

Neonatal Respiratory Distress Syndrome

Surfactant deficiency, hyaline membranes, and the consequences of premature lung development

Hyaline membrane disease

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

- Explain how surfactant deficiency produces progressive atelectasis and respiratory failure.
- Recognize the characteristic gross and microscopic morphology of hyaline membrane disease.
- Relate risk factors, clinical evolution, prevention, and treatment to the underlying mechanism.
- Explain the pathogenesis of retinopathy of prematurity and bronchopulmonary dysplasia.

Respiratory distress in newborns has several causes

Surfactant-deficient RDS

- Most common cause described in the neonatal section
- Also called hyaline membrane disease
- Strongly linked to prematurity

Other causes listed

- Excessive maternal sedation
- Fetal head injury during delivery
- Aspiration of blood or amniotic fluid
- Intrauterine hypoxia from cord compression

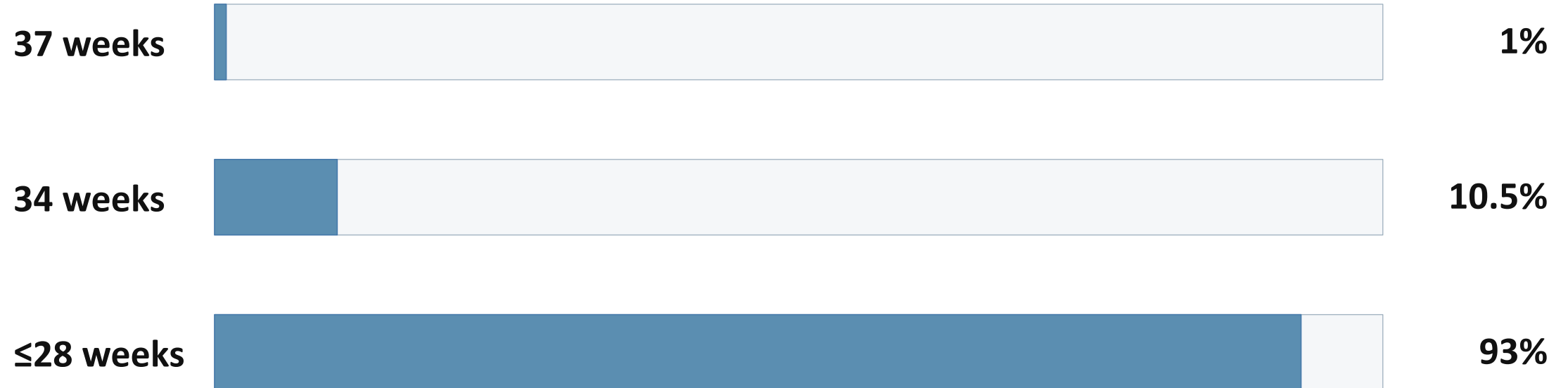
Hyaline membrane disease is a form of neonatal RDS

- Pulmonary immaturity creates inadequate surfactant at the alveolar air–liquid interface.
- Repeated alveolar collapse initiates epithelial and endothelial injury.
- Protein-rich eosinophilic membranes form within peripheral airspaces.

The membrane is a consequence of injury—not the primary initiating defect.

RDS risk increases steeply with prematurity

Reported incidence without preventive treatment



Source: Robbins, 11th ed. • Not a contemporary population estimate

- Textbook incidence values in infants without preventive treatment.
- Gestational maturity is a major determinant of surfactant availability.

Prematurity and growth restriction are not equivalent

Preterm infant

- Born before full gestational maturation
- Weight is often appropriate for gestational age
- Lung immaturity underlies classic RDS

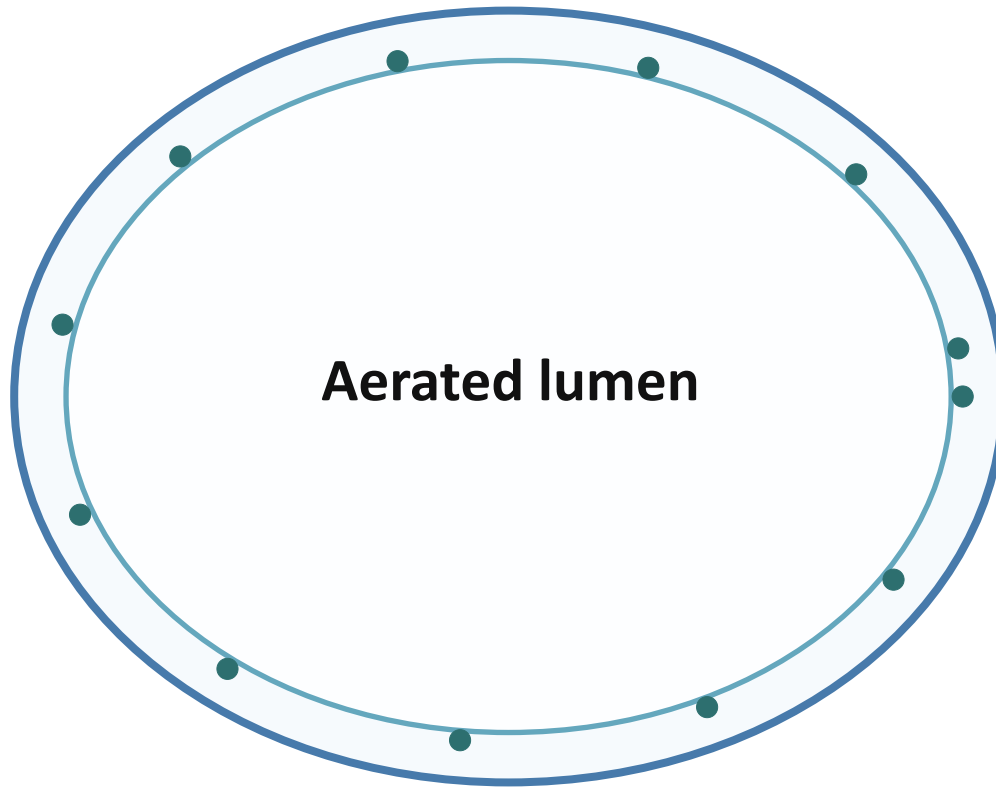
Growth-restricted infant

- Small for gestational age due to impaired fetal growth
- May be born at term
- Intrauterine stress may accelerate surfactant maturation

Clinical associations identify vulnerable neonates

- Affected infants are almost always preterm and often appropriate in weight for their gestational age.
- RDS is associated with male sex.
- Infants of diabetic mothers have a higher risk.
- Cesarean delivery, particularly before onset of labor, is another risk association.

Surfactant acts at the alveolar air–liquid interface



Schematic: Surfactant film at air–liquid interface

- A lipid–protein film lowers surface tension along the fluid-lined alveolar surface.
- Lower surface tension reduces the pressure needed to keep alveoli open.

Pulmonary surfactant is a lipid–protein complex

Lipid components

- Predominantly dipalmitoyl phosphatidylcholine (lecithin)
- Smaller amounts of phosphatidylglycerol

Surfactant proteins

- Hydrophilic: SP-A and SP-D
- Hydrophobic: SP-B and SP-C

Phosphatidylcholine is the predominant surfactant lipid

- Dipalmitoyl phosphatidylcholine is the dominant phospholipid.
- Surfactant lipids act with hydrophobic proteins at the alveolar air–liquid boundary.
- Surface-tension reduction is central to preventing alveolar collapse.

A compositional defect becomes a mechanical lung defect.

SP-A and SP-D participate in innate host defense

SP-A

Hydrophilic surfactant-associated glycoprotein.

SP-D

Hydrophilic surfactant-associated glycoprotein.

Function

Both contribute to pulmonary host defense (innate immunity).

SP-B and SP-C support low surface tension

SP-B

Hydrophobic surfactant-associated protein.

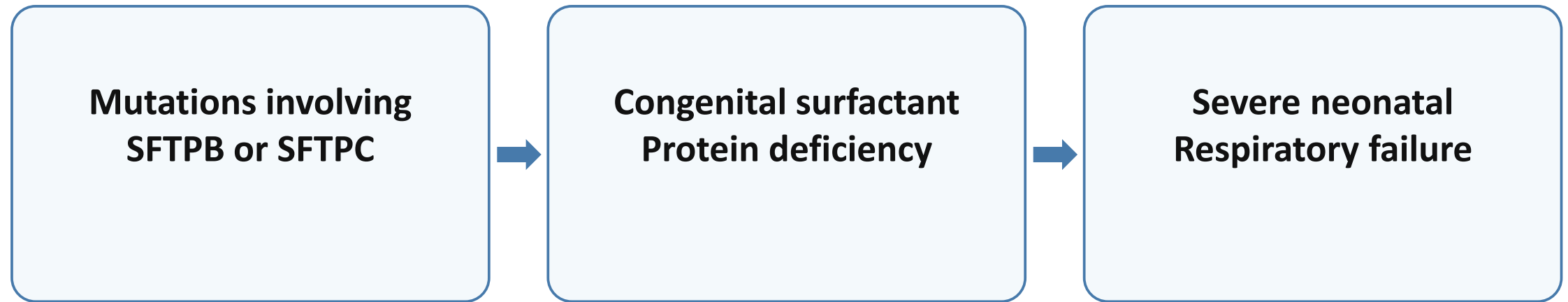
SP-C

Hydrophobic surfactant-associated protein.

