Treatment of ARDS*

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Improved understanding of the pathogenesis of acute lung injury (ALI)/ARDS has led to important advances in the treatment of ALI/ARDS, particularly in the area of ventilator-associated lung injury. Standard supportive care for ALI/ARDS should now include a protective ventilatory strategy with low tidal volume ventilation by the protocol developed by the National Institutes of Health ARDS Network. Further refinements of the protocol for mechanical ventilation will occur as current and future clinical trials are completed. In addition, novel modes of mechanical ventilation are being studied and may augment standard therapy in the future. Although results of anti-inflammatory strategies have been disappointing in clinical trials, further trials are underway to test the efficacy of late corticosteroids and other approaches to modulation of inflammation in ALI/ARDS. ***(CHEST 2001; 120:1347–1367)***

Key words: acute lung injury; mechanical ventilation; pulmonary edema; ventilator-associated lung injury

Abbreviations: ALI = acute lung injury; APRV = airway pressure-release ventilation; $ECCO_2R$ = extracorporeal carbon dioxide removal; ECMO = extracorporeal membrane oxygenation; FIO_2 = fraction of inspired oxygen; HFV = high-frequency ventilation; I:E = ratio of the duration of inspiration to the duration of expiration; IL = interleukin; IMPRV = intermittent mandatory pressure-release ventilation; IRV = inverse-ratio ventilation; LFPPV = low-frequency positive-pressure ventilation; NIH = National Institutes of Health; NIPPV = noninvasive positive-pressure ventilation; NO = nitric oxide; PEEP = positive end-expiratory pressure; PSB = protected specimen brushing; TGI = tracheal gas insufflation; TNF = tumor necrosis factor

The syndrome of acute respiratory distress in adults was first described in 1967.[1] Until recently, most reported mortality rates exceeded 50%. However, the mortality from acute lung injury (ALI) and ARDS (ALI/ARDS) has decreased as laboratory and clinical studies have provided new evidence to improve therapeutic strategies. This article reviews the results of these studies and summarizes current recommendations for standard supportive therapy. New treatment strategies that are being evaluated in ongoing clinical trials are also reviewed. Information regarding clinical definitions, epidemiology, and pathogenesis of ALI/ARDS is available in other reviews.[2–7]

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Standard Supportive Therapy

Standard supportive therapy for ALI/ARDS is directed toward identification and management of pulmonary and nonpulmonary organ dysfunction.

Treatment of the Inciting Clinical Disorder in Patients With ARDS

Identification and treatment of the inciting clinical disorder is an important aspect of the initial management of a patient with ALI/ARDS. The most common disease processes associated with ALI include sepsis, pneumonia, aspiration of gastric contents, trauma, multiple transfusions, and ischemia reperfusion (Table 1). In some circumstances, the underlying cause of ALI can be treated directly. For example, patients with pneumonia from bacterial or opportunistic infections may respond to specific antimicrobial therapy. A careful search for a treatable cause of pulmonary infection, such as bacterial pneumonia, atypical pneumonia from Mycoplasma or Legionella, or an opportunistic infection from fungi, tuberculosis, or *Pneumocystis carinii* is warranted. The diagnostic evaluation should be guided by the clinical history. In other patients, an infectious cause of ALI may be related to an extrapulmonary site of infection, such as the biliary tract, peritoneal cavity, or urinary tract. The diagnosis of intra-ab-

Table 1—*Inciting Clinical Disorders Associated With ALI and ARDS*

Pulmonary disorders
Pneumonia
Bacterial
Fungal
Parasitic
Viral
Aspiration of gastric contents
Pulmonary contusion
Fat emboli
Near-drowning
Inhalational injury
Reperfusion pulmonary edema after lung transplantation
Extrapulmonary disorders
Sepsis
Trauma with multiple transfusions
Cardiopulmonary bypass
Drug overdose
Acute pancreatitis
Blood product transfusions

dominal sepsis should be considered early in patients with sepsis syndrome and ALI of uncertain etiology. Prompt surgical intervention to eradicate an intra-abdominal source of sepsis is associated with better outcomes.[8] Factors associated with positive findings at exploratory laparotomy include objective findings on physical examination and ultrasound, or CT findings suggestive of an intra-abdominal focus of infection.[9] Although the prognosis for recovery from sepsis-induced lung injury is worse than from any other cause,[10,11] specific medical and surgical treatment of the pulmonary or extrapulmonary source of sepsis is indicated to enhance the chance of survival. In many ALI/ARDS patients, the insult that caused lung injury, such as aspiration or multiple transfusions, cannot be treated except to prevent recurrence and provide optimal supportive care as outlined below.

Mechanical Ventilation

In many ALI/ARDS patients, intrapulmonary shunt and ventilation-perfusion imbalances cause life-threatening hypoxemia. Moreover, high work of breathing from increased alveolar dead space and reduced respiratory system compliance may cause ventilatory failure with hypercapnia and respiratory acidosis. The mainstay of supportive care of ALI/ARDS is mechanical ventilation.[12] By stabilizing respiration, mechanical ventilation allows time for administration of treatment for the underlying cause of ALI/ARDS (*eg*, infection) and for the evolution of natural healing processes. Arterial oxygenation can be supported by raising the fraction of inspired oxygen (F_{IO_2}) and applying positive end-expiratory pressure (PEEP). Ventilation can be supported with intermittent positive airway pressure. This section addresses approaches to mechanical ventilation that are commonly used and accepted as standard supportive care in patients with ALI/ARDS. Mechanical ventilation approaches that are not in common use or have not yet been proven to be beneficial are reviewed in the subsequent section on "Potential New Treatment Strategies."

Lung-Protective Ventilation With Small Tidal Volumes: One of the clinical hallmarks of ALI/ARDS is decreased respiratory system compliance.[13] This is caused by atelectasis and flooding of alveoli and by increased surface tension at air-fluid interfaces. Chest radiographs frequently suggest that the disease is distributed homogeneously throughout the lungs. However, CT images and physiologic studies demonstrate that the lung is affected in a patchy, heterogeneous manner.[14,15] The lungs of ALI/ARDS patients can be modeled as consisting of three different compartments: (1) regions of severe inflammation, alveolar filling, and atelectasis in which little lung volume can be recruited with airway pressures that are traditionally considered safe; (2) regions with normal compliance and aeration, appearing to be uninvolved with disease; and (3) intermediate regions in which alveolar collapse and flooding are apparent but where aeration can be restored by raising airway pressures within a safe range.

