
- Aspirin or barbiturate overdose
- Paraquat and other chemicals

Pathology implication

- A chemical or medication exposure may precede ALI.
- The common consequence is alveolar wall injury.
- Drug history helps identify the initiating condition.

Multiple concurrent insults may coexist

Concurrent systemic insults

- Sepsis and severe tissue injury
- Shock and extensive trauma
- More than one trigger may be present

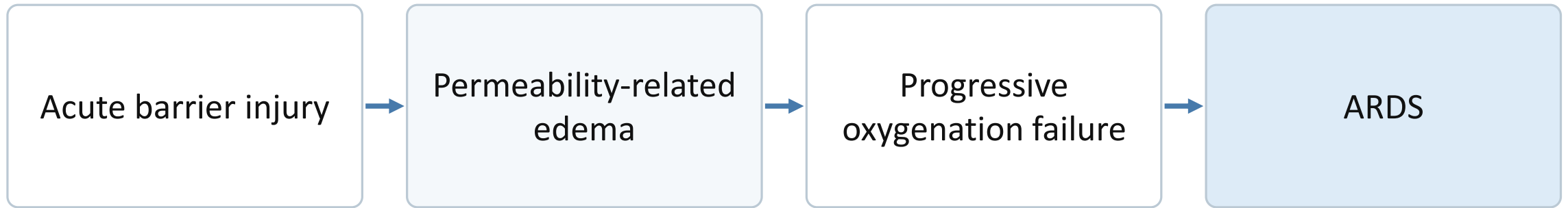
Coexisting pulmonary stresses

- Oxygen therapy may coexist
- Diffuse pulmonary infection may coexist
- Combined insults can worsen lung damage

ALI is a clinicopathologic lung-injury syndrome

- An abrupt onset of hypoxemia.
- Bilateral pulmonary edema occurs without cardiac failure as the explanation.
- Increased pulmonary vascular permeability accompanies epithelial cell death.
- The resulting histologic injury pattern is diffuse alveolar damage.

ARDS represents severe acute lung injury



Severe permeability edema is coupled to worsening gas-exchange failure.

ARDS and DAD are not interchangeable labels

ARDS

- Clinical syndrome
- Severe acute respiratory insufficiency
- Often occurs with identifiable systemic or pulmonary trigger

Diffuse alveolar damage (DAD)

- Histologic pattern of injury
- Edema, epithelial damage, hyaline membranes
- May evolve into organizing/fibroproliferative injury

Acute interstitial pneumonia: No identified trigger

- A minority of acute presentations occur without known initiating conditions.
- The source calls this rapidly progressive presentation acute interstitial pneumonia.
- Distinction from triggered ALI/ARDS is clinical, chiefly whether a precipitant is found.
- Similar forms of acute lung injury may occur in either setting.

The early injury has multiple cellular targets

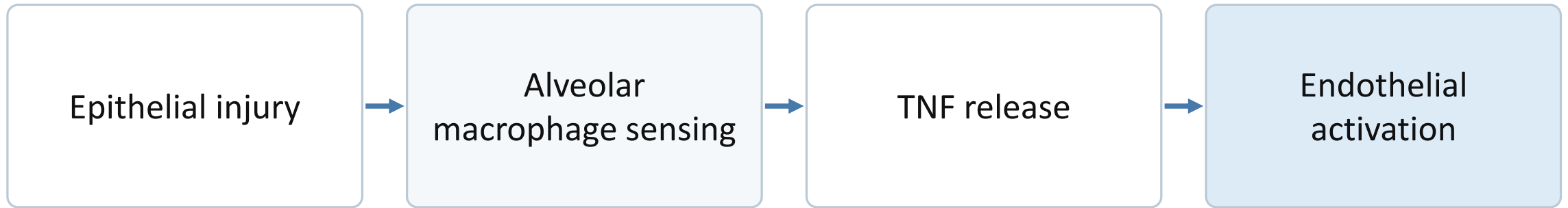
Alveolar compartment

- Type I and type II pneumocytes
- Resident alveolar macrophages
- Injury may begin at epithelial surfaces