Function

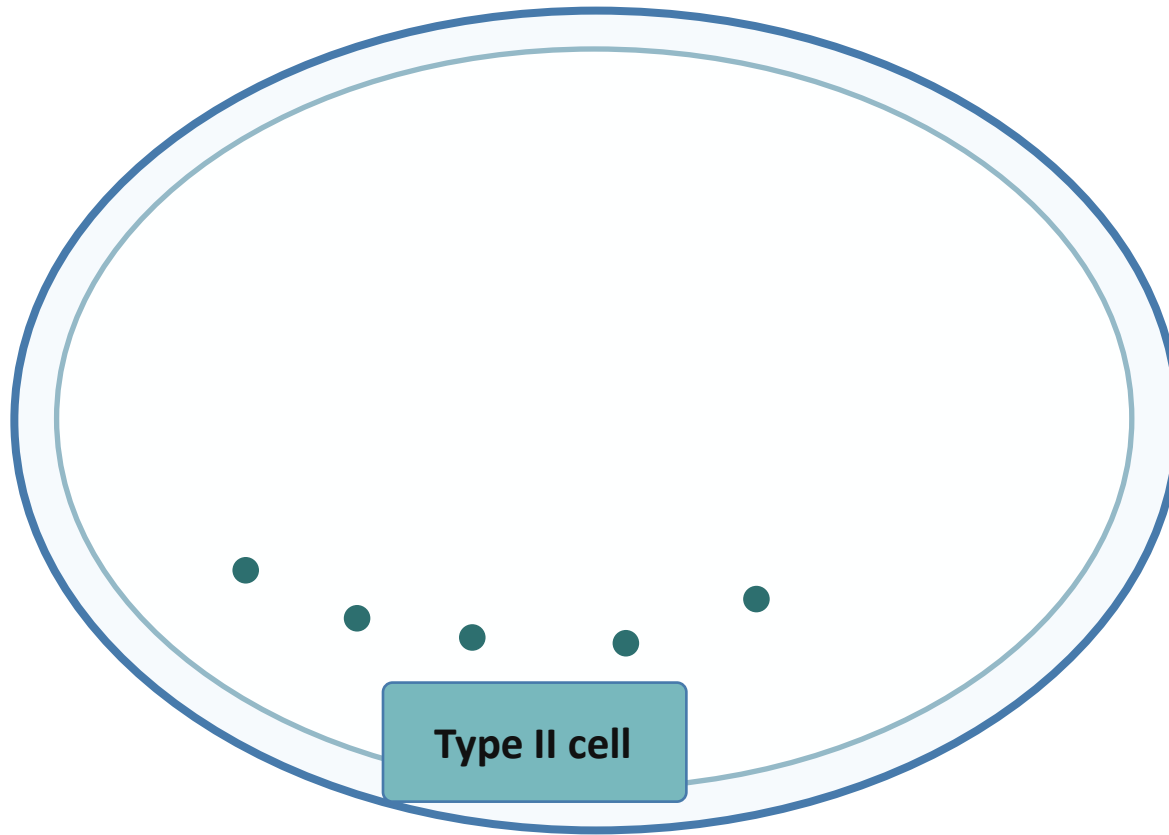
Cooperate with surfactant lipids to lower alveolar surface tension.

Congenital protein deficiency illustrates surfactant necessity



- This molecular example supports the essential mechanical role of surfactant proteins.

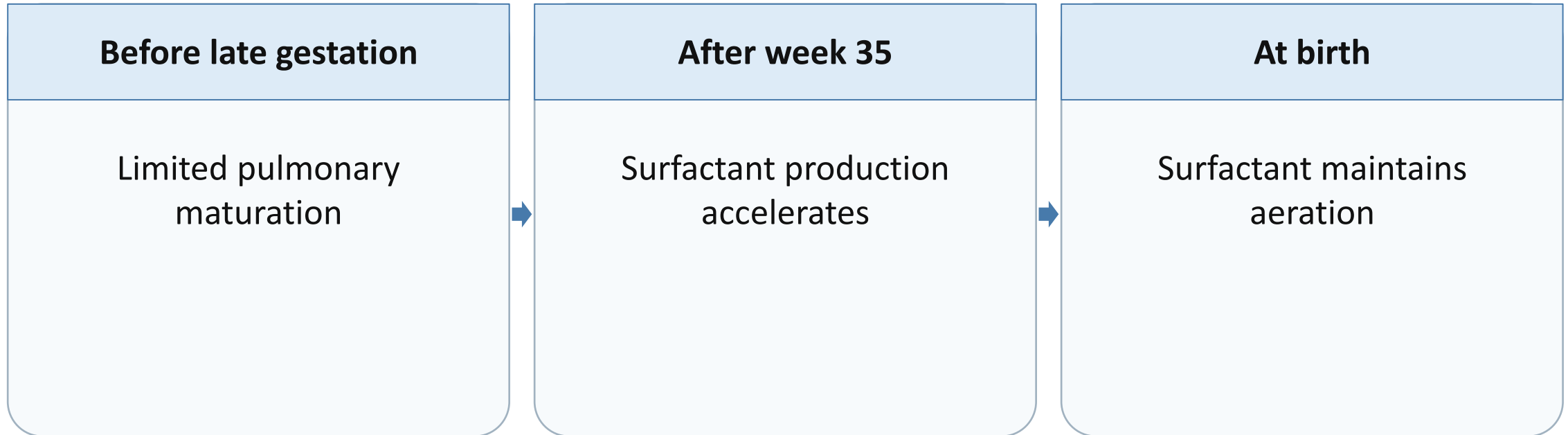
Type II pneumocytes are the source of surfactant



- Type II alveolar epithelial cells synthesize and release surfactant.
- Functional immaturity of this cell population limits surfactant availability after preterm birth.

Schematic: Epithelial source of surfactant

Surfactant production accelerates late in gestation



- The timetable helps explain the marked risk gradient by gestational age.

Hormones and growth factors regulate surfactant synthesis

Glucocorticoids

Particularly important promoters of fetal lung maturation.

Other hormones

Insulin, prolactin, and thyroxine modulate synthesis.

Growth factors

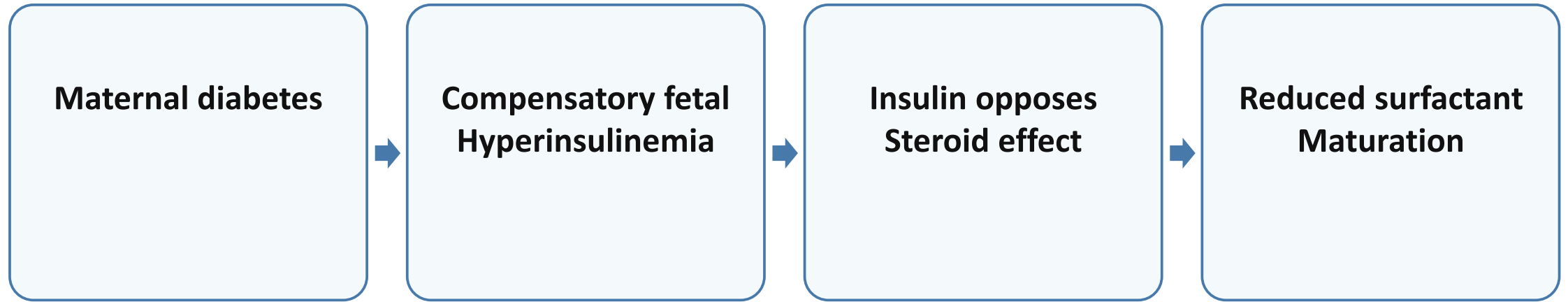
TGF- β is among the regulators listed.

Intrauterine stress may reduce RDS risk



- This is a relative protective association, not a claim that growth restriction is desirable.

Maternal diabetes can delay functional maturation



- The source presents this mechanism as one explanation for increased RDS risk.

Labor is associated with increased surfactant synthesis

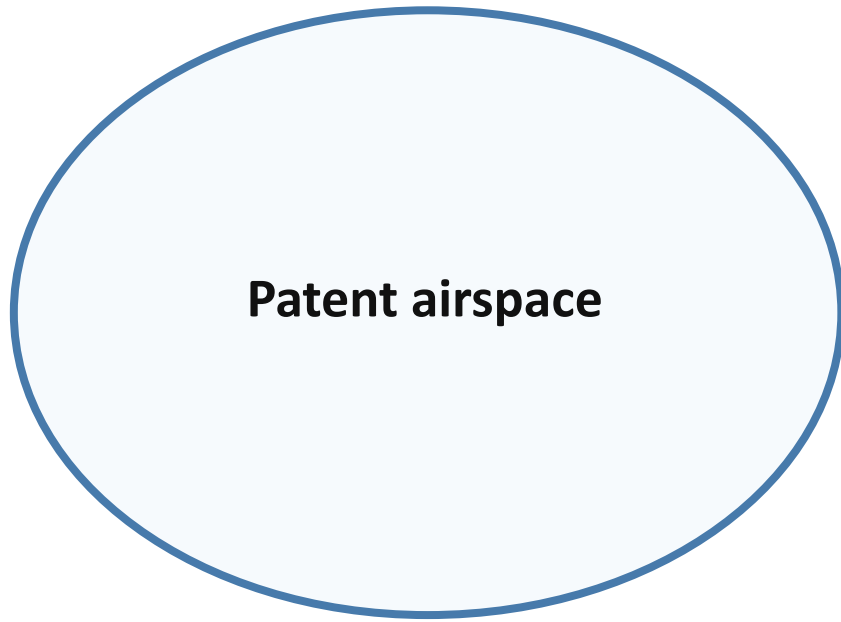
Labor before birth

- Labor increases surfactant synthesis.
- Favors functional adaptation at delivery.