When traditional tidal volumes of 10 to 15 mL/kg are used in patients with ALI/ARDS receiving mechanical ventilation, the resulting airway pressures are frequently elevated, reflecting overdistention of the less-affected lung regions. In many laboratory experiments,[16–21] ventilation with high airway pressures caused increased pulmonary vascular permeability, acute inflammation, alveolar hemorrhage, intrapulmonary shunt, and diffuse radiographic infiltrates. Most of these studies were conducted in normal animals with very large tidal volumes, and thus were not directly applicable to the experience in patients with ALI/ARDS. However, rats with experimental ALI had significantly less edema when receiving ventilation with smaller tidal volumes.[22] Moreover, although the tidal volumes that caused injury in the animal models were approximately three to four times greater than those used by most clinicians, most of the tidal volume in ALI/ARDS patients is directed to a relatively small amount of aerated lung. These studies suggest that in some patients with ALI/ARDS, traditional approaches to mechanical ventilation exacerbate or perpetuate lung injury by causing excessive stretch of aerated lung regions during inspiration.

Ventilation with small tidal volumes and limited

airway pressures can reduce ventilator-associated lung injury from overdistention. However, small tidal volume ventilation may cause complications from acute respiratory acidosis.[23–26] Thus, to achieve the beneficial effect of this approach requires some compromise of traditional objectives with respect to gas exchange and acid-base balance. Clinical evidence supporting this strategy came initially from two observational studies[24,25] in which mortality rates of ARDS patients treated with small tidal volumes and permissive hypercapnia were compared to mortality rates predicted from historical control subjects. These studies were not conclusive because they lacked concurrent control groups treated with a traditional ventilation approach.

Three small prospective, randomized trials[27–29] of traditional vs lower tidal volume ventilation in patients with or at risk for ALI/ARDS did not demonstrate beneficial effects of the lower tidal volume approach. However, mortality was reduced substantially from 40% (traditional strategy) to 31% (lower tidal volume strategy) in a larger trial by the National Institutes of Health (NIH) ARDS Network[30] (Fig 1). There were also more ventilator-free and organ failure-free days in patients who received the lower tidal volume strategy. In the lower tidal volume group, the target tidal volume was 6 mL/kg of predicted body weight. This was reduced further to 5 mL/kg or 4 mL/kg if necessary to maintain the end-inspiratory plateau pressure (0.5-s pause) $\leq$ 30 cm H_2O. An important difference between the ARDS Network trial and the previous studies is that the tidal volumes in the lower tidal volume strategy of the ARDS Network trial were smaller. Management of acidosis was also different in the ARDS Network trial,[30] which required high respiratory rates and allowed sodium bicarbonate infusion to compensate for respiratory acidosis.

The ARDS Network trial[30] excluded patients with elevated intracranial pressure and with sickle hemoglobin because hypercapnia and acidosis could have adverse effects in these conditions. However, the lower tidal volume approach is recommended for most other patients with ALI/ARDS. The complete methodology for the trial procedures is available at www.ardsnet.org and from the National Auxiliary Publications Service (c/o Microfiche Publications, 248 Hempstead Turnpike, West Hempstead, NY 11552; document 05542). The lower tidal volume strategy is summarized in Table 2. Except for the lower tidal volumes with permissive hypercapnia, this approach is consistent with previously accepted standard supportive treatment for ALI/ARDS. With the substantial improvements in important clinical outcomes demonstrated in the ARDS Network trial,[30] the lower tidal volume strategy may now be considered standard supportive treatment for patients with ALI/ARDS, until another mechanical ventilation strategy is demonstrated to be superior.

Support of Arterial Oxygenation (PEEP vs F_{IO_2}):

Most ALI/ARDS patients require support for arterial oxygenation with a combination of increased F_{IO_2} and PEEP. Both of these treatments have potential adverse effects that must be carefully considered in individual patients. In laboratory animals, high levels of inspired oxygen cause physiologic and pathologic changes that are similar to other forms of ALI.[31–35]

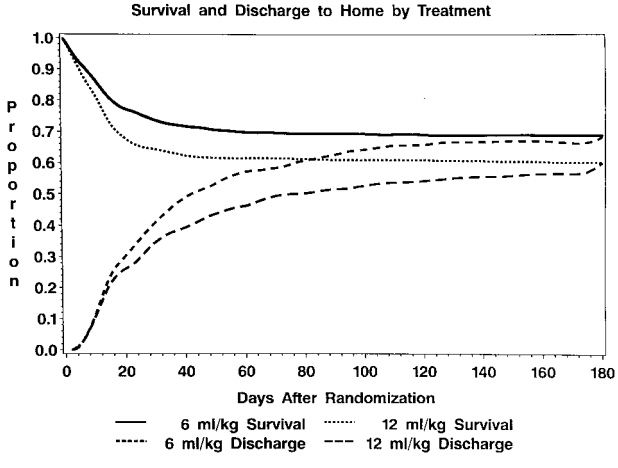

FIGURE 1. Proportions of patients surviving and achieving discharge home in traditional (12 mL/kg) and lower tidal volume (6 mL/kg) study groups. Mortality before discharge home with unassisted breathing was significantly lower in the lower tidal volume study group (39.8% vs 31.0%). Reprinted with permission of the ARDS Network.[30]

Table 2—*NIH ARDS Network Lower Tidal Volume Ventilation for ALI/ARDS Protocol Summary***