Vascular and recruited cells

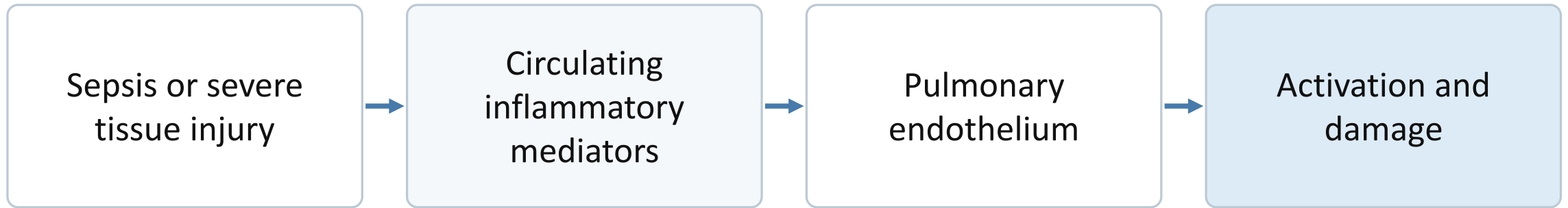
- Pulmonary endothelial cells
- Circulating and migrating neutrophils
- Cell interactions amplify barrier dysfunction

Macrophages translate epithelial injury into signals



Resident macrophages connect tissue damage with endothelial inflammation.

Systemic mediators provide a second initiating route



Endothelial activation can occur even without a primary airway insult.

Endothelial activation changes the vessel surface

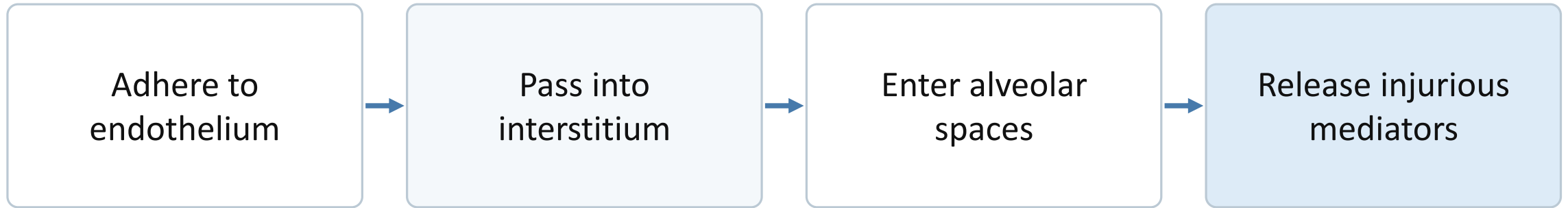
Functional change

- Increased adhesion molecules
- Increased procoagulant proteins
- Chemokine expression

Pathologic effect

- Facilitates neutrophil attachment
- Promotes a procoagulant endothelial phenotype
- Supports leukocyte recruitment into lung

Neutrophils cross the activated capillary wall



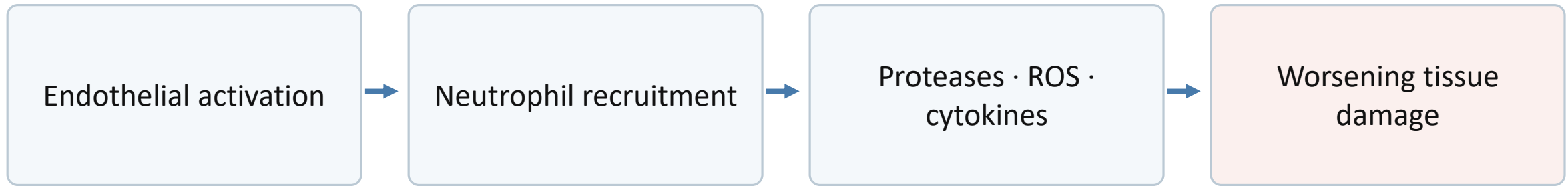
Activated neutrophils amplify damage

- Proteases can damage cellular and extracellular components.
- Reactive oxygen species contribute to inflammatory tissue injury.
- Cytokines reinforce recruitment and activation of inflammatory cells.
- This amplifies microvascular and alveolar epithelial damage.

NETs: A possible additional source of damage

- Neutrophil extracellular traps (NETs) may be released in ALI/ARDS.
- Experimental evidence supporting a direct damaging contribution.
- NETs supplement, rather than replace, protease and oxidant-mediated injury.
- The degree of contribution is not quantified in the supplied source.