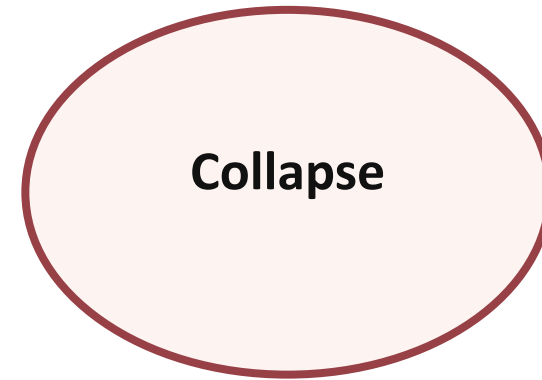
Cesarean before labor

- Lacks the labor-associated stimulus.
- May increase RDS risk.

Surfactant reduces the pressure needed for patency



Surfactant sufficient

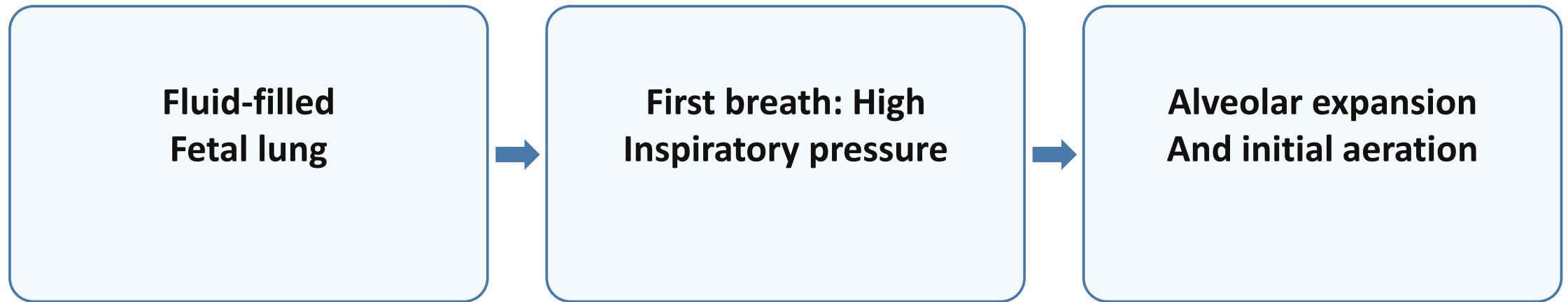


Surfactant deficient

Schematic: Relative expansion only

- Low surface tension supports expansion at physiologically attainable pressures.
- High surface tension promotes collapse and increases respiratory work.

The first breath requires a large inspiratory effort



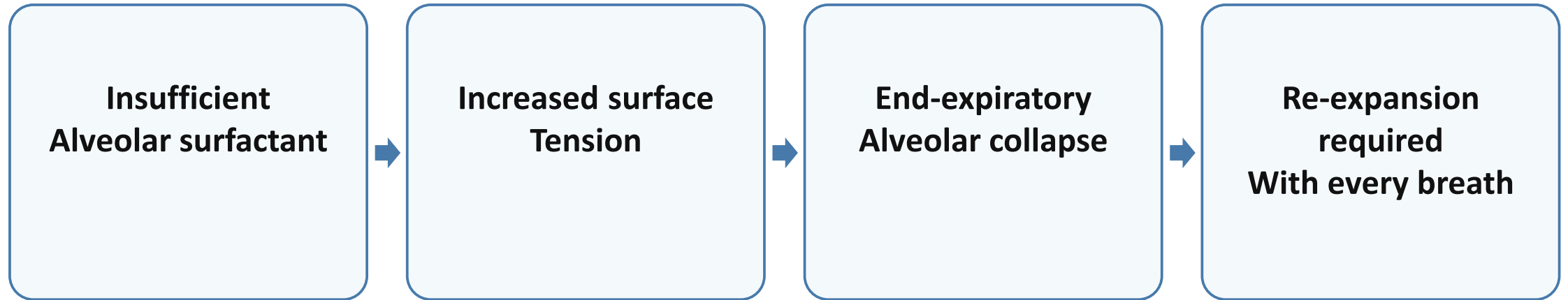
- A normal surfactant film helps preserve this newly achieved aeration.

After the first breath, surfactant preserves residual air

- With adequate surfactant, lungs retain up to 40% of the residual air volume after the first breath (Robbins wording).
- Retained air means subsequent breaths require substantially lower inspiratory pressures.
- Failure to preserve this air creates repetitive reopening of collapsed units.

The decisive function is sustaining aeration from one breath to the next.

Surfactant deficiency causes repeated collapse



An immature chest wall compounds respiratory effort

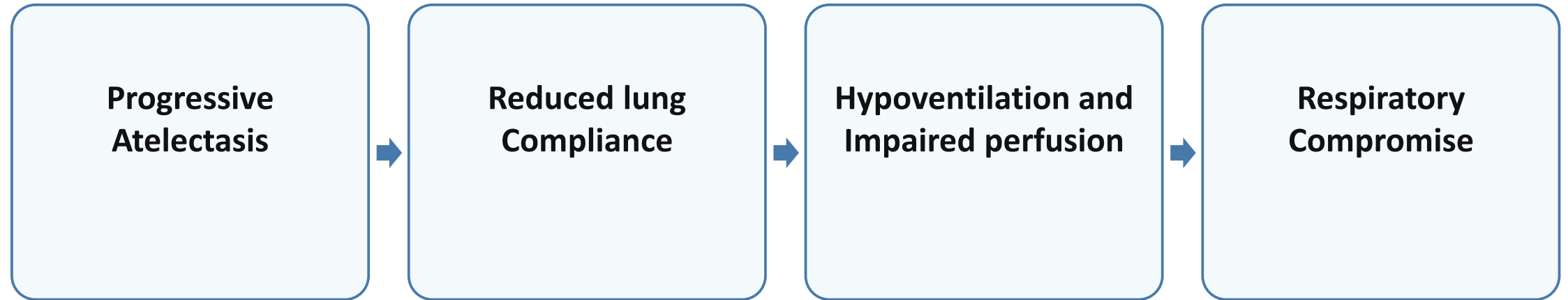
Stiff atelectatic lung

- Low compliance: Difficult to inflate
- Each breath requires high pressure

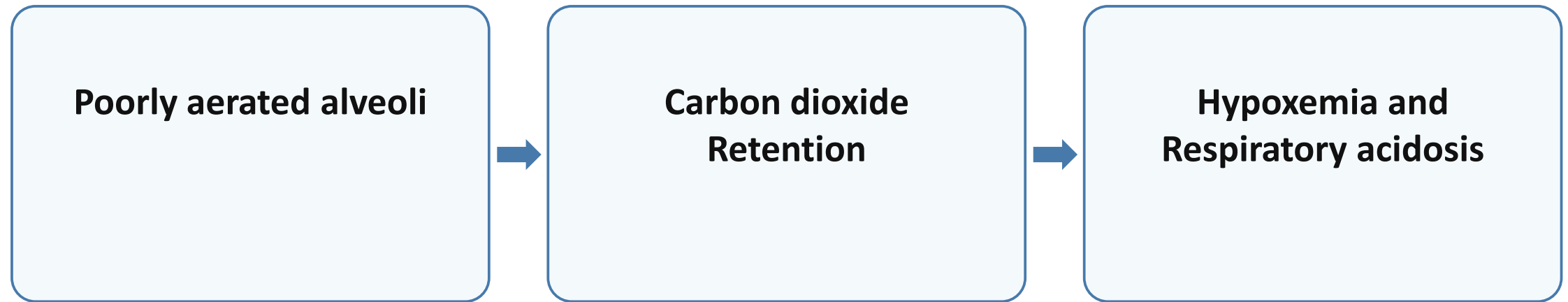
Soft thoracic wall

- Pulled inward during diaphragmatic descent
- Chest-wall retraction worsens work of breathing

Atelectasis progresses to impaired ventilation

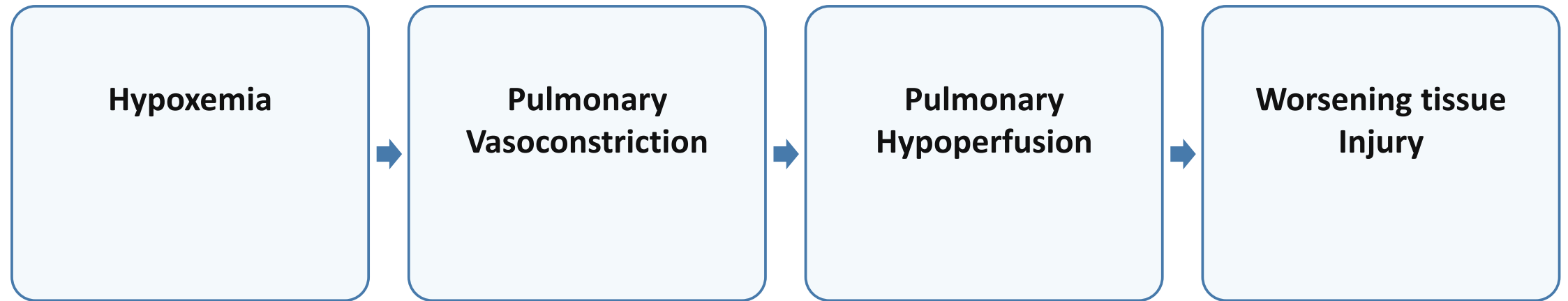


Gas exchange failure causes hypoxemia and acidosis



- The source links these abnormalities to downstream pulmonary vascular and epithelial injury.