Variables	Protocol
Ventilator mode	Volume assist-control
Tidal volume	$\leq$ 6 mL/kg predicted body weight†
Plateau pressure	$\leq$ 30 cm H_2O
Ventilation set rate/ pH goal	6–35/min, adjusted to achieve arterial pH $\geq$ 7.30 if possible
Inspiratory flow, I:E	Adjust flow to achieve I:E of 1:1–1:3
Oxygenation goal	$55 \leq Pa_{O_2} \leq$ mm Hg or $88 \leq Sp_{O_2} \leq 95\%$
F_{IO_2}/PEEP (mm Hg) combinations‡	0.3/5, 0.4/5, 0.4/8, 0.5/8, 0.5/10, 0.6/10, 0.7/10, 0.7/12, 0.7/14, 0.8/14, 0.9/14, 0.9/16, 0.9/18, 1.0/18, 1.0/22, 1.0/24
Weaning	Attempts to wean by pressure support required when F_{IO_2}/PEEP $\leq$ .40/8

*Sp_{O_2} = oxyhemoglobin saturation by pulse oximetry.
†Predicted body weight for male subjects = 50 + (2.3 × [height in inches − 60]) or 50 + (0.91 × [height in centimeters − 152.4]); predicted body weight for female subjects = 4.5 + (2.3 × [height in inches − 60]) or 4.5 + (0.91 × [height in centimeters − 152.4]).
‡Further increases in PEEP to 34 cm H_2O allowed but not required.

In humans, no detectable oxygen toxicity occurred in normal subjects when the F_{IO_2} was $< 50\%$,[36] but impaired gas exchange was apparent after breathing 100% oxygen at sea level for approximately 40 h.[37] Diseased lungs may be more susceptible to injury from moderate hyperoxia.[38] However, initial exposures to a moderate F_{IO_2} or to endotoxin may confer some protection from hyperoxic lung injury.[39–42] Also, plasma proteins that leak into the pulmonary airspaces may have antioxidant properties.[43] Although the relationship of F_{IO_2} to oxygen-induced lung injury has not been clearly defined in ALI/ARDS patients, an $F_{IO_2} \leq 0.6$ is usually considered to be safe.[44]

PEEP reduces intrapulmonary shunt and improves arterial oxygenation,[1,12] thus allowing adequate arterial oxygenation at a lower F_{IO_2}, which may reduce pulmonary oxygen toxicity. However, adverse effects of PEEP include decreased cardiac output,[45–51] increased pulmonary edema formation,[52–54] increased dead space, increased resistance of the bronchial circulation,[55] and increased lung volume and stretch during inspiration, which may cause further lung injury or barotrauma.[19,20,56] These adverse effects of PEEP may be more pronounced in patients with direct lung injury (pneumonia and aspiration pneumonitis), in whom PEEP is not as effective at recruiting airspaces. Thus, beneficial effects of PEEP on arterial oxygenation must be weighed carefully in relation to potential adverse effects. Some investigators have suggested using higher PEEP to minimize F_{IO_2},[57] or to protect the lung from injurious mechanical forces that occur from ventilation with atelectasis at end-expiration.[58] The best strategy for using PEEP and F_{IO_2} in individual patients has not yet been defined. The levels of PEEP and F_{IO_2} shown in Table 2 represent a consensus among investigators and clinicians working in the NIH ARDS Network centers since 1995 and were used in the recent clinical trial that was associated with a 22% reduction in mortality in ALI/ARDS patients. This approach is recommended for most patients as standard therapy pending evidence for a better approach.

Volume-Cycled vs Pressure-Controlled Ventilation: Volume-cycled modes (volume-assist/control and intermittent mandatory ventilation) are used most frequently in ALI/ARDS patients,[59,60] but pressure-cycled modes can provide similar levels of ventilatory support. Inspiratory increments in transmural alveolar pressure and volume vary directly with each other according to the pressure-volume characteristics of the lung, regardless of ventilator mode. Hence, for a given tidal volume, there is no advantage or disadvantage of pressure-controlled vs volume-cycled modes in relation to risks of barotrauma or stretch-induced lung injury. Some have suggested that the rapid inspiratory airflow that occurs with pressure-controlled modes is more favorable for gas exchange. However, there were no differences in Pa_{O_2} or Pa_{CO_2} when ALI/ARDS patients received ventilation with volume-cycled vs pressure-controlled modes at constant tidal volume, end-expiratory alveolar pressure, and ratio of the duration of inspiration to the duration of expiration (I:E).[61,62] Some patients may be more comfortable receiving pressure-support ventilation, especially when there are substantial respiratory efforts. However, volume-cycled modes provide greater control over tidal volume, which is an important determinant of ventilator-associated lung injury.[56]

Sufficient gas exchange can usually be achieved with conventional mechanical ventilation. However, this may not be possible in some ALI/ARDS patients without causing ventilator-associated lung injury or oxygen toxicity. Numerous additional treatments to improve gas exchange or reduce ventilation or hyperoxia-associated lung injury are currently under investigation. Some new treatments utilize novel methods of mechanical ventilation. Others utilize pharmacologic mechanisms to improve gas exchange and lung mechanics. These approaches are discussed in the subsequent section on "Potential New Treatments Strategies."

Hemodynamic Management: Fluids, Vasopressors, and Oxygen Delivery

Optimal fluid management in patients with ALI/ARDS is a controversial issue. Substantial data from animal experimentation suggest that fluid restriction may reduce pulmonary edema in patients with increased pulmonary vascular permeability, as in ALI/ARDS. However, other experimental data[63,64] suggest that ALI/ARDS patients may benefit from a hemodynamic management strategy that increases oxygen delivery, which may require increased vascular volume.

Edema formation occurs at lower pulmonary capillary pressures when pulmonary vascular permeability is increased.[63–67] The experimental data that support fluid restriction in patients with ALI are supported by some observational clinical studies. Treatment of ARDS patients with diuretics or dialysis has been shown[68] to improve oxygenation and respiratory system lung compliance. One study[69] reported that survival in ARDS patients was related to negative fluid balance, while another study[70] reported that survival was greater in patients in whom there was a 25% reduction in pulmonary arterial wedge pressure. In a third study,[71] patients

who gained < 1 L of fluid after 36 h of being recruited into a study of ALI had a better survival rate (74%) than the others (50%). However, these observations do not prove that fluid restriction is efficacious. Fluid accumulation may have been a marker of the severity of systemic and pulmonary capillary permeability.