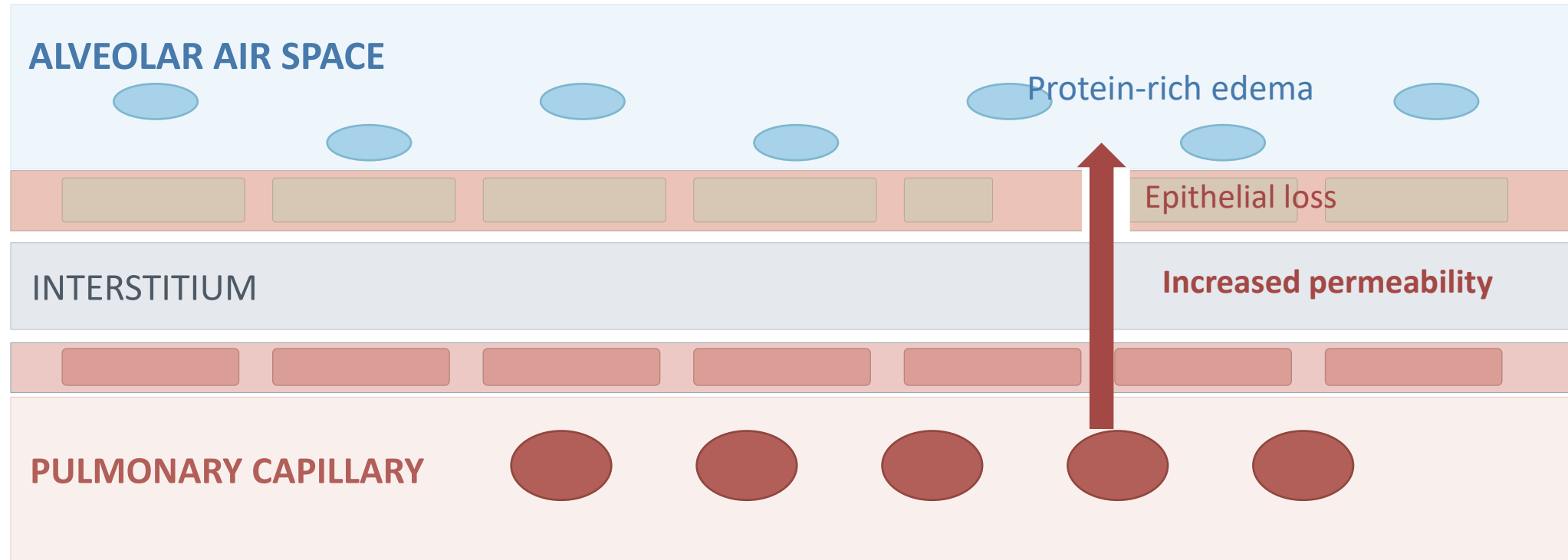
Inflammation creates a self-amplifying loop



Amplified inflammation feeds back to injure the barrier

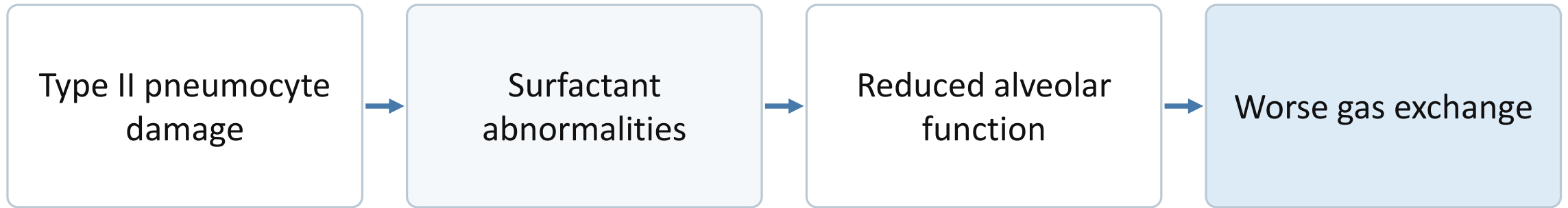
Further endothelial damage perpetuates permeability and leukocyte activation.

The damaged barrier permits alveolar exudation



Schematic · Endothelial–epithelial injury allows exudation into air spaces

Type II cell injury compromises surfactant



Surfactant disruption adds mechanical dysfunction to barrier leakage.

