Acute respiratory distress syndrome (ARDS) is a clinical syndrome of severe dyspnea of rapid onset, hypoxemia, and diffuse pulmonary infiltrates leading to respiratory failure. ARDS is caused by diffuse lung injury from many underlying medical and surgical disorders. The lung injury may be direct, as occurs in toxic inhalation, or indirect, as occurs in sepsis (Table 268-1). The clinical features of ARDS are listed in Table 268-2. Acute lung injury (ALI) is a less severe disorder but has the potential to evolve into ARDS (Table 268-2). The arterial (a) PO2 (in mmHg)/FIO2 (inspiratory O2 fraction) <200 mmHg is characteristic of ARDS, while a PaO2/FIO2 between 200 and 300 identifies patients with ALI who are likely to benefit from aggressive therapy.

The annual incidences of ALI and ARDS are estimated to be up to 80/100,000 and 60/100,000, respectively. Approximately 10% of all intensive care unit (ICU) admissions suffer from acute respiratory failure, with ∼20% of these patients meeting criteria for ALI or ARDS.

### ETIOLOGY

While many medical and surgical illnesses have been associated with the development of ALI and ARDS, most cases (>80%) are caused by a relatively small number of clinical disorders, namely, severe sepsis syndrome and/or bacterial pneumonia (40–50%), trauma, multiple transfusions, aspiration of gastric contents, and drug overdose. Among patients with trauma, pulmonary contusion, multiple bone fractures, and chest wall trauma/flail chest are the most frequently reported surgical conditions in ARDS, whereas head trauma, near-drowning, toxic inhalation, and burns are rare causes. The risks of developing ARDS are increased in patients suffering from more than one predisposing medical or surgical condition; e.g., the risk for ARDS increases from 25% in patients with severe trauma to 56% in patients with trauma and sepsis.

Several other clinical variables have been associated with the development of ARDS. These include older age, chronic alcohol abuse, metabolic acidosis, and severity of critical illness. Trauma patients with an acute physiology and chronic health evaluation (APACHE) II score ≥16 (Chap. 267) have a 2.5-fold increase in the risk of developing ARDS, and those with a score >20 have an incidence of ARDS that is more than threefold greater than those with APACHE II scores ≤9.

### CLINICAL COURSE AND PATHOPHYSIOLOGY

The natural history of ARDS is marked by three phases—exudative, proliferative, and fibrotic—each with characteristic clinical and pathologic features (Fig. 268-1).

#### Exudative Phase

(Figure. 268-2) In this phase, alveolar capillary endothelial cells and type I pneumocytes (alveolar epithelial cells) are injured, leading to the loss of the normally tight alveolar barrier to fluid and macromolecules. Edema fluid that is rich in protein accumulates in the interstitial and alveolar spaces. Significant concentrations of cytokines (e.g., interleukin 1, interleukin 8, and tumor necrosis factor α) and lipid mediators (e.g., leukotriene B4) are present in the lung in this acute phase. In response to proinflammatory mediators, leukocytes (especially neutrophils) traffic into the pulmonary interstitium and alveoli. In addition, condensed

<table>
<thead>
<tr>
<th>Table 268-2</th>
<th>Diagnostic Criteria for ALI and ARDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygenation</td>
<td>Onset</td>
</tr>
<tr>
<td>ALI: PaO2/FIO2 ≤ 300 mmHg</td>
<td>Acute</td>
</tr>
<tr>
<td>ARDS: PaO2/FIO2 ≤ 200 mmHg</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ALI, acute lung injury; ARDS, acute respiratory distress syndrome; PaO2, arterial partial pressure of O2; FIO2, inspired O2 percentage; PCWP, pulmonary capillary wedge pressure.