This issue was addressed in a prospective, randomized trial in which diuresis, fluid restriction, and hemodynamic management were directed either by measuring the extravascular lung water using a double-indication technique[71,72] or with standard clinical information, which included pulmonary arterial catheter data.[72] After 24 h of treatment, lung water was significantly lower in the extravascular lung water management group.[72] These patients also required a shorter duration of mechanical ventilation and a shorter stay in the ICU, but survival was not significantly different between the groups. Furthermore, the study population included patients with hydrostatic pulmonary edema, who would be expected to benefit from aggressive fluid restriction.

Fluid restriction may reduce cardiac output and tissue perfusion, which could cause or worsen nonpulmonary organ dysfunction. In many ALI/ARDS patients, dysfunction of multiple organs and systems occurs from a systemic inflammatory response.[10,11,73–76] A related explanation for multiple organ dysfunction is that tissue oxygen delivery is inadequate in some systemic inflammatory conditions such as sepsis or severe trauma, even when cardiac output and oxygen delivery are normal.[77,78] Some investigators[78,79] have suggested that organ function and clinical outcomes in ALI/ARDS patients would improve if supranormal levels of oxygen delivery were achieved with vigorous volume repletion, transfusions of packed RBCs, or inotropic medications. Several clinical trials addressed this question, but the results were disparate. In postoperative or posttrauma patients, there were trends toward decreased mortality with supranormal oxygen delivery.[79–87] However, there were no beneficial effects of this strategy in ALI/ARDS patients.[88,89] Furthermore, one randomized trial[90] reported increased mortality in patients who received a supranormal oxygen delivery strategy.

A recent international consensus conference[91] on tissue hypoxia provided guidelines for management of oxygen delivery and for reduction of oxygen demand in critically ill patients. The consensus committee concluded that ". . . timely resuscitation and achievement of normal hemodynamics is essential." To promote oxygen delivery, initial management should ensure adequate vascular volume. There was no clear evidence favoring colloid vs crystalloid solutions for this purpose. Blood transfusion should be considered when hemoglobin concentration is < 10 g/dL. However, a higher threshold may be better in patients without cardiovascular disease.[92] Reduction in oxygen demand should be achieved first with sedation and analgesia. Neuromuscular blocking agents are occasionally useful when sedation and analgesia are ineffective at reducing excessive muscular activity. However, use of neuromuscular blocking agents in critically ill patients may contribute to neuromuscular complications such as myopathy and neuropathy. Judicious and sparing use of these drugs is recommended.[93] Hyperpyrexia should also be treated, but excessive active cooling may increase oxygen demands if it causes shivering. Mechanical ventilation of patients in shock can reduce oxygen requirements from the high work of breathing. The consensus committee[91] on tissue hypoxia concluded that ". . . aggressive attempts to increase oxygen delivery to supranormal values in all critically ill patients are unwarranted."

Vasopressors are needed to support systemic BP or to increase cardiac output in patients with shock. There is no clear evidence that any vasopressor or combination of vasopressors is superior. In general, a prudent approach in ALI/ARDS patients is to restore intravascular volume to euvolemic levels (central venous pressure of approximately 4 to 12 mm Hg or pulmonary capillary wedge pressure of approximately 6 to 14 mm Hg) and then to use a vasopressor such as dopamine to achieve a mean arterial pressure of 55 to 65 mm Hg (perhaps higher in patients with chronic systemic hypertension). However, both fluid and vasopressor therapy must be guided by clinical indexes of organ perfusion. Urine output, blood pH, and base deficit are helpful to assess the adequacy of organ perfusion. In some patients, a pulmonary arterial catheter may provide useful additional information (cardiac output and pulmonary arterial wedge pressure), especially when there is left ventricular dysfunction or pulmonary hypertension, which are common in patients with ALI/ARDS.[63] Dobutamine may be useful as a positive inotropic agent and, in some patients, to reduce systemic vascular resistance. More details regarding use of vasopressors in ALI/ARDS patients are available in several sources.[63,94,95] New information on the issue of fluid management and the value of a central venous vs a pulmonary arterial catheter will be forthcoming from a large prospective NIH ARDS Network trial that is currently underway.

Vasodilators

Most ALI/ARDS patients have mild-to-moderate pulmonary arterial hypertension. A progressive rise in pulmonary vascular resistance has been observed

in patients who die from ALI.[46] The cause of pulmonary arterial hypertension is multifactorial, and may include hypoxic vasoconstriction, destruction and/or obstruction of the pulmonary vascular bed, and high levels of PEEP.[63] In some patients, pulmonary arterial hypertension can lead to cardiac dysfunction from right ventricular overload.[63] In several studies, investigators have attempted to improve ALI/ARDS management by lowering pulmonary arterial pressure with pulmonary vasodilators. For example, hydralazine appears to be more efficacious in increasing cardiac output than nitroprusside without increasing the shunt fraction,[96] probably because it does not influence hypoxic vasoconstriction.[97] However, hydralazine has not been evaluated in randomized, controlled trials. Preliminary studies[98] suggested that a continuous infusion of prostaglandin E_1 could improve survival in addition to cardiac output and oxygen delivery, but a randomized, double-blind, multicenter study[99] did not confirm these results. IV prostacyclin was also promising, but its vasodilator effect caused adverse effects in systemic hemodynamics.[100]

Nitric oxide (NO) is a powerful endogenous vasodilator.[101,102] Because it is rapidly inactivated, its vasodilatory effects are restricted to the blood vessels at the site of generation or administration. NO inhalation dilates pulmonary vessels perfusing aerated lung units, diverting blood flow from poorly ventilated or shunt regions. Because of these pharmacologic and physiologic effects, gaseous NO is potentially an ideal agent to treat pulmonary hypertension and severe hypoxemia in ALI/ARDS patients. Encouraging results in some animal models[103–105] led to the evaluation of the therapeutic potential of NO in ALI/ARDS patents. In 9 of 10 consecutive ALI/ARDS patients, inhaled NO at a concentration of 18 ppm reduced mean pulmonary artery pressure from a mean of 37 to 30 mm Hg. This was associated with a decrease in intrapulmonary shunt from 36 to 31% and an increase in Pao_2/Fio_2 of 47.[106] Important clinical outcomes were not assessed in this study. In a randomized, double-blind study of different doses of inhaled NO (1.25 to 80 ppm) in ALI/ARDS patients, improvements in oxygenation were modest and not sustained after the first day of treatment.[107] Interestingly, the results of a recent unpublished, prospective, double-blinded, randomized French phase III study of inhaled NO for ARDS in 208 patients also demonstrated no effect on mortality or the duration of mechanical ventilation.[108] The results of these recent trials suggest that NO will not become part of standard therapy for ALI/ARDS. There may a role for NO in some ALI/ARDS patients with severe refractory hypoxemia and pulmonary arterial hypertension.