Hypoxemia stimulates pulmonary vasoconstriction



Endothelial and epithelial damage occur together

Endothelial injury

- Increased vascular permeability
- Plasma constituents leak toward alveolar airspaces

Epithelial injury

- Injury and necrosis of lining cells
- Necrotic cellular debris enters small airways

Plasma leakage creates protein-rich alveolar exudate

**Microvascular
Endothelial damage**



**Plasma proteins and
Fibrin enter airspaces**



**Proteinaceous material
Coats injured airways**

Cell necrosis contributes to membrane formation

**Type II pneumocyte
Injury and necrosis**

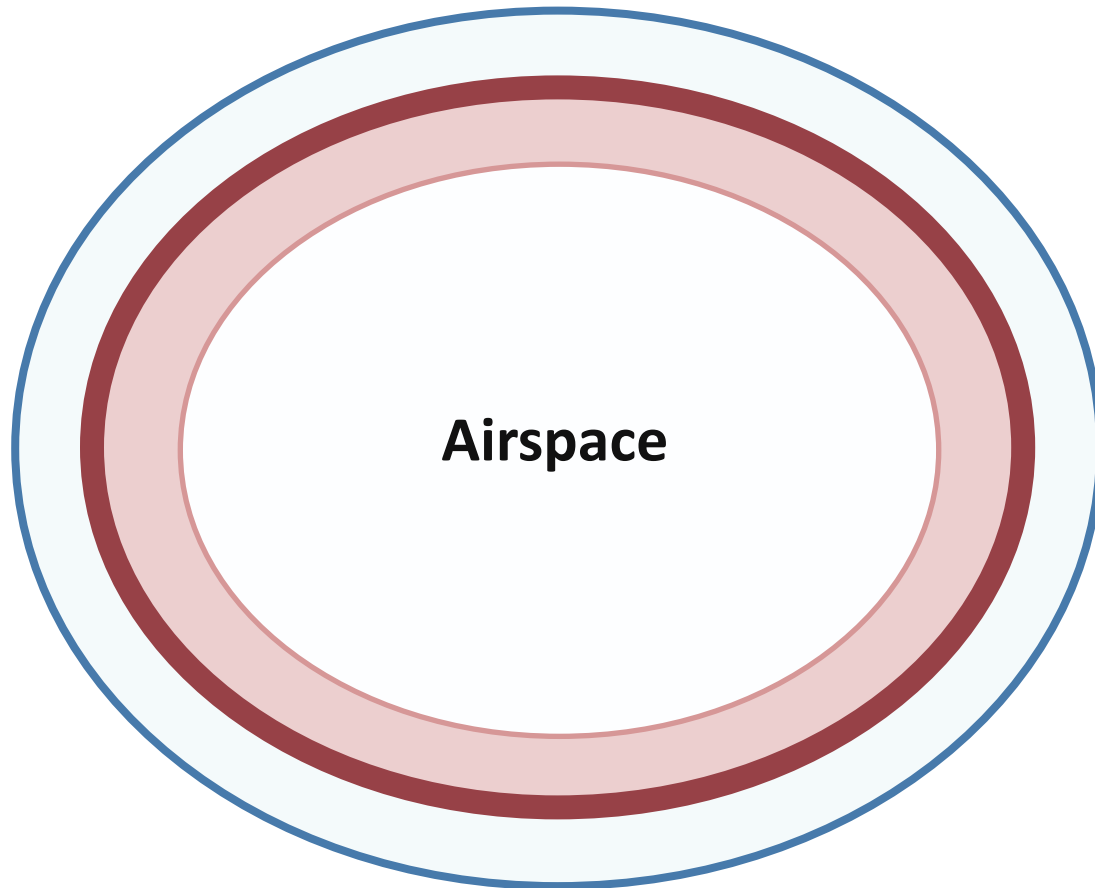


**Cellular debris in distal
Airways and ducts**



**Debris admixed with
Fibrin-rich exudate**

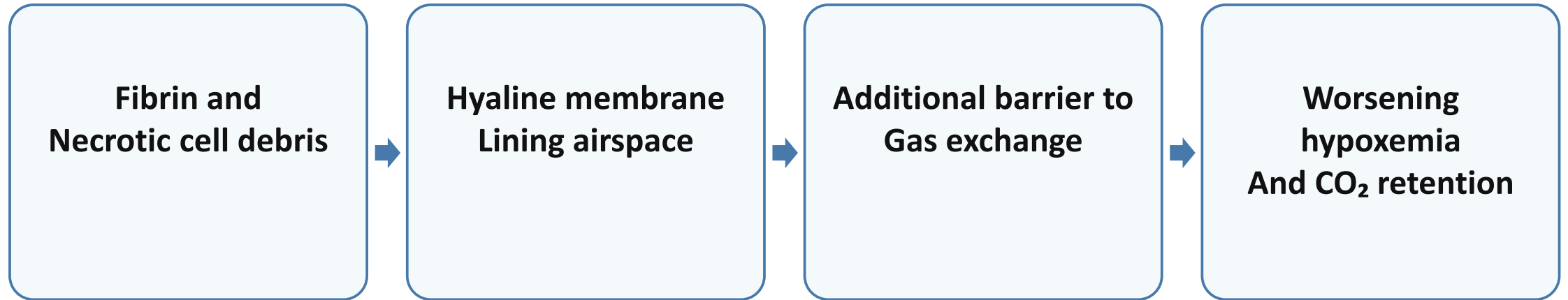
Hyaline membranes are a secondary injury product



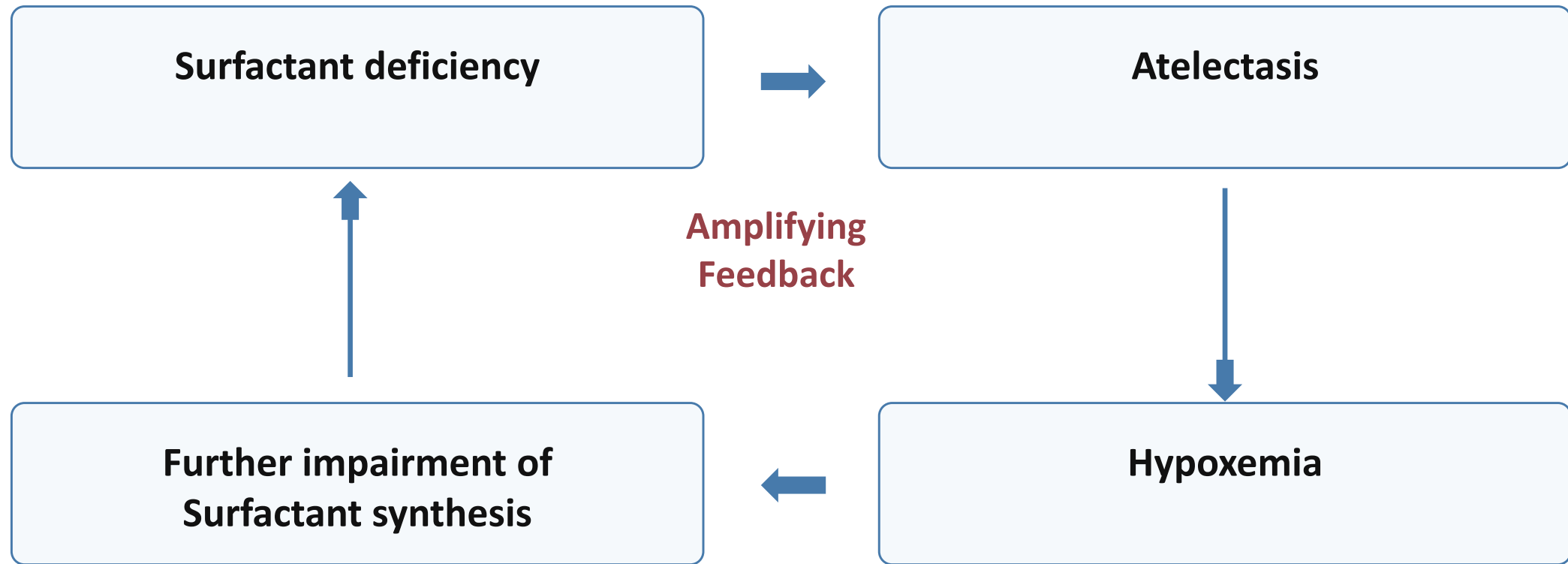
Schematic: Membrane is not an H&E image

- Eosinophilic material lines respiratory bronchioles, alveolar ducts, and alveoli.
- Composition: Fibrin plus cellular debris, chiefly from necrotic type II pneumocytes.