#### Table 268-1

Clinical Disorders Commonly Associated With ARDS

<table>
<thead>
<tr>
<th>Direct Lung Injury</th>
<th>Indirect Lung Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>Sepsis</td>
</tr>
<tr>
<td>Aspiration of gastric contents</td>
<td>Severe trauma</td>
</tr>
<tr>
<td>Pulmonary contusion</td>
<td>Multiple bone fractures</td>
</tr>
<tr>
<td>Near-drowning</td>
<td>Flail chest</td>
</tr>
<tr>
<td>Toxic inhalation injury</td>
<td>Head trauma</td>
</tr>
<tr>
<td>Burns</td>
<td></td>
</tr>
<tr>
<td>Multiple transfusions</td>
<td></td>
</tr>
<tr>
<td>Drug overdose</td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td></td>
</tr>
<tr>
<td>Post-cardiopulmonary bypass</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 268-1** Diagram illustrating the time course for the development and resolution of ARDS. The exudative phase is notable for early alveolar edema and neutrophil-rich leukocytic infiltration of the lungs with subsequent formation of hyaline membranes from diffuse alveolar damage. Within 7 days, a proliferative phase ensues with prominent interstitial inflammation and early fibrotic changes. Approximately 3 weeks after the initial pulmonary injury, most patients recover. However, some patients enter the fibrotic phase, with substantial fibrosis and bullae formation.
plasma proteins aggregate in the air spaces with cellular debris and dysfunctional pulmonary surfactant to form hyaline membrane whorls. Pulmonary vascular injury also occurs early in ARDS, with vascular obliteration by microthrombi and fibrocellular proliferation (Fig. 268-3).

Alveolar edema predominantly involves dependent portions of the lung, leading to diminished aeration and atelectasis. Collapse of large sections of dependent lung markedly decreases lung compliance. Consequently, intrapulmonary shunting and hypoxemia develop and the work of breathing rises, leading to dyspnea. The pathophysiological alterations in alveolar spaces are exacerbated by microvascular occlusion, which leads to reductions in pulmonary arterial blood flow to ventilated portions of the lung, increasing the dead space, and to pulmonary hypertension. Thus, in addition to severe hypoxemia, hypercapnia secondary to an increase in pulmonary dead space is also prominent in early ARDS.

The exudative phase encompasses the first 7 days of illness after exposure to a precipitating ARDS risk factor, with the patient experiencing the onset of respiratory symptoms. Although usually present within 12–36 h after the initial insult, symptoms can be delayed by 5–7 days. Dyspnea develops with a sensation of rapid

Figure 268-2  A representative anteroposterior (AP) chest x-ray in the exudative phase of ARDS that shows diffuse interstitial and alveolar infiltrates, which can be difficult to distinguish from left ventricular failure.

Figure 268-3  The normal alveolus (left-hand side) and the injured alveolus in the acute phase of acute lung injury and the acute respiratory distress syndrome (right-hand side). In the acute phase of the syndrome (right-hand side), there is sloughing of both the bronchial and alveolar epithelial cells, with the formation of protein-rich hyaline membranes on the denuded basement membrane. Neutrophils are shown adhering to the injured capillary endothelium and marginating through the interstitium into the air space, which is filled with protein-rich edema fluid. In the air space, an alveolar macrophage is secreting cytokines, interleukin 1, 6, 8, and 10 (IL-1, -6, -8, and -10) and tumor necrosis factor α (TNF-α), which act locally to stimulate chemotaxis and activate neutrophils. Macrophages also secrete other cytokines, including IL-1, -6, and -10. IL-1 can also stimulate the production of extracellular matrix by fibroblasts. Neutrophils can release oxidants, proteases, leukotrienes, and other proinflammatory molecules, such as platelet-activating factor (PAF). A number of antiinflammatory mediators are also present in the alveolar milieu, including IL-1 receptor antagonist, soluble TNF-α receptor, autoantibodies against IL-8, and cytokines such as IL-10 and -11 (not shown). The influx of protein-rich edema fluid into the alveolus has led to the inactivation of surfactant. MIF, macrophage inhibitory factor. (From Ware and Matthay, with permission)
shallow breathing and an inability to get enough air. Tachypnea and increased work of breathing frequently result in respiratory fatigue and ultimately in respiratory failure. Laboratory values are generally nonspecific and primarily indicative of underlying clinical disorders. The chest radiograph usually reveals alveolar and interstitial opacities involving at least three-quarters of the lung fields (Fig. 268-2). While characteristic for ARDS or ALI, these radiographic findings are not specific and can be indistinguishable from cardiogenic pulmonary edema (Chap. 272). Unlike the latter, however, the chest x-ray in ARDS rarely shows cardiomegaly, pleural effusions, or pulmonary vascular redistribution. Chest computed tomographic (CT) scanning in ARDS reveals extensive heterogeneity of lung involvement (Fig. 268-4).