Management of Infection in the ALI/ARDS Patient

Patients with ALI/ARDS frequently die from uncontrolled infection. The infection may have been the initial cause of ALI/ARDS, as in nonpulmonary sepsis (see section on "Treatment of the Inciting Clinical Disorder"). There is also a high risk of developing nosocomial infections, such as pneumonia and catheter-related sepsis. Since uncontrolled infection of any cause is associated with the development of multiple organ dysfunction, a major objective of standard supportive care in patients with ALI/ARDS is to identify, treat, and prevent infections. The remainder of this section will give an overview of the incidence, diagnosis, treatment, and prevention of nosocomial pneumonia in patients with ALI/ARDS. The diagnosis and treatment of other infections such as catheter-related sepsis are not substantially different in ALI/ARDS than in other critically ill patients.

Almost all aspects of the management of nosocomial pneumonia in ALI/ARDS are controversial, including the incidence. Several prospective studies have attempted to quantify the incidence prospectively, with varied results. In a study[109] of scheduled BAL and protected specimen brushing (PSB) in 105 patients with ALI/ARDS in Seattle, WA, the incidence of nosocomial pneumonia diagnosed by quantitative BAL or PSB cultures was only 15%. However, antibiotic use may have inhibited bacterial growth in culture in this study, leading to underdiagnosis of pneumonia. Two prospective French studies of ALI/ARDS patients with suspected ventilator-associated pneumonia used either BAL[110] or BAL and plugged telescoping catheter sampling[111] for quantitative cultures and reported a much higher incidence, 55 to 60%. Sampling of distal airway secretions was done prior to any changes in antibiotic therapy in both studies, probably accounting for the much higher yield from quantitative cultures. Most pneumonias occurred late in the course of ALI/ARDS, after the first 7 days. Interestingly, in all three studies, the presence or absence of ventilator-associated pneumonia had little or no effect on mortality.

The diagnosis of nosocomial pneumonia in patients with ALI/ARDS is particularly difficult. The usual clinical criteria for pneumonia such as a new radiographic infiltrate, fever, and leukocytosis are commonly present in ALI/ARDS patients, even when infection is absent.[112] However, many ALI/ARDS patients have evidence of pneumonia at autopsy that was not recognized before death.[113–115] Culture of endotracheal aspirates may be misleading, since most patients receiving prolonged ventilatory support develop colonization of the upper airway and

trachea. Several attempts have been made to assess the value of bronchoscopy with PSB or lavage to sample distal airway secretions in patients with suspected lung infections. The results have been variable and controversial. Only one study[116] has attempted to study the effect of different diagnostic techniques on morbidity and mortality. In this trial,[116] 413 patients receiving mechanical ventilation with suspected ventilator-associated pneumonia were randomized to antibiotic management strategies using endotracheal aspirates or bronchoscopy with protected specimens. Mortality at 14 days was significantly lower in the bronchoscopy group. However, only a minority of patients in this study[116] had ALI/ARDS, and management of the noninvasive arm of the study may have been suboptimal.

Regardless of whether bronchoscopic or more conservative techniques are used for diagnosis, the prompt initiation of appropriate empiric therapy while awaiting the results of cultures is critically important. Empiric therapy should be guided by local patterns of microbial incidence and resistance. It is also important to remember that administration of adequate antibiotics does not always improve outcome.[114] It is beyond the scope of this review to present an in-depth discussion of antibiotic treatment for ventilator-associated pneumonia. The reader is referred to the recent consensus statement from the American Thoracic Society for detailed recommendations.[117]

Given the high incidence of nosocomial pneumonia in patients with ALI/ARDS receiving ventilation, strategies for the prevention of nosocomial pneumonia are an important area of investigation.[117] Hand washing by medical personnel is of proven value but is often overlooked. Other areas that are currently being studied in clinical trials include the continuous suctioning of subglottic secretions to prevent their aspiration, and the development of new endotracheal tubes that resist the formation of a bacterial biofilm that can be embolized distally with suctioning.

Nutrition

The provision of adequate nutrition via the enteral or parenteral routes has become the standard of care for critically ill patients, including those with ALI/ARDS, and is recommended by the authors. Guidelines for nutrition in ICU patients have recently been summarized by a consensus group of the American College of Chest Physicians.[118] The goals of nutritional support include the provision of adequate nutrients for the patient's level of metabolism, and the prevention and treatment of deficiencies of macronutrients and micronutrients while attempting to minimize complications related to the mode of nutritional support. It is worth noting that the benefits of nutritional support in critically ill patients have not been conclusively demonstrated by comparison to a control group which did not receive nutritional support. The lack of controlled clinical trials in this area has led at least one expert[119] to recommend that nutritional supplementation be withheld from critically ill patients. Nevertheless, the authors believe that the available evidence supports the administration of nutritional support in ALI/ARDS patients.

The route of administration of nutrition in ALI/ARDS will be influenced by the individual patient's condition and ability to tolerate enteral feeding. Parenteral nutrition has been used frequently in ALI/ARDS patients, but experimental and clinical trials suggest that enteral nutrition may be superior.[118] In animal models, lack of enteral nutrition promoted bacterial translocation from the gut.[120] Normal human volunteers who received parenteral nutrition had higher levels of systemic and hepatic vein tumor necrosis factor (TNF), arterial glucagon and epinephrine, and increased febrile responses to endotoxin compared to subjects who received enteral nutrition.[121] Enteral nutrition is also associated with a lower incidence of infectious complications than parenteral nutrition,[122] and is less costly. Thus, there is enough evidence to support the use of enteral feeding over parenteral nutrition when possible. However, since enteral nutrition is sometimes not tolerated in critically ill patients,[123] parenteral nutrition will frequently be needed. It is reassuring to note that in a meta-analysis[124] of studies comparing total parenteral nutrition to enteral nutrition after major surgery or critical illness, there was no difference in mortality between the two groups. In addition, when Cerra et al[125] examined the impact of parenteral vs enteral nutrition in 66 patients with sepsis at high risk for organ failure, they found no difference in the incidence of organ failure or mortality in the two groups.