Hyaline membranes further impair gas exchange

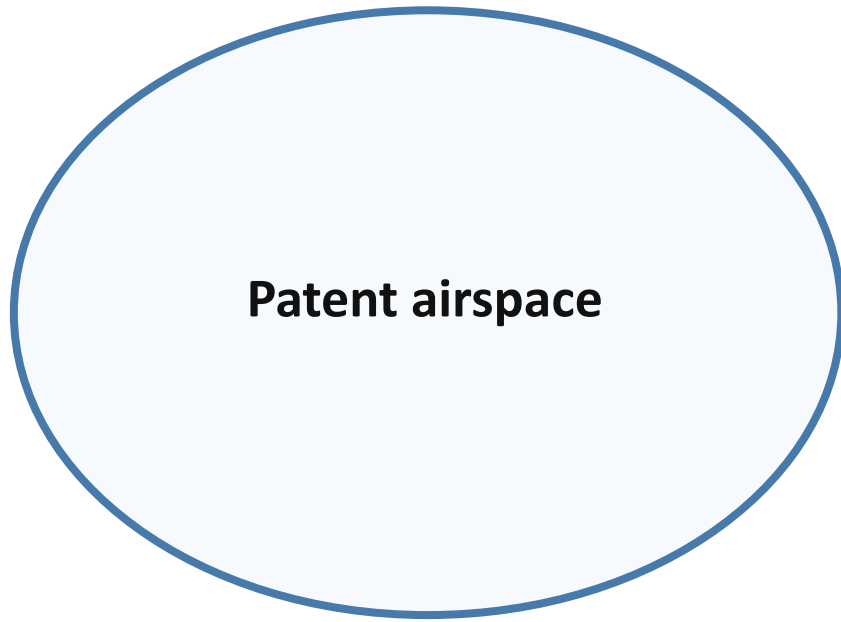


RDS reinforces itself through a vicious cycle

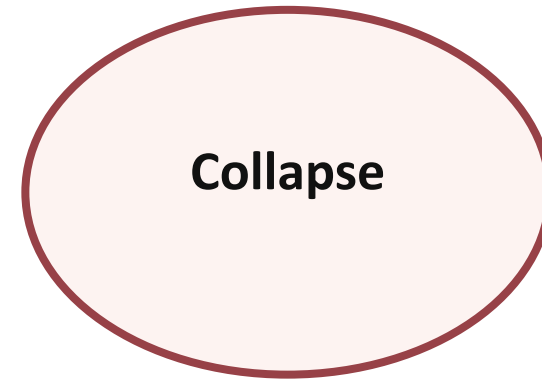


- The feedback loop helps explain clinical deterioration after an initially adequate transition.

Normal aeration contrasts with RDS atelectasis



Surfactant sufficient



Surfactant deficient

Schematic: Relative expansion only

- Normal surfactant preserves expanded alveolar units.
- RDS lungs contain poorly inflated or collapsed distal airspaces.

Gross lungs are solid and poorly aerated

- Lungs are usually of normal size but have an airless, firm, liver-like character.
- They are described as reddish purple.
- This appearance reflects widespread lack of aerated lung tissue.

Grossly normal size does not imply normal alveolar aeration.

Affected lungs may sink in water

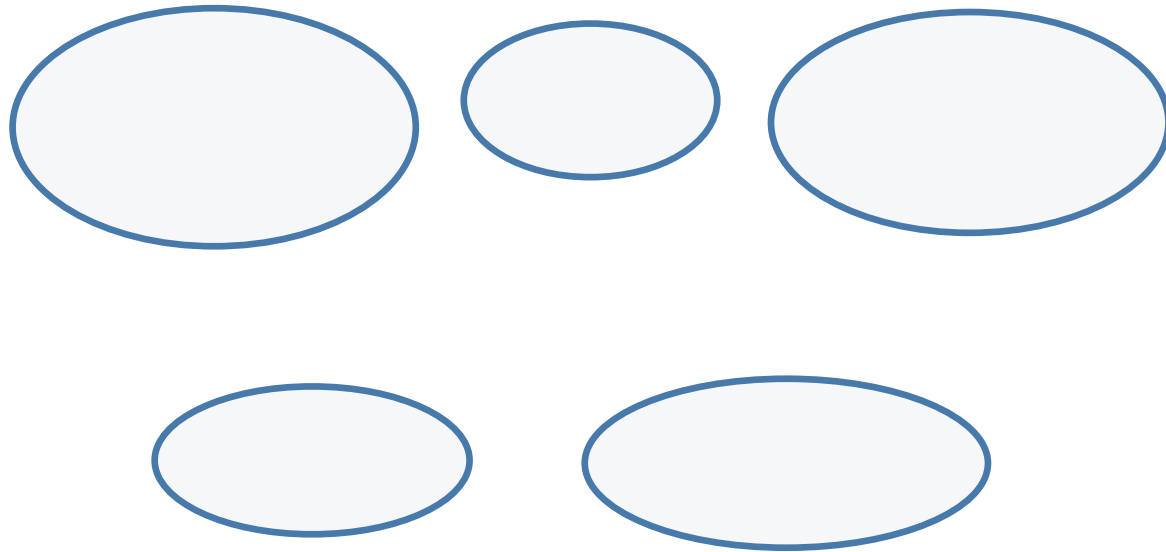
Aerated lung

- Entrapped air provides buoyancy.
- Normal postnatal ventilation introduces air.

RDS lung

- Relative lack of entrapped air
- Tends to sink in water at autopsy

Alveolar development and inflation are impaired



- Alveoli are poorly developed and commonly collapsed.
- Remaining immature airspaces may be lined by cuboidal epithelium.

Immature, variably collapsed airspaces

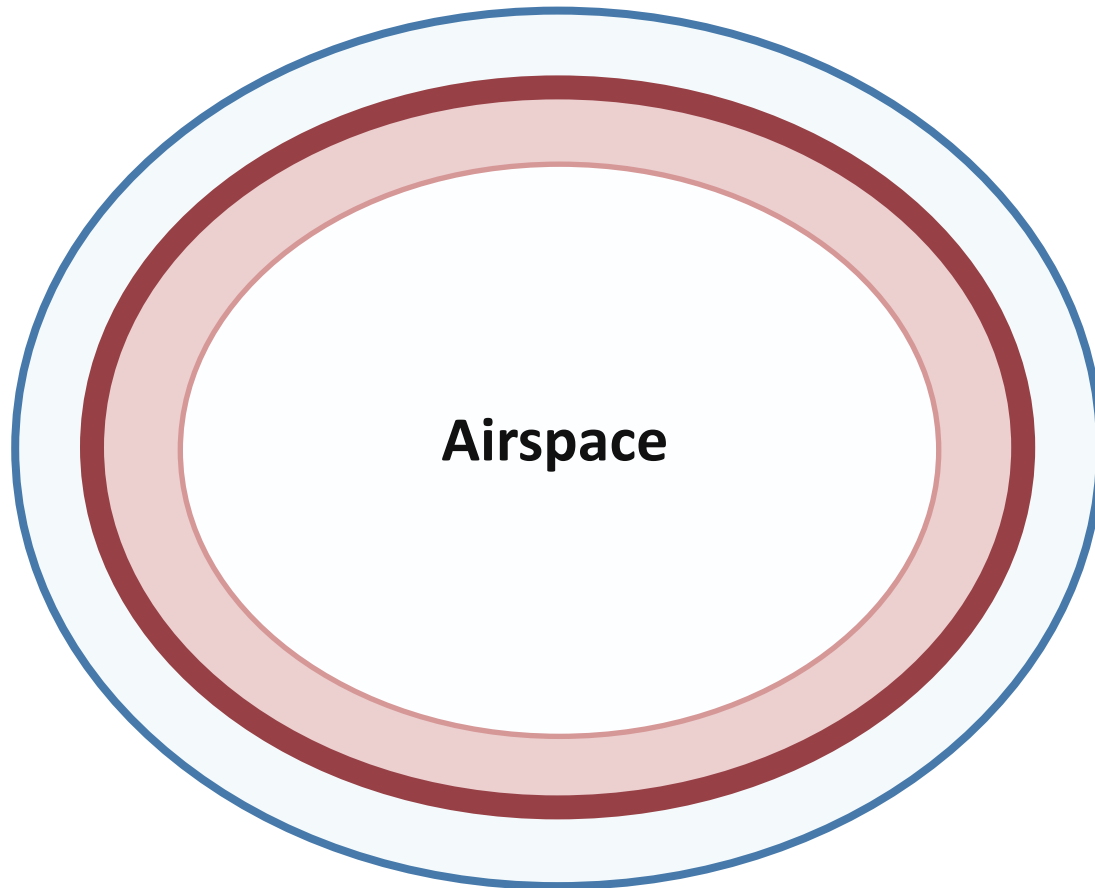
Schematic—not histologic evidence

Necrotic debris is prominent in early fatal disease

- Early in the disease, necrotic material is present in terminal bronchioles and alveolar ducts.
- It later becomes incorporated into hyaline membranes.
- This temporally links epithelial damage with the classical histologic lesion.

Early cell injury precedes organized membrane formation.

The hyaline material lines peripheral airspaces



Schematic: Membrane is not an H&E image

- Respiratory bronchioles, alveolar ducts, and alveoli can be outlined by hyaline material.
- The distribution is within distal airspaces, not simply inside blood vessels.

Eosinophilic membranes contain fibrin and cell debris

Membrane material

- Extravasated fibrin and plasma proteins
- Necrotic cellular debris, predominantly type II cells

Associated tissue response

- Collapsed or immature distal airspaces
- Remarkably little neutrophilic inflammation

Neutrophilic inflammation is notably sparse

- Hyaline membranes are not accompanied by a marked neutrophilic infiltrate.
- The lesion reflects epithelial–endothelial injury and plasma leakage, not a neutrophil-dominant process.
- Interpret the membranes in the context of prematurity and respiratory failure.