Hyaline membranes form from edema and cell debris

Exudative fluid component

- Protein-rich alveolar edema fluid
- Fibrin-rich deposits along injured walls
- Contributes the proteinaceous matrix

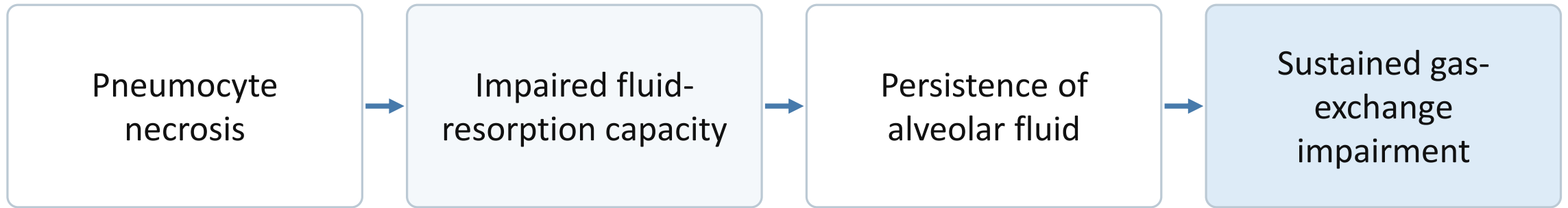
Necrotic cellular component

- Damaged pneumocyte remnants
- Cellular debris admixed with fibrin
- Combined material forms hyaline membranes

Hyaline membranes identify exudative DAD

- The membranes line injured alveolar walls.
- They are composed of fibrin-rich fluid and epithelial necrotic debris.
- They appear waxy on histologic sections.
- They are characteristic of DAD, but are not a separate ARDS diagnostic test.

Edema removal is impaired by epithelial injury



The same injury that causes flooding also slows fluid resolution.

ALI/ARDS is patchy at the functional level

Poorly aerated regions

- Lower regional compliance
- Alveolar edema and epithelial damage
- Persisting pulmonary perfusion

Relatively preserved regions

- Near-normal compliance may remain
- Ventilation can be relatively maintained
- Substantial within-lung heterogeneity

Perfused but underventilated units worsen hypoxemia

Relatively preserved unit

Ventilation preserved

Perfusion continues

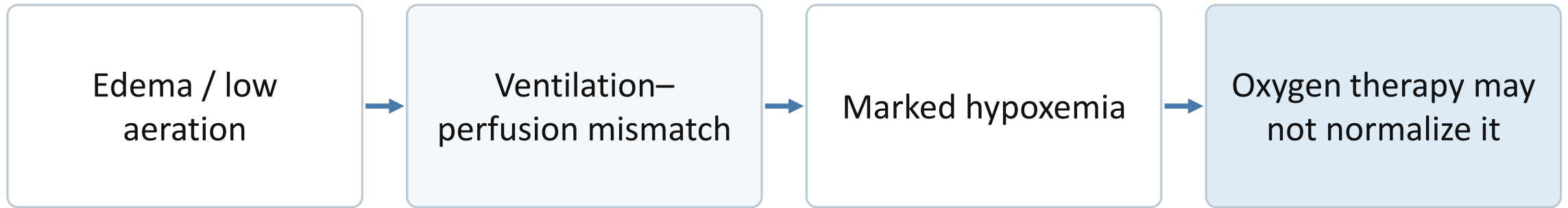
Poorly aerated injured unit

Ventilation ↓

Perfusion continues

Perfusion of poorly ventilated alveoli worsens arterial hypoxemia.

Why supplemental oxygen may be insufficient



Poorly aerated but perfused alveoli contribute to severe oxygenation defects.

Reduced lung compliance increases ventilatory demand

- Loss of functional surfactant contributes to stiff lungs.
- Some involved units become poorly aerated and low-compliance.
- Severe respiratory failure may require intubation.
- High ventilatory pressures may be necessary to maintain gas exchange.