The composition of nutritional supplementation in patients with ALI/ARDS is an area of ongoing research. One study[126] has reported that a high-fat, low-carbohydrate diet can reduce the duration of ventilation in patients receiving mechanical ventilation, presumably by reducing the respiratory quotient and the level of carbon dioxide production. However, the most common cause of a high respiratory quotient in critically ill patients is simple overfeeding.[118] Another approach has been to supplement feeding with immunomodulatory nutrients including amino acids such as arginine and glutamine, ribonucleotides, and omega-3 fatty acids. A meta-analysis[127] of immunomodulatory nutritional supplementation in patients with critical illness

showed a decrease in infectious complications and duration of hospital stay, but no difference in mortality. In the only study[128] to date (and to our knowledge) of patients with ALI/ARDS, a diet high in fish oil, γ-linolenic acid, and antioxidants shortened the duration of mechanical ventilation and reduced new organ failures but had no effect on mortality. Until larger multicenter trials of immunomodulatory nutritional supplementation in patients with ALI/ARDS are available, standard nutritional formulations are recommended with avoidance of overfeeding.

Potential New Treatment Strategies for ALI/ARDS

Several promising new approaches for improving pulmonary gas exchange are currently being assessed in clinical trials and could contribute further to improved outcomes in patients with ALI/ARDS. It is important to realize, however, that mortality in patients with ALI/ARDS is closely related to factors such as hepatic failure and severe infections.[10,11,73,129] Reduction of mortality in these patients may require improved management of the conditions that cause or contribute to the dysfunction of nonpulmonary organ systems.

New Approaches to Mechanical Ventilation

Lung-Protective Ventilation With Higher PEEP: PEEP is traditionally used to achieve adequate arterial oxygenation without resorting to potentially toxic oxygen concentrations.[59] However, there may also be lung-protective effects of PEEP. Several animal studies[19,130,131] suggest that PEEP may prevent lung injury from repeated opening and closing of small bronchioles and alveoli, or from excessive stress at margins between atelectatic and aerated lung units. This mechanism of ventilator-associated lung injury may be more likely in patients with indirect causes of ALI/ARDS, as in sepsis and trauma, in which elevations in airway pressure typically cause substantial airspace recruitment.[132,133] Some investigators[58] have suggested that PEEP should be customized in individual patients after assessments of the pressure-volume characteristics of the respiratory system or lungs. Studies with experimental ALI[134] and humans with ALI/ARDS[135] demonstrated reductions in inflammatory cytokines in the alveolar lavage fluid and plasma when higher PEEP was used. This protective effect may require PEEP levels that are substantially higher than those typically used to support arterial oxygenation. In a prospective, randomized trial,[58] clinical outcomes improved in patients who received mechanical ventilation with higher PEEP levels compared to those who received traditional PEEP levels. However, in this study,[58] higher PEEP was used in conjunction with lower tidal volumes and other measures to reduce ventilator-associated lung injury. Because of the many potential adverse effects of PEEP, it is important to confirm that mechanical ventilation with higher PEEP levels, independent of other lung-protective strategies, will improve important clinical outcomes in ALI/ARDS patients. The NIH ARDS Network is currently conducting a trial to test the value of higher levels of PEEP.

Noninvasive Positive-Pressure Ventilation: Endotracheal intubation is required for most applications of positive-pressure ventilation. Complications of endotracheal intubation include upper-airway injuries, tracheomalacia, tracheal stenosis, sinusitis, and ventilator-associated pneumonia. Noninvasive positive-pressure ventilation (NIPPV) uses a tight-fitting face mask as an alternative interface between the patient and ventilator to avoid these complications.[136] NIPPV has additional advantages of allowing some verbal communication by patients, and some patients can eat during short respites from the face mask. Studies[137–139] in ALI/ARDS patients demonstrated fewer cases of nosocomial pneumonia and shorter requirements for ventilator assistance in patients who received NIPPV as compared to those who received ventilation via endotracheal tubes. However, NIPPV is not feasible in delirious or obtunded patients.[140] Moreover, air leaks from the face mask may prevent adequate ventilatory assistance in patients who require high inspiratory airway pressures. Additional time commitments by nurses or respiratory therapists may be needed during the initial period of support with NIPPV.[141]

High-Frequency Ventilation: High-frequency ventilation (HFV) utilizes very small tidal volumes with very high respiratory rates.[142,143] It is an attractive approach to mechanical ventilation in patients with ALI/ARDS because it achieves the two main lung-protective objectives (avoiding both overdistention and ventilation with atelectasis at end-expiration) while maintaining normal $PaCO_2$ as well as arterial oxygenation.[144] A trial[145] of HFV in premature infants with respiratory distress did not demonstrate a significant effect on morbidity or mortality. However, the ventilation procedures in this study[145] did not use high mean airway pressures to achieve high levels of alveolar recruitment, as is currently recommended.[146] More recent studies[147–149] of HFV in patients with neonatal respiratory distress demonstrated reduced chronic lung disease in survivors and other encouraging trends toward improved outcomes.

The results of a large randomized, controlled trial[150] of HFV in adults with acute respiratory failure were disappointing, but this study included a heterogeneous group of patients. Moreover, the HFV procedures in this trial[150] were not designed to avoid ventilation with atelectasis at end-expiration. Uncontrolled studies[151,152] reported that gas exchange could be maintained at acceptable levels with HFV in patients with severe ARDS. Randomized trials will be necessary to determine if important clinical outcomes improve with HFV when compared to conventional ventilator-based lung-protective strategies.