Because the early features of ARDS and ALI are nonspecific, alternative diagnoses must be considered. In the differential diagnosis of ARDS, the most common disorders are cardiogenic pulmonary edema, diffuse pneumonia, and alveolar hemorrhage. Less frequent diagnoses to consider include acute interstitial lung diseases [e.g., acute interstitial pneumonitis (Chap. 261)], acute immunologic injury [e.g., hypersensitivity pneumonitis (Chap. 255)], toxic injury (e.g., radiation pneumonitis), and neoplastic pulmonary edema.

**Proliferative phase**

This phase of ARDS usually lasts from day 7 to day 21. Most patients recover rapidly and are liberated from mechanical ventilation during this phase. Despite this improvement, many still experience dyspnea, tachypnea, and hypoxemia. Some patients develop progressive lung injury and early changes of pulmonary fibrosis during the proliferative phase. Histologically, the first signs of resolution are often evident in this phase with the initiation of lung repair, organization of alveolar exudates, and a shift from a neutrophil- to a lymphocyte-predominant pulmonary infiltrate. As part of the reparative process, there is a proliferation of type II pneumocytes along alveolar basement membranes. These specialized epithelial cells synthesize new pulmonary surfactant and differentiate into type I pneumocytes. The presence of alveolar type III procollagen peptide, a marker of pulmonary fibrosis, is associated with a protracted clinical course and increased mortality from ARDS.

**Fibrotic phase**

While many patients with ARDS recover lung function 3–4 weeks after the initial pulmonary injury, some will enter a fibrotic phase that may require long-term support on mechanical ventilators and/or supplemental oxygen. Histologically, the alveolar edema and inflammatory exudates of earlier phases are now converted to extensive alveolar duct and interstitial fibrosis. Acinar architecture is markedly disrupted, leading to emphysema-like changes with large bullae. Intimal fibroproliferation in the pulmonary microcirculation leads to progressive vascular occlusion and pulmonary hypertension. The physiologic consequences include an increased risk of pneumothorax, reductions in lung compliance, and increased pulmonary dead space. Patients in this late phase experience a substantial burden of excess morbidity. Lung biopsy evidence for pulmonary fibrosis in any phase of ARDS is associated with increased mortality.

**TREATMENT**

**Acute Respiratory Distress Syndrome**

**GENERAL PRINCIPLES** Recent reductions in ARDS/ALI mortality are largely the result of general advances in the care of critically ill patients (Chap. 267). Thus, caring for these patients requires close attention to (1) the recognition and treatment of the underlying medical and surgical disorders (e.g., sepsis, aspiration, trauma); (2) minimizing procedures and their complications; (3) prophylaxis against venous thromboembolism, gastrointestinal bleeding, aspiration, excessive sedation, and central venous catheter infections; (4) the prompt recognition of nosocomial infections; and (5) provision of adequate nutrition.

**MANAGEMENT OF MECHANICAL VENTILATION** (See also Chap. 269) Patients meeting clinical criteria for ARDS frequently fatigue from increased work of breathing and progressive hypoxemia, requiring mechanical ventilation for support.