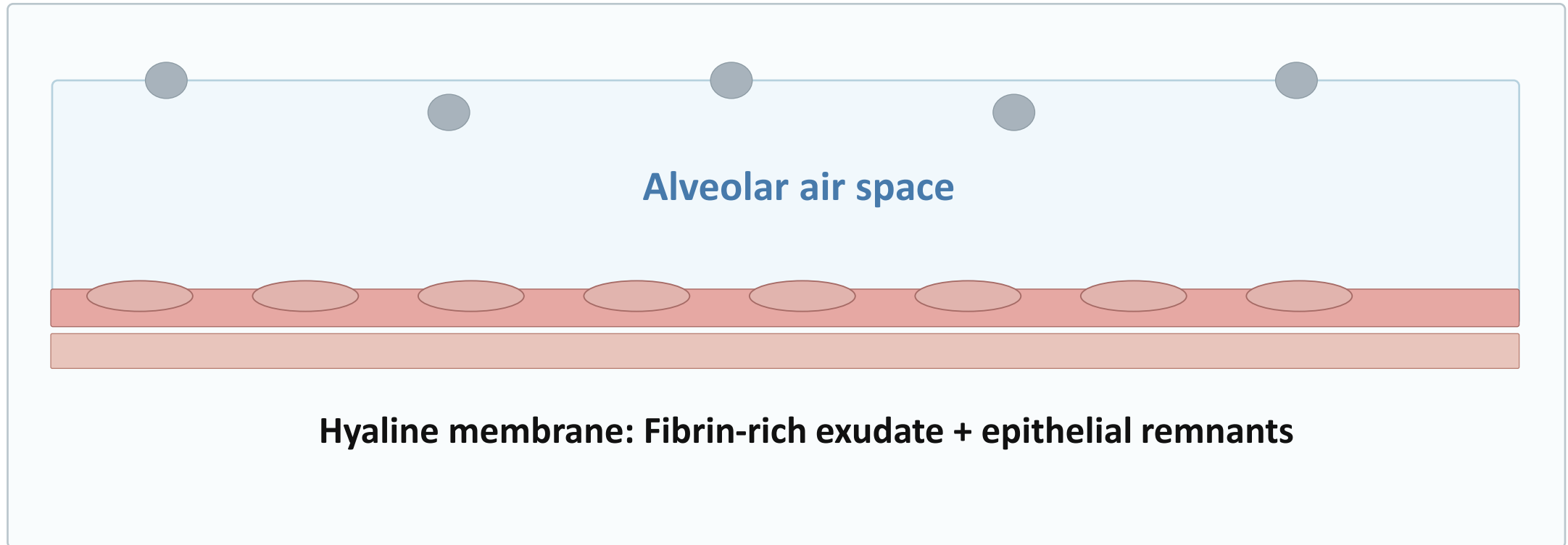
The exudative phase changes gross lung appearance

- Lungs become heavy and firm because of accumulated fluid and tissue injury.
- They are characteristically red and boggy.
- Capillary congestion and interstitial edema occur together.
- In more advanced involvement, alveolar spaces contain exudate.

Exudative DAD: Core microscopic changes

- Congestion accompanies interstitial and intraalveolar edema.
- Inflammation and fibrin deposition are present.
- Necrosis of alveolar epithelial cells contributes to tissue damage.
- Hyaline membranes line injured alveoli.

Schematic recognition of hyaline membranes



Schematic only — not H&E photomicrograph

Membrane composition explains its appearance

Derived from edema fluid

- Protein-rich exudate
- Fibrin accumulation
- Inspissated material along alveolar surfaces

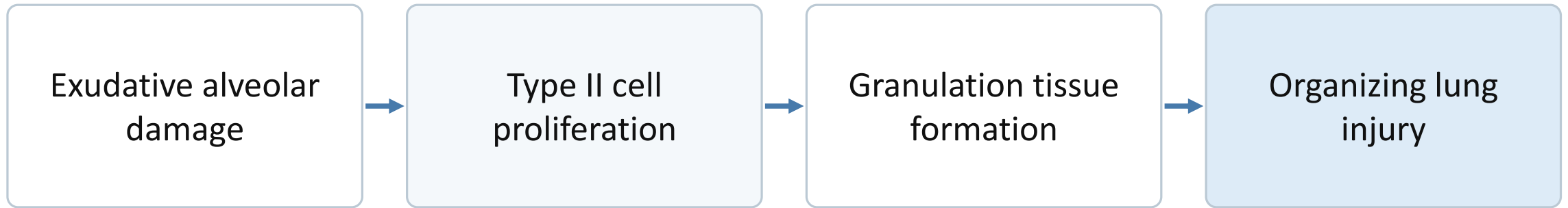
Derived from damaged epithelium

- Necrotic epithelial fragments
- Cellular debris
- Admixture with fibrinous exudate

Radiology mirrors uneven airspace injury

- Acute disease can show patchy ground-glass opacities.
- Consolidation may coexist with ground-glass regions.
- Diffuse bilateral infiltrates develop with clinical respiratory failure.
- Imaging findings complement but do not replace pathologic context.