Tracheal Gas Insufflation: Physiologic dead space is elevated in patients with ALI/ARDS, and small tidal volume ventilation frequently causes hypercapnia and acute acidosis. Tracheal gas insufflation (TGI) is an adjunct to mechanical ventilation that reduces dead space.[153–157] It is therefore attractive for use with small tidal volume ventilation in ALI/ARDS patients to attenuate the resulting hypercapnia and acidosis.

Without TGI, the bronchi and trachea are filled with alveolar gas at the end of exhalation. This carbon dioxide-laden gas is forced back into the alveoli during the next inspiration. With TGI, a stream of fresh gas (approximately 4 to 8 L/min) is insufflated through a small catheter or through small channels in the wall of the endotracheal tube into the lower trachea, flushing the carbon dioxide-laden gas out prior to the next inspiration. TGI may cause desiccation of secretions and airway mucosal injury, and the TGI catheter may become a nidus for accumulation of secretions. TGI may also cause auto-PEEP from the expiratory flow and resistance of the ventilator-exhalation tubes and valve. The development of special equipment and explicit guidelines may allow clinicians to use TGI in the near future to manage patients with severe hypercapnia and acidosis.

Proportional-Assist Ventilation: Like other modes of positive-pressure ventilation, proportional-assist ventilation elevates airway pressure during inspiration. Unlike other modes, the inspiratory airway pressure assistance varies directly with patient effort.[158] This allows breath-to-breath variations in inspiratory airflow and tidal volume, as with pressure-support ventilation, but the magnitude of the pressure assistance increases with patient effort. Moreover, the inspiratory assistance can be customized to the elastance and resistance properties of each patient's respiratory system. Proportional-assist ventilation can also be adjusted to provide more or less positive-pressure assistance, depending on a patient's ability to sustain some ventilation. This mode is most favorable for breathing comfort and for reducing unnecessary work of breathing. It may be the best mode to use with NIPPV.[159]

Inverse-Ratio Ventilation and Airway Pressure-Release Ventilation: Some investigators[160,161] have suggested that atelectatic alveoli may be recruited and stabilized by extending the duration of inspiration and shortening the duration of expiration. If so, then shunt could be reduced and arterial oxygenation improved without increasing PEEP, inspiratory airway pressures, tidal volume, or lung stretch.

Inverse-ratio ventilation (IRV) is associated with shunt reduction and improved arterial oxygenation in patients with ALI/ARDS.[161–163] However, the short exhalation times of IRV probably cause some auto-PEEP.[164,165] Thus, improved gas exchange in previous studies with IRV may have occurred because of an increase in end-expiratory alveolar pressure. In three studies[61,62,166] in ARDS patients, effects of IRV on shunt and oxygenation were compared with effects of PEEP without IRV. When end-expiratory alveolar pressures or thoracic volumes were matched during IRV and conventional ventilation, arterial oxygenation and shunt were similar. These studies suggest that the mechanism by which IRV improves oxygenation is the same as with externally applied PEEP: that shunt reduction does not occur with IRV unless there is increased end-expiratory alveolar pressure.[167] Because IRV is very uncomfortable, most patients will require heavy sedation, and many will require neuromuscular blockade. There is growing awareness of complications from sedation and paralysis in critically ill patients.[93,168]

Airway pressure-release ventilation (APRV) is similar to IRV, but patients can breathe spontaneously during the prolonged periods of elevated airway pressure.[169–171] Thus, APRV may be considered a hybrid of pressure-controlled IRV and intermittent mandatory ventilation. A related mode, intermittent mandatory pressure-release ventilation (IMPRV), provides an inspiratory pressure support to some or all of the spontaneous efforts that occur independent of the IRV-like cycle of the ventilator.[172] This can further reduce work of breathing and oxygen cost of breathing and enhance alveolar ventilation while retaining some potential lung-protective effects of IRV. Arterial oxygenation may improve with APRV and IMPRV, but as with IRV, air trapping may occur from the very short periods of exhalation. If improved oxygenation requires air trapping, then it is not clear that lung protection can be achieved with these modes. To our knowledge, there are no controlled studies demonstrating improvements in key clinical outcomes in patients who received IRV, APRV, or IMPRV.

Surfactant Replacement Therapy

Surfactant, which is normally produced by type II pneumocytes, decreases surface tension at the air-fluid interface of small airways and alveoli. Without the beneficial effect of surfactant, alveoli may collapse and resist opening, even with high airway pressures. In respiratory distress syndrome of premature infants, surfactant production by the immature lung is deficient and surfactant replacement therapy is beneficial.[173] In ALI/ARDS, injured type II pneumocytes produce less surfactant, and plasma proteins that leak into the alveolar airspaces inactivate existing surfactant. Moreover, a change in the lipid composition of surfactant contributes to poor surfactant function.[174] The resulting increase in surface tension leads to atelectasis and decreased lung compliance[174] and may also increase edema formation.[175] Several experimental studies in ALI models demonstrated improved pulmonary function, including lung compliance and oxygenation, when exogenous surfactant was administered.[174]

Initial clinical studies[176] of exogenous surfactant therapy in patients with ARDS were encouraging. However, in a multicenter, randomized, placebo-controlled trial[177] in 725 patients with sepsis-induced ARDS, an artificial protein-free surfactant given by aerosol did not affect arterial oxygenation, duration of mechanical ventilation, or survival. There are several possible explanations for these results. First, surfactant delivery to the alveoli may have been inadequate. It is estimated that only 5% of the aerosolized dose administered in this trial reached the distal airspaces.[178] Second, artificial protein-free surfactants may not be as effective as natural surfactants or protein-containing artificial surfactant.[174] Third, the inflammatory injury in patients with ARDS often progresses to fibrotic destruction of the lung. This may not be ameliorated by surfactant replacement. Fourth, most patients with ALI/ARDS do not die from respiratory failure but instead from dysfunction or failure of multiple nonpulmonary organ systems.[10,11,74] Surfactant therapy, even if optimally effective in reducing surface tension, alveolar collapse, and shunt, would not have a direct effect on uncontrolled infections and nonpulmonary organ dysfunction. Some newer surfactant preparations with recombinant surfactant proteins are in current clinical trials in ALI/ARDS patients. In these studies, the surfactant preparations are being delivered into the lung through the endotracheal tube or by bronchoscopic instillation.