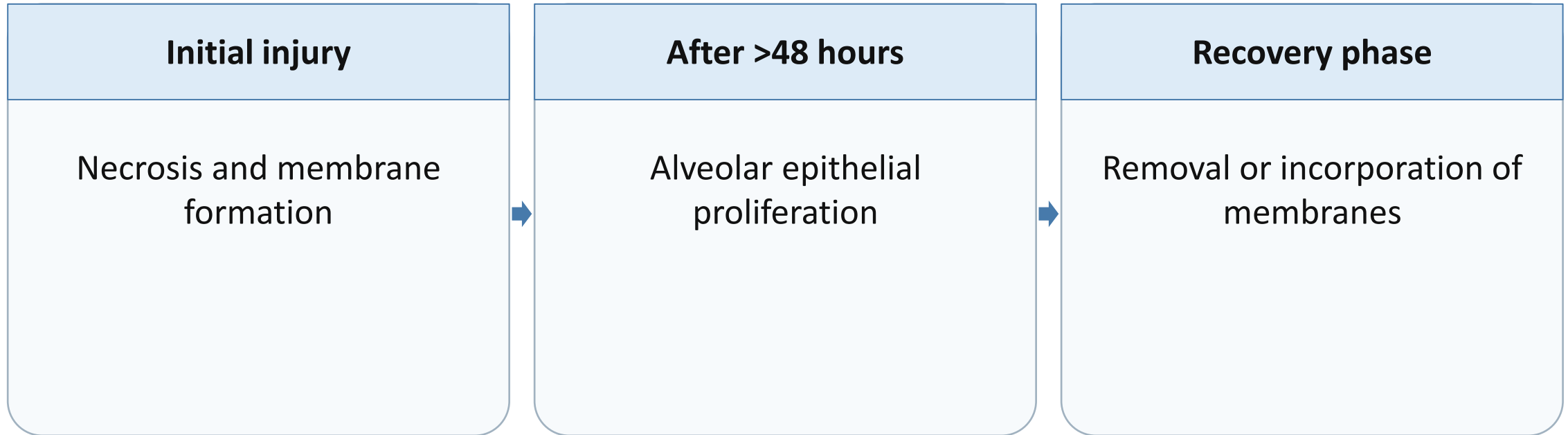
Protein-rich membranes should not be mistaken for a purulent exudate.

The characteristic lesions require postnatal breathing

- These lesions are never seen in stillborn infants.
- The pathogenesis depends on pulmonary transition, repeated atelectasis, and postnatal injury.
- Timing is therefore an important clue to the lesion mechanism.

Hyaline membranes are a postnatal pathological response.

Survivors beyond 48 hours show epithelial repair



Membranes may detach and undergo clearance

**Epithelial growth
Beneath membrane**



**Membrane separation
Into airspace**

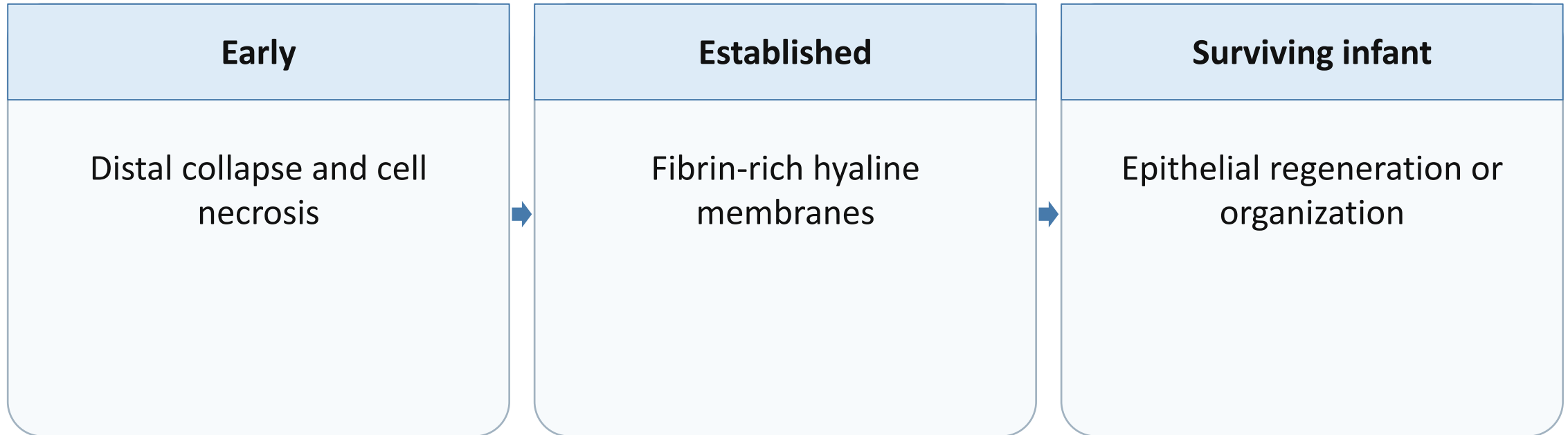


**Partial digestion or
Macrophage clearance**

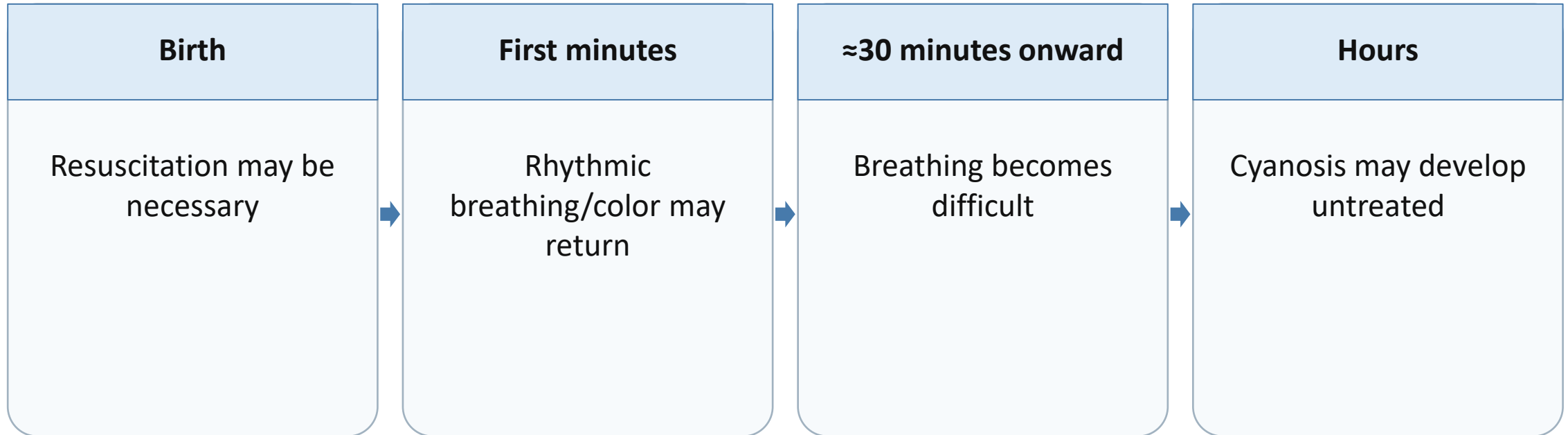
Persistent membranes may become organized



Histologic changes follow a recognizable sequence



Initial stabilization may precede deterioration



Untreated disease produces progressive respiratory distress

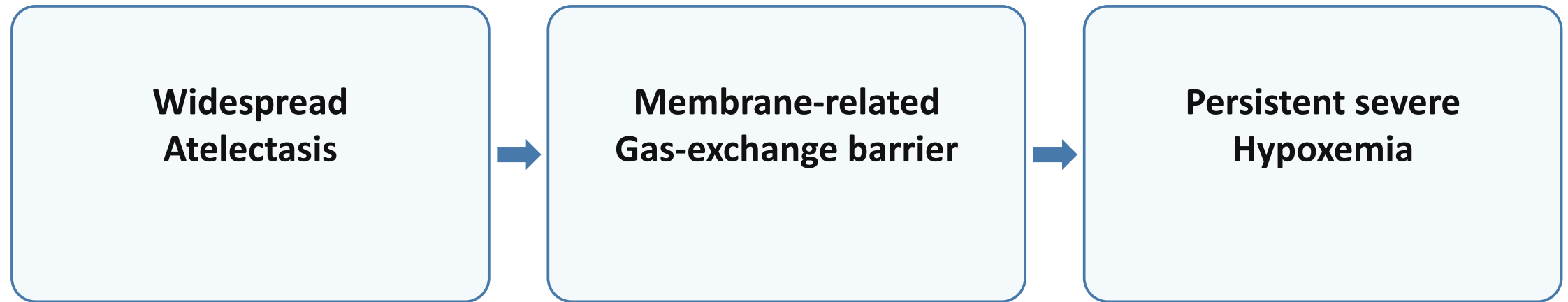
- Breathing becomes increasingly difficult soon after birth.
- Cyanosis becomes apparent within hours in untreated infants.
- Fine rales may be heard over both lung fields.
- Increasing oxygen needs indicate impaired gas exchange.

Chest radiography typically has a ground-glass pattern

- The source describes uniform, minute reticulogranular densities.
- The distributed opacification produces a ground-glass appearance.
- Clinical presentation and gestational history provide the diagnostic context.

Radiography supports the clinicopathologic picture; It is not a substitute for it.