Organizing injury follows the exudative phase



Inflammatory injury is followed by regeneration and fibroblastic organization.

Type II pneumocytes participate in repair

- Proliferation of surviving type II pneumocytes is characteristic of organizing DAD.
- Residual type II cells can replace lost type I pneumocytes.
- Re-epithelialization helps restore the alveolar lining.
- Repair can progress over an extended period.

Granulation tissue appears in organizing DAD

- The organizing phase involves granulation tissue in alveolar walls.
- Granulation tissue can also develop within alveolar spaces.
- Fibroblastic activity follows prior injury and inflammation.
- The extent of organization influences subsequent structural recovery.

DAD evolves through recognizable responses

Exudative injury

Capillary leak; Edema; Epithelial death; Hyaline membranes



Organizing response

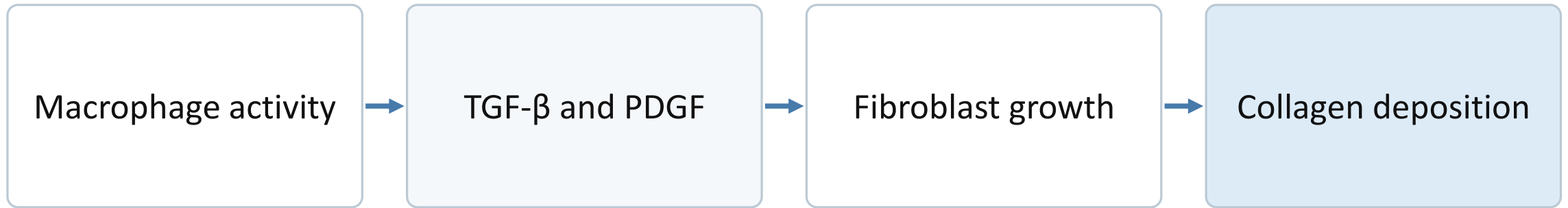
Type II pneumocyte proliferation and granulation tissue



Divergent outcome

Alveolar repair and recovery or collagen deposition with fibrosis

Fibrogenic mediators follow inflammatory clearance

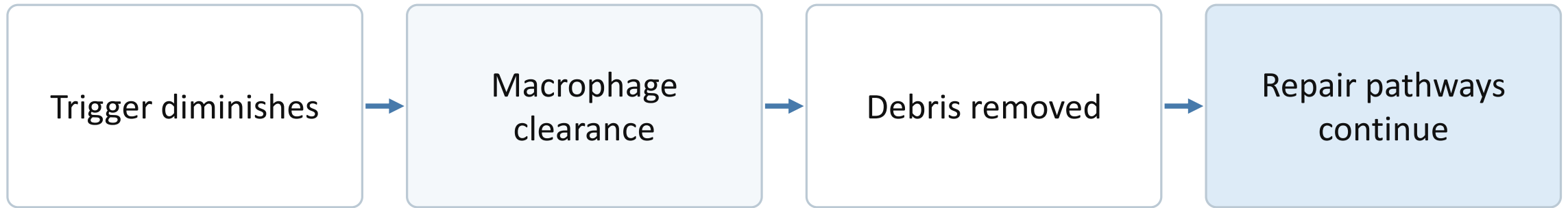


Tissue repair can become a fibrogenic response after severe injury.