**Ventilator-Induced Lung Injury** Despite its life-saving potential, mechanical ventilation can aggravate lung injury. Experimental models have demonstrated that ventilator-induced lung injury appears to require two processes: repeated alveolar overdistention and recurrent alveolar collapse. Clearly evident by chest CT (Fig. 268-4), ARDS is a heterogeneous disorder, principally involving dependent portions of the lung with relative sparing of other regions. Because of their differing compliance, attempts to fully inflate the consolidated lung may lead to overdistention and injury to the more “normal” areas of the lung. Ventilator-induced injury can be demonstrated in experimental models of ALI with high tidal volume ventilation resulting in additional, synergistic alveolar damage. These findings led to the hypothesis that ventilating patients suffering from ALI or ARDS with lower tidal volumes would protect against ventilator-induced lung injury and improve clinical outcomes.

A large-scale, randomized controlled trial sponsored by the National Institutes of Health and conducted by the ARDS Network compared low tidal volume (6 mL/kg predicted body weight) ventilation to conventional tidal volume (12 mL/kg predicted body weight) ventilation. Mortality was significantly lower in the low tidal volume patients (31%) compared to the conventional tidal volume patients (40%). This improvement in survival represents the most substantial benefit in ARDS mortality demonstrated for any therapeutic intervention in ARDS to date.

**Prevention of Alveolar Collapse** In ARDS, the presence of alveolar and interstitial fluid and the loss of surfactant can lead to a marked reduction of lung compliance. Without an increase in end-expiratory pressure, significant alveolar collapse can occur at end-expiration, impairing oxygenation. In most clinical settings, positive end-expiratory pressure (PEEP) is empirically set to minimize FiO2 and maximize PaO2. On most modern mechanical ventilators, it is possible to construct a static...
pressure–volume curve for the respiratory system. The lower
inflection point on the curve represents alveolar opening (or
“recruitment”). The pressure at this point, usually 12–15 mmHg
in ARDS, is a theoretical “optimal PEEP” for alveolar recruit-
ment. Titration of the PEEP to the lower inflection point on the
static pressure–volume curve has been hypothesized to keep the
lung open, improving oxygenation and protecting against lung
injury. Three large randomized trials have investigated the util-
ity of PEEP-based strategies to keep the lung open. In all three
trials, improvement in lung function was evident but there were
no significant differences in overall mortality. Until more data
become available on the clinical utility of high PEEP, it is advisable
to set PEEP to minimize FIO2, and optimize PaO2 (Chap. 269).
Measurement of esophageal pressures to estimate transpulmonary
pressure may help identify an optimal PEEP in some patients.

Oxygenation can also be improved by increasing mean airway
pressure with “inverse ratio ventilation.” In this technique, the
inspiratory (I) time is lengthened so that it is longer than the
expiratory (E) time (I/E > 1:1). With diminished time to exhale,
dynamic hyperinflation leads to increased end-expiratory pressure,
similar to ventilator-prescribed PEEP. This mode of ventilation has
the advantage of improving oxygenation with lower peak pressures
than conventional ventilation. Although inverse ratio ventilation
may improve oxygenation and help reduce FIO2 to ≤0.60 to avoid
possible oxygen toxicity, no mortality benefit in ARDS has been
demonstrated. Recruitment maneuvers that transiently increase
PEEP to “recruit” atelectatic lung can also increase oxygenation,
but a mortality benefit has not been established.

In several randomized trials, mechanical ventilation in the
prone position improved arterial oxygenation, but its effect on
survival and other important clinical outcomes remains uncer-
tain. Moreover, unless the critical-care team is experienced in
“proning,” repositioning critically ill patients can be hazardous,
leading to accidental endotracheal extubation, loss of central
venous catheters, and orthopedic injury. Until validation of its
efficacy, prone-position ventilation should be reserved for only
the most critically ill ARDS patients.

