Edema Caused by Microvascular (Alveolar) Injury

Noncardiogenic pulmonary edema is due to injury to the alveolar septa. Primary injury to the vascular endothelium or damage to alveolar epithelial cells (with secondary microvascular injury) produces an inflammatory exudate that leaks into the interstitial space and, in more severe cases, into the alveoli. In most forms of pneumonia the edema remains localized and is overshadowed by the manifestations of infection. When diffuse, however, alveolar edema is an important contributor to a serious and often fatal condition, *acute respiratory distress syndrome* (discussed below).

Acute Lung Injury and Acute Respiratory Distress Syndrome (Diffuse Alveolar Damage)

Acute lung injury (ALI) (also called noncardiogenic pulmonary edema) is characterized by the abrupt onset of significant hypoxemia and bilateral pulmonary infiltrates in the absence of cardiac failure. Acute respiratory distress syndrome (ARDS) is a manifestation of severe ALI. Both ARDS and ALI are associated with inflammation-associated increases in pulmonary vascular permeability, edema and epithelial cell death. The histologic manifestation of these diseases is *diffuse alveolar damage* (DAD).

ALI is a well-recognized complication of diverse conditions, including both direct injuries to the lungs and systemic disorders (Table 15-2). In many cases, a combination of predisposing conditions is responsible (e.g., shock, oxygen therapy, and sepsis). Nonpulmonary organ dysfunction may also be present in severe cases.

Table 15-2 Conditions Associated with Development of Acute Respiratory Distress Syndrome

Infection
Sepsis*
Diffuse pulmonary infections*
Viral, *Mycoplasma*, and *Pneumocystis* pneumonia; miliary tuberculosis
Gastric aspiration*
Physical/Injury
Mechanical trauma, including head injuries*
Pulmonary contusions
Near-drowning
Fractures with fat embolism
Burns
Ionizing radiation
Inhaled Irritants
Oxygen toxicity
Smoke
Irritant gases and chemicals
Chemical Injury
Heroin or methadone overdose
Acetylsalicylic acid
Barbiturate overdose
Paraquat
Hematologic Conditions
Transfusion associated lung injury (TRALI)
Disseminated intravascular coagulation
Pancreatitis
Uremia
Cardiopulmonary Bypass
Hypersensitivity Reactions
Organic solvents
Drugs

*More than 50% of cases of acute respiratory distress syndrome are associated with these four conditions.

Pathogenesis. ALI/ARDS is initiated by injury of pneumocytes and pulmonary endothelium, setting in motion a viscous cycle of increasing inflammation and pulmonary damage (Fig. 15-3).

- *Endothelial activation* is an important early event. In some instances, endothelial activation is secondary to pneumocyte injury, which is sensed by resident alveolar macrophages. In response, these immune sentinels secrete mediators such as TNF that act on the neighboring endothelium. Alternatively, circulating inflammatory mediators may activate pulmonary endothelium directly in the setting of severe tissue injury or sepsis. Some of these mediators injure endothelial cells, while others (notably cytokines) activate endothelial cells to express increased levels of adhesion molecules, procoagulant proteins and chemokines.
- *Adhesion and extravasation of neutrophils.* Neutrophils adhere to the activated endothelium and migrate into the interstitium and the alveoli, where they degranulate and release inflammatory mediators, including proteases, reactive oxygen species, and cytokines. Macrophage migration inhibitory factor (MIF) released into the local milieu also helps to sustain the ongoing proinflammatory response. The result is increased recruitment and adhesion of leukocytes, causing more endothelial injury, and local thrombosis. This cycle of inflammation and endothelial damage lies at the heart of ALI/ARDS.
- *Accumulation of intraalveolar fluid and formation of hyaline membranes.* Endothelial activation and injury make pulmonary capillaries leaky, allowing interstitial and intraalveolar edema fluid to form. Damage and necrosis of type II alveolar pneumocytes leads to surfactant abnormalities, further compromising alveolar gas exchange. Ultimately, the inspissated protein-rich edema fluid and debris from dead alveolar epithelial cells organize into hyaline membranes, a characteristic feature of ALI/ARDS.
- *Resolution of injury* is impeded in ALI/ARDS due to epithelial necrosis and inflammatory damage that impairs the ability of remaining cells to assist with edema resorption. Eventually, however, if the inflammatory stimulus lessens, macrophages remove intraalveolar debris and release fibrogenic cytokines such as transforming growth factor β (TGF-β) and platelet-derived growth factor (PDGF). These factors stimulate fibroblast growth and collagen deposition, leading to fibrosis of alveolar walls. Bronchiolar stem cells proliferate to replace pneumocytes. Endothelial restoration occurs through proliferation of uninjured capillary endothelium.