Collagen deposition can remodel alveolar walls

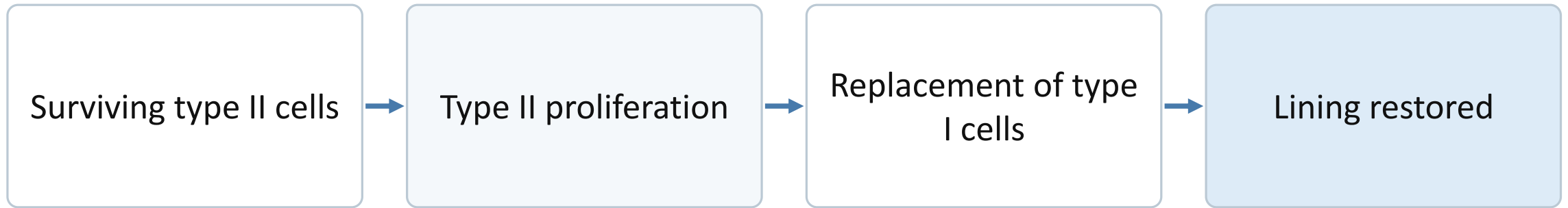
- Fibroblasts deposit collagen in previously injured alveolar septa.
- The wall becomes fibrotic when repair remains fibroproliferative.
- Fibrosis reduces normal architectural flexibility.
- Persistent interstitial fibrosis can contribute to chronic pulmonary disease.

Inflammatory clearance is part of resolution



Resolution requires the original inflammatory trigger to subside.

Epithelial repair reconstitutes alveolar lining



Surviving type II cells supply regenerative potential for the epithelial surface.

Endothelial integrity can also recover

- Proliferation of uninjured capillary endothelial cells supports restoration.
- Repair must occur on the vascular side as well as in the alveolar lining.
- Edema resolution becomes more feasible as epithelial function recovers.
- The balance between restoration and fibrosis helps determine outcome.

The recovery pathway is not uniform

Recovery / resolution

- Inflammatory stimuli subside
- Debris clearance and cell regeneration
- Most survivors recover pulmonary function

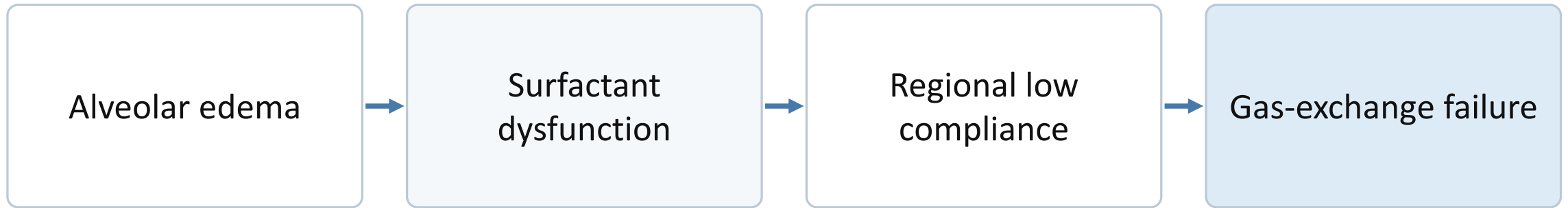
Persistent structural disease

- Fibroproliferation and collagen deposition
- Residual interstitial fibrosis
- Potential chronic pulmonary limitation

Clinical onset is often abrupt and severe

- Profound dyspnea and rapid breathing are prominent early findings.
- Progressive hypoxemia may produce cyanosis.
- Respiratory failure evolves with increasing bilateral lung opacities.
- The syndrome is commonly observed in critically ill patients.

Respiratory failure reflects several coupled lesions



Barrier failure, surfactant loss, and regional low compliance act together.

Morphology, physiology, and imaging align

Structural lesion

- Interstitial / alveolar edema
- Hyaline membranes and cell necrosis
- Uneven airspace involvement

Functional consequence

- Impaired diffusion and ventilation
- Reduced functional surfactant
- V/Q mismatch and refractory hypoxemia

Outcomes depend on injury and systemic illness

- Fatal outcomes may be associated with sepsis and multiorgan failure.
- Severe lung injury itself also contributes to mortality.
- Most survivors recover pulmonary function.
- A minority develop interstitial fibrosis with chronic pulmonary disease.

Historical ICU data: Interpret within its period

- A 2016 study conducted in ICUs across 50 countries.
- ARDS accounted for 10.4% in that reported ICU study.
- Reported mortality was 35%, 40%, and 46% for mild, moderate, and severe ARDS.
- These are historical study estimates—not present-day universal probabilities.

Host factors may modify risk

- Epidemiologic studies cited link smoking with worse ARDS prognosis.
- Alcohol use disorder is also associated with greater susceptibility and poorer outcomes.
- Genetic variants associated with risk include loci connected to inflammation or coagulation.
- The supplied text does not define a clinical genetic risk test.