Other Strategies in Mechanical Ventilation Several additional
mechanical ventilation strategies that utilize specialized equip-
ment have been tested in ARDS patients, most with mixed or
disappointing results in adults. These include high-frequency
ventilation (HFV), i.e., ventilating at extremely high respiratory
rates (5–20 cycles per second) and low tidal volumes (1–2 mL/kg).
Partial liquid ventilation (PLV) with perfluorocarbon, an inert,
high-density liquid that easily solubilizes oxygen and carbon
dioxide, has revealed promising preliminary data on pulmonary
function in patients with ARDS but also without survival benefit.
Lung-replacement therapy with extracorporeal membrane oxy-
genation (ECMO), which provides a clear survival benefit in
neonatal respiratory distress syndrome, may also have utility in
select adult patients with ARDS.

Data in support of the efficacy of “adjunctive” ventilator
therapies (e.g., high PEEP, inverse ratio ventilation, recruitment
maneuvers, prone positioning, HFV, ECMO, and PLV) remain
incomplete, so these modalities are not routinely used.

FLUID MANAGEMENT (See also Chap. 267) Increased pulmo-
nary vascular permeability leading to interstitial and alveolar
edema rich in protein is a central feature of ARDS. In addition,
impaired vascular integrity augments the normal increase in
extravascular lung water that occurs with increasing left atrial
pressure. Maintaining a normal or low left atrial filling pressure
minimizes pulmonary edema and prevents further decrements in
arterial oxygenation and lung compliance, improves pulmonary
mechanics, shortens ICU stay and the duration of mechanical
ventilation, and is associated with a lower mortality in both
medical and surgical ICU patients. Thus, aggressive attempts
to reduce left atrial filling pressures with fluid restriction and
diuretics should be an important aspect of ARDS management,
limited only by hypotension and hypoperfusion of critical
organs, such as the kidneys.

GLUCOCORTICOIDS Inflammatory mediators and leukocytes are
abundant in the lungs of patients with ARDS. Many attempts
have been made to treat both early and late ARDS with glucocor-
ticoids to reduce this potentially deleterious pulmonary inflam-
mation. Few studies have shown any benefit. Current evidence
does not support the use of high-dose glucocorticoids in the care
of ARDS patients.

OTHER THERAPIES Clinical trials of surfactant replacement and
multiple other medical therapies have proved disappointing.
Inhaled nitric oxide (NO) can transiently improve oxygenation
but does not improve survival or decrease time on mechanical
ventilation. Therefore, the use of NO is not currently recom-
manded in ARDS.

RECOMMENDATIONS Many clinical trials have been under-
taken to improve the outcome of patients with ARDS; most
have been unsuccessful in modifying the natural history. The
large number and uncertain clinical efficacy of ARDS therapies
can make it difficult for clinicians to select a rational treatment
plan, and these patients’ critical illness can tempt physicians to
try unproven and potentially harmful therapies. While results of
large clinical trials must be judiciously administered to individu-
al patients, evidence-based recommendations are summarized in
Table 268-3, and an algorithm for the initial therapeutic goals
and limits in ARDS management is provided in Fig. 268-5.

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**TABLE 268-3 Evidence-Based Recommendations for ARDS Therapies**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Recommendation*</th>
</tr>
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<tbody>
<tr>
<td>Mechanical ventilation:</td>
<td></td>
</tr>
<tr>
<td>Low tidal volume</td>
<td>A</td>
</tr>
<tr>
<td>Minimize left atrial filling pressures</td>
<td>B</td>
</tr>
<tr>
<td>High-PEEP or “open lung”</td>
<td>C</td>
</tr>
<tr>
<td>Prone position</td>
<td>C</td>
</tr>
<tr>
<td>Recruitment maneuvers</td>
<td>C</td>
</tr>
<tr>
<td>ECMO</td>
<td>C</td>
</tr>
<tr>
<td>High-frequency ventilation</td>
<td>D</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>D</td>
</tr>
<tr>
<td>Surfactant replacement, inhaled nitric oxide,</td>
<td>D</td>
</tr>
<tr>
<td>and other anti-inflammatory therapy (e.g.,</td>
<td></td>
</tr>
<tr>
<td>ketoconazole, PGE1, NSAIDs)</td>
<td></td>
</tr>
</tbody>
</table>