Severe untreated RDS may resist high inspired oxygen



- Severe cases refractory even to high concentrations of administered oxygen.

Mechanical failure and membrane injury are linked

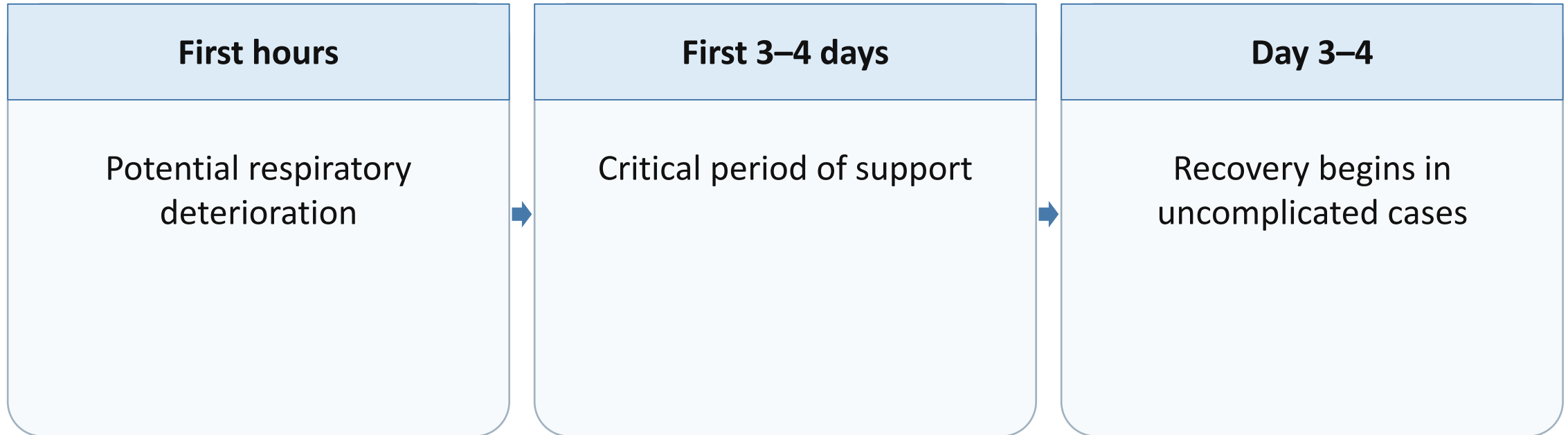
Primary mechanical abnormality

- Insufficient surfactant
- Repeated airspace collapse
- Decreased compliance

Secondary tissue injury

- Hypoxemia and hypoperfusion
- Epithelial and endothelial damage
- Protein leakage and hyaline membranes

Recovery commonly begins after the first several days



- Survival through the early critical interval is associated with a good chance of recovery.

Prognosis depends on maturity and timely therapy

Gestational maturity

Determines degree of pulmonary developmental immaturity.

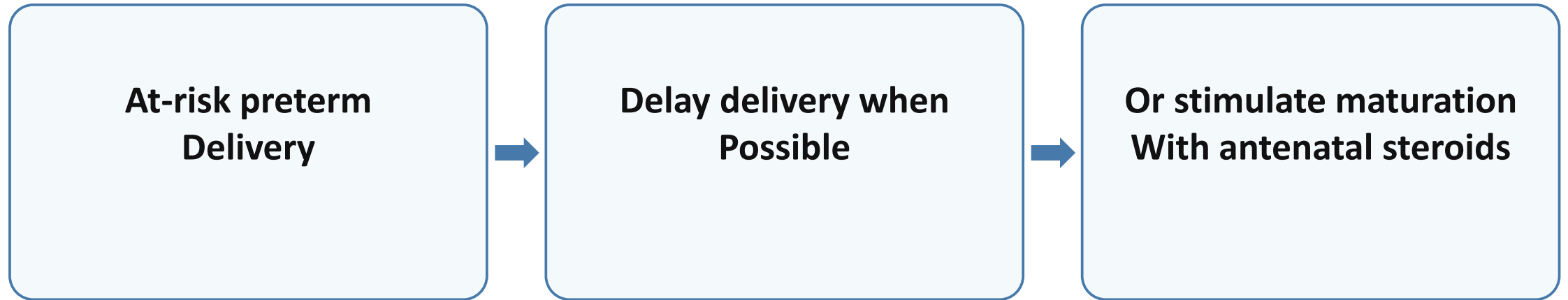
Birth weight

Influences clinical course and prognosis.

Timely therapy

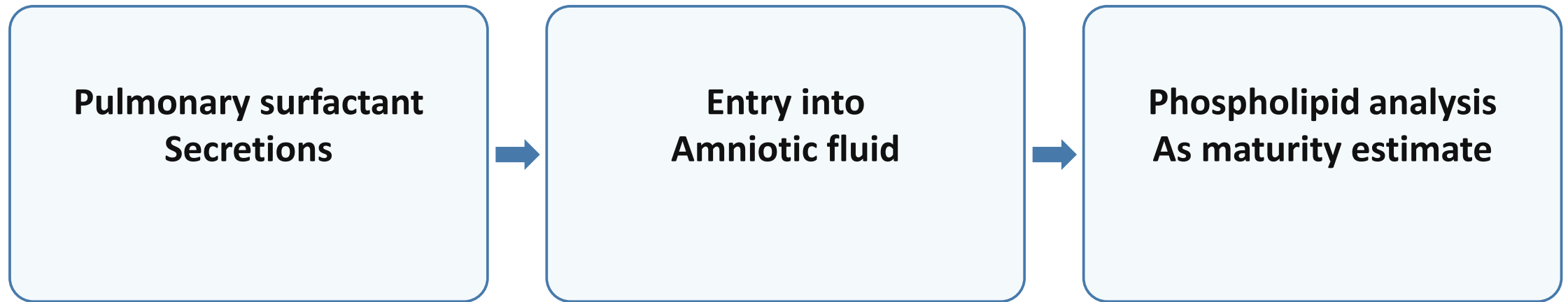
Prompt surfactant treatment alters clinical trajectory.

Prevention aims to improve fetal lung maturity



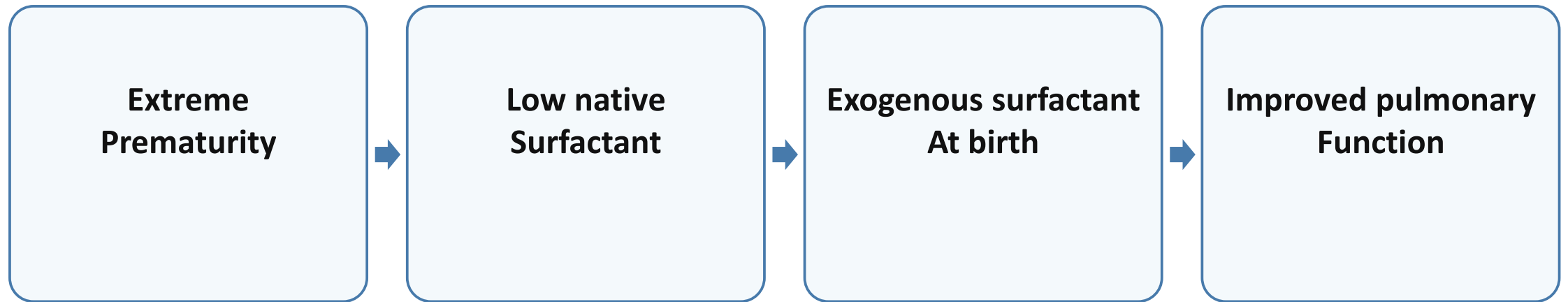
- These are prevention principles, not a management algorithm for an individual pregnancy.

Amniotic-fluid phospholipids reflect fetal lung maturity



- Biochemical assessment as a means of estimating alveolar surfactant status.

Exogenous surfactant addresses the primary deficiency



- Prophylactic use for extremely preterm infants (<28 weeks); Contemporary use is protocol-dependent.

Assisted ventilation supports gas exchange during recovery

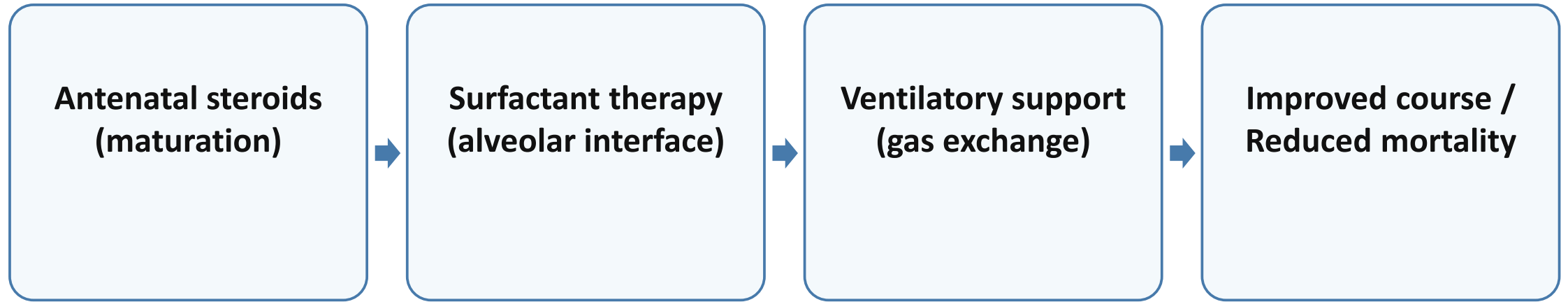
Surfactant replacement

- Targets the surface-tension defect.
- Helps maintain airspace patency.