Extracorporeal Gas Exchange

Despite maximal supportive care with mechanical ventilation, some patients with ALI/ARDS experience refractory hypoxemia, leading some investigators to suggest that extracorporeal membrane oxygenation (ECMO) would be useful in these patients.[179] A prospective, multicenter, randomized trial[180] was conducted to compare ECMO to conventional ventilation alone; mortality in both groups of patients was approximately 90%.

Since the initial experience with ECMO, extracorporeal gas exchange technology has been improved to decrease complications and improve outcomes. In the early ECMO trial, oxygenation was the primary objective. To achieve effective arterial oxygenation, blood flow through the extracorporeal device had to be $> 50\%$ of cardiac output. Extracorporeal carbon dioxide removal ($ECCO_2R$) has now been developed with the primary objective of reducing the high respiratory rates and tidal volumes required to achieve normal $PaCO_2$, thereby decreasing ventilator-associated lung injury. This goal can be achieved with lower extracorporeal blood flow rates, but achieves only 20 to 30% of total oxygen requirements.[181] In $ECCO_2R$, most oxygenation is still achieved through the lungs, but this requires much less mechanical ventilation support than mechanical ventilation without $ECCO_2R$.

In 1986, Gattinoni et al[182] reported mortality of 50% in 47 patients treated with low-frequency positive-pressure ventilation (LFPPV) and $ECCO_2R$. This was a striking reduction compared to the 90% mortality in a historical control group.[180] Brunet et al[183,184] also reported mortality of about 50% in their 23 patients treated with $ECCO_2R$, and mortality in a larger group of patients treated with $ECCO_2R$ was 53%. These results were encouraging, but many factors in addition to extracorporeal gas exchange may have contributed to the lower mortality rates. A prospective, randomized trial[185] compared important clinical outcomes in 40 patients with severe ARDS who received either conventional mechanical ventilation or LFPPV with $ECCO_2R$. There was no significant difference in mortality between the two treatment groups. Perhaps the beneficial effects from LFPPV were counteracted by complications from $ECCO_2R$, such as bleeding with increased transfusion requirements. These findings suggest that the improved mortality in the earlier, uncontrolled trials[182–184] was not from LFPPV with $ECCO_2R$, but instead from improvements in other aspects of critical care.

Prone Positioning

Prone positioning leads to substantial improvements in arterial oxygenation in approximately 65% of ARDS patients.[186–189] There is little information to predict which patients will respond positively to

prone positioning. However, the improvements in some patients are quite striking, allowing substantial reduction in F_{IO_2} and PEEP.

The mechanism by which the prone position improves oxygenation has been investigated experimentally. In a pig model of ALI, Lamm et al[190] demonstrated improved ventilation to previously dependent (dorsal) regions in the prone position. In the supine position, pleural pressures were higher near the more dependent dorsal regions due to hydrostatic gradients. Higher pleural pressures reduced transmural pressures of dependent bronchioles and alveoli, contributing to the tendency for atelectasis in these lung zones. In the prone position, pleural pressures appeared more uniform, allowing some dorsal regions to open and participate in ventilation and gas exchange. This suggests that prone positioning could prevent ventilator-associated lung injury by promoting more uniform distribution of tidal volume and by recruiting dorsal lung regions, preventing repeated opening and closing of small airways or excessive stress at margins between aerated and atelectatic dorsal lung units.

Pelosi et al[188] assessed lung mechanics and analyzed CT images of ARDS patients in the supine and prone positions. Chest wall compliance tended to decrease in the prone position, and tidal volume tended to redistribute toward previously atelectatic dorsal regions. Thus, in the prone position, the anterior chest wall may be constricted between the bed surface and the weight of the body above it, resulting in some redistribution of tidal volume to dorsal lung units close to the diaphragm, recruiting atelectatic lung units in this region, with an improvement in arterial oxygenation. There could also be lung-protective effects of prone positioning from the overall decrease in atelectasis at end-expiration.

Several ICU personnel are required to safely implement prone positioning. One person must ensure stability of the airway during the position change, since dislodgment of the endotracheal tube may not be immediately apparent and is difficult to manage in the prone position. Others must manipulate chest tubes, IV catheters, and monitoring devices. Once patients are in the prone position, procedures for routine care, such as bathing and daily assessments of IV catheter sites, must be adjusted and are frequently compromised. In a recent trial, clinical outcomes did not improve in ARDS patients randomized to prone positioning for at least 6 h/d vs patients randomized to remain supine.[191] More prolonged periods of prone positioning may be necessary to achieve lung protection and survival benefits.

There are no clinical studies to guide clinicians regarding the length of time each day that prone positioning should be maintained to achieve maximal beneficial effects. Moreover, there are no clear guidelines regarding when prone positioning should be initiated or discontinued. Some investigators recommend using prone positioning early in the course of ALI/ARDS, to improve lung recruitment, minimize ventilator-associated lung injury, and reduce requirements for PEEP and F_{IO_2}.[192] An aggressive approach maintains prone positioning for $\geq$ 20 h/d, allowing relatively brief periods of supine positioning for bathing, servicing of vascular catheters, and for relief of pressure on ventral surfaces. This schedule may be maintained until requirements for ventilator assistance diminish and weaning appears feasible.

Fluorocarbon Liquid-Assisted Gas Exchange

As previously discussed, reduced surfactant function and increased surface tension cause collapse of small airways and alveoli in ARDS patients. Surface tension can be eliminated by filling the lungs with a liquid such as saline solution. However, because of the low carrying capacity of saline solution for oxygen and carbon dioxide, it is impossible to maintain adequate gas exchange with saline solution ventilation. Organic fluorocarbon liquids can dissolve 17 times more oxygen than water,[192] have low surface tension, and spread quickly over the respiratory epithelium. They appear to be nontoxic, are minimally absorbed, and are eliminated by evaporation through the lungs. Reduced surface tension may improve alveolar recruitment, arterial oxygenation, and increase lung compliance, even with small amounts of the substance instilled into the