* A, recommended therapy based on strong clinical evidence from randomized clinical
  trials; B, recommended therapy based on supportive but limited clinical data;
  C, indeterminate evidence: recommended only as alternative therapy; D, not
  recommended based on clinical evidence against efficacy of therapy.

*Abbreviations: ARDS, acute respiratory distress syndrome; PEEP, positive
  end-expiratory pressure; ECMO, extracorporeal membrane oxygenation;
PGE1, prostaglandin E1; NSAIDs, nonsteroidal anti-inflammatory drugs.*
Mortality

Recent mortality estimates for ARDS range from 26 to 44%. There is substantial variability, but a trend toward improved ARDS outcomes appears evident. Of interest, mortality in ARDS is largely attributable to nonpulmonary causes, with sepsis and nonpulmonary organ failure accounting for >80% of deaths. Thus, improvement in survival is likely secondary to advances in the care of septic/infected patients and those with multiple organ failure (Chap. 267).

Several risk factors for mortality to help estimate prognosis have been identified. Similar to the risk factors for developing ARDS, the major risk factors for ARDS mortality are also nonpulmonary. Advanced age is an important risk factor. Patients >75 years have a substantially increased mortality (~60%) compared to those <45 (~20%). Also, patients >60 years with ARDS and sepsis have a threefold higher mortality compared to those <60. Preexisting organ dysfunction from chronic medical illness is an important additional risk factor for increased mortality. In particular, chronic liver disease, cirrhosis, chronic alcohol abuse, chronic immunosuppression, sepsis, chronic renal disease, any nonpulmonary organ failure, and increased APACHE III scores (Chap. 267) have also been linked to increased ARDS mortality. Several factors related to the presenting clinical disorders also increase risk for ARDS mortality. Patients with ARDS from direct lung injury (including pneumonia, pulmonary contusion, and aspiration; Table 268-1) have nearly twice the mortality of those with indirect causes of lung injury, while surgical and trauma patients with ARDS, especially those without direct lung injury, have a better survival rate than other ARDS patients.

Surprisingly, there is little value in predicting ARDS mortality from the PaO₂/FiO₂ ratio and any of the following measures of the severity of lung injury: the level of PEEP used in mechanical ventilation, the respiratory compliance, the extent of alveolar infiltrates on chest radiography, and the lung injury score (a composite of all these variables). However, recent data indicate that an early (within 24 h of presentation) elevation in dead space and the oxygenation index may predict increased mortality from ARDS.

Functional recovery in ARDS survivors

While it is common for patients with ARDS to experience prolonged respiratory failure and remain dependent on mechanical ventilation for survival, it is a testament to the resolving powers of the lung that the majority of patients recover nearly normal lung function. Patients usually recover their maximum lung function within 6 months. One year after endotracheal extubation, more than a third of ARDS survivors have normal spirometry values and diffusion capacity. Most of the remaining patients have only mild abnormalities in their pulmonary function. Unlike the risk for mortality, recovery of lung function is strongly associated with the extent of lung injury in early ARDS. Low static respiratory compliance, high levels of required PEEP, longer durations of mechanical ventilation, and high lung injury scores are all associated with worse recovery of pulmonary function. When caring for ARDS survivors, it is important to be aware of the potential for a substantial burden of emotional and respiratory symptoms. There are significant rates of depression and posttraumatic stress disorder in ARDS survivors.

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WEBSITES

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ARDS Network clinical trials information: www.ardsnet.org

ARDS Foundation: www.ardsusa.org