Assisted ventilation

- Supports ventilation and oxygenation.
- Newer techniques improve the clinical course.

Therapy intervenes at multiple points in the mechanism



- Major improvements to combined prevention, replacement, and respiratory support.

Major sequelae involve the retina and developing lung

Retinopathy of prematurity

A two-phase abnormal retinal angiogenic response.

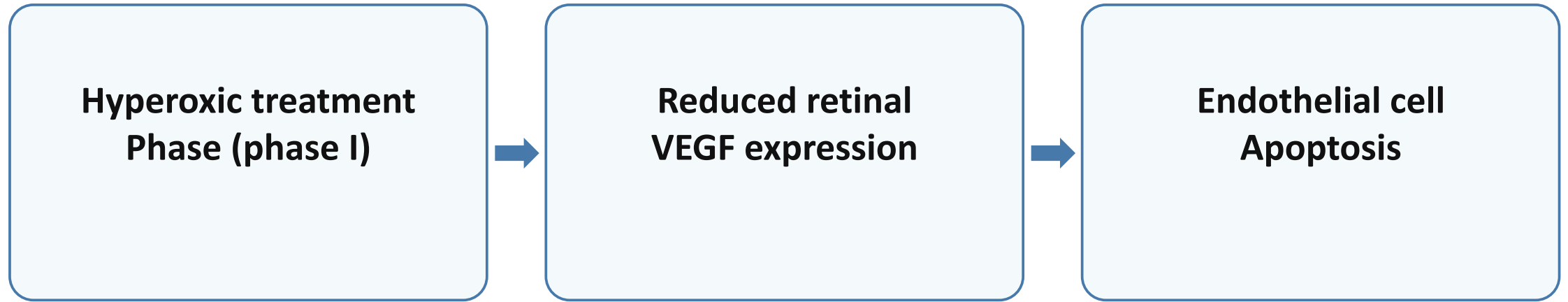
Bronchopulmonary dysplasia

Impaired alveolar septation and abnormal vascular development.

Changing frequency

Both have become less frequent and less severe with improved care.

Retinopathy: Hyperoxia suppresses VEGF



- This is the first phase described model of retinopathy of prematurity.

Retinopathy: Relative hypoxia drives neovascularization



- The second phase produces characteristic pathological neovascularization.

Two retinal phases explain opposite VEGF responses

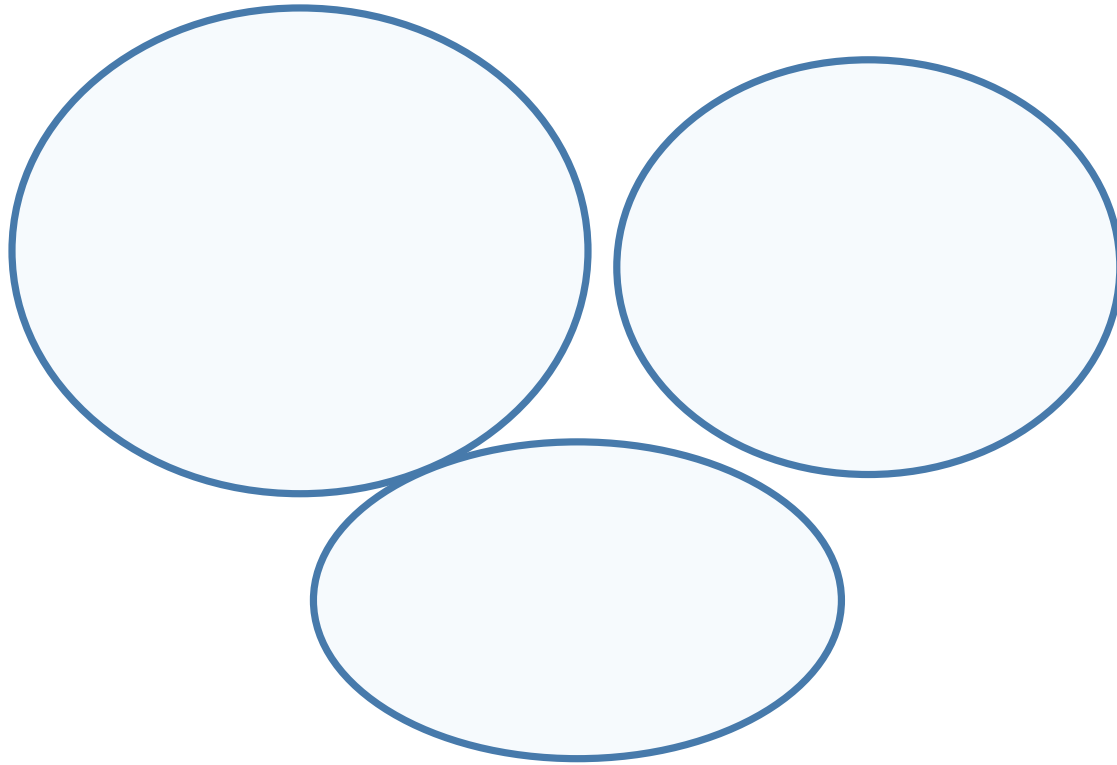
Phase I: Hyperoxic

- VEGF expression decreases
- Endothelial apoptosis is promoted

Phase II: Relatively hypoxic

- VEGF expression rebounds
- Pathological retinal neovascularization occurs

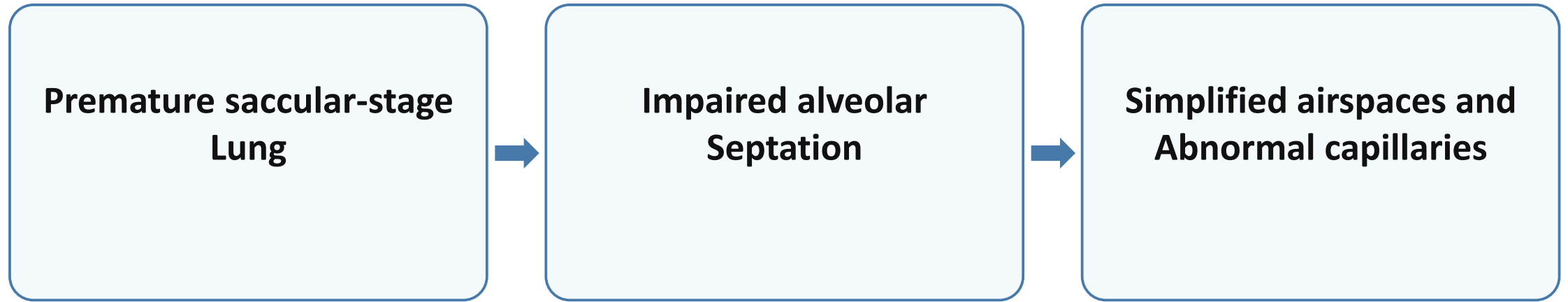
Bronchopulmonary dysplasia disrupts alveolar development



- Marked reduction in alveolar septation produces large, simplified airspaces.
- Capillary configuration is also dysmorphic.

Schematic: Simplified airspaces; Not histology

BPD is viewed as arrested saccular-stage development



- A potentially reversible disturbance of alveolar development.

Multiple factors contribute to bronchopulmonary dysplasia

Physical and oxygen stress

Hyperoxemia and hyperventilation may contribute.

Developmental susceptibility

Prematurity and vascular maldevelopment.

Inflammation

Inflammatory cytokines may arrest alveolar development.

Inflammatory cytokines are increased in affected alveoli

TNF / IL-1 β

Proinflammatory mediators noted in affected lungs.

IL-6 / IL-8

Also reported to be increased in alveoli.

Interpretation

Associations support a possible role in impaired septation.

Prematurity carries complications beyond RDS

Patent ductus arteriosus

A common associated complication of premature birth.

Intraventricular hemorrhage

Another major prematurity-related risk.

Necrotizing enterocolitis

Intestinal complication often seen in preterm infants.

Case: Severe distress in an extremely preterm infant

- A neonate delivered at 27 weeks develops worsening breathing difficulty soon after birth.
- Radiography shows fine diffuse reticulogranular opacities.
- What is the primary physiological defect—and what tissue lesion results?

Mechanistic answer

Insufficient surfactant → repeated atelectasis → alveolar injury with fibrin-rich hyaline membranes.

Case: Diabetic pregnancy and cesarean delivery

- A preterm infant of a mother with diabetes is delivered by cesarean section before labor.
- Respiratory distress develops shortly after an initially stable transition.
- Identify two mechanisms linking the obstetric context to RDS risk.

Mechanistic answer

Fetal hyperinsulinemia may oppose corticosteroid-driven surfactant maturation; Absence of labor may reduce the usual surfactant-synthesis stimulus.

Five mechanisms to retain

Initiation

Surfactant deficiency in an immature lung.

Mechanical failure

Increased tension, collapse, and low compliance.

Tissue lesion

Fibrin and epithelial debris form hyaline membranes.

Clinical expression

Early distress, hypoxemia, ground-glass imaging.

Complications

Retinopathy and disrupted alveolar development.

Primary textbook reference

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026).
- Chapter 10: Diseases of Infancy and Childhood.
- Neonatal Respiratory Distress Syndrome, printed pp. 416–418.
- Source figure descriptions: Fig. 10.6 (mechanism), Fig. 10.7 (histopathology).