Injury edema and hemodynamic edema differ

Feature	Hemodynamic pulmonary edema	Microvascular injury edema
Principal mechanism	Hydrostatic pressure increase	Endothelial / epithelial injury
Common context	Left-sided cardiac failure	Sepsis, aspiration, severe lung injury
Fluid character	Transudate	Protein-rich inflammatory exudate
Characteristic histology	Congestion; Heart-failure cells possible	DAD; Hyaline membranes may develop

Clinical case: Septic patient with bilateral edema

A critically ill patient with sepsis develops abrupt breathlessness, hypoxemia, and bilateral pulmonary opacities. No cardiac failure is identified.

Interpretation prompts

- What makes permeability edema likely?
- Which pulmonary cell surface is activated early?
- Name the characteristic histologic injury pattern.

Case interpretation: Sepsis-associated lung injury

- Systemic mediators may directly activate pulmonary microvascular endothelium.
- Neutrophil recruitment and epithelial injury produce permeability exudation.
- The associated histologic pattern is diffuse alveolar damage.
- Hyaline membranes may occur in the exudative phase.

Clinical case: Hydrostatic or permeability edema?

One patient with left-sided cardiac failure develops congested, fluid-filled lungs. Another has acute respiratory failure after gastric aspiration.

Interpretation prompts

- Which is more consistent with increased hydrostatic pressure?
- Which is more consistent with direct alveolar wall injury?
- How would the expected edema character differ?

Case interpretation: Identify the mechanism

- Left-sided heart failure commonly raises hydrostatic pressure and produces transudative edema.
- Gastric aspiration directly injures lung tissue and may cause inflammatory edema.
- Microvascular injury can cause DAD with hyaline membranes.
- Clinical context and tissue changes distinguish the mechanisms.

Clinical case: Organizing lung injury

Following severe acute lung injury, surviving tissue shows type II pneumocyte proliferation, granulation tissue, and emerging collagen deposition.

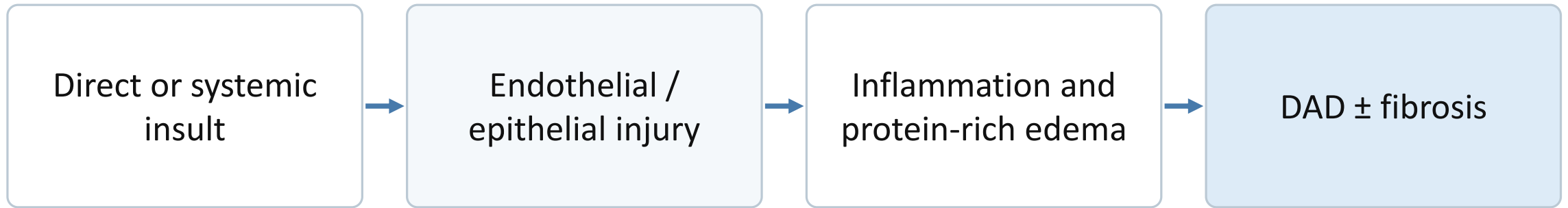
Interpretation prompts

- Which phase of diffuse alveolar damage is represented?
- What cells rebuild the alveolar epithelial surface?
- What could determine persistent physiologic impairment?

Case interpretation: Organizing DAD

- The proliferative or organizing phase follows exudative alveolar injury.
- Residual type II pneumocytes regenerate lining cells, including type I cells.
- Fibrogenic mediators stimulate fibroblast growth and collagen deposition.
- Extensive fibrosis can contribute to chronic lung dysfunction.

Integrated pathogenesis of injury-related edema



Histologic DAD and the clinical ARDS phenotype are related but distinct.

Five mechanistic points to retain

- The defining mechanism is alveolar wall injury with increased vascular permeability.
- Local epithelial damage or systemic inflammation can activate endothelium.
- Neutrophil mediators sustain an injury–inflammation feedback loop.
- Protein-rich edema plus epithelial debris produces hyaline membranes.
- Recovery requires epithelial/endothelial repair; Some cases evolve toward fibrosis.

Primary references and source boundaries

Robbins, Cotran & Kumar

Pathologic Basis of Disease, 11th edition (2026), Chapter 15: The Lung

Pulmonary edema, acute lung injury, ARDS, and diffuse alveolar damage; printed pages 614–617.

Relevant source tables: 15.1 and 15.2; referenced textbook figures: 15.3 and 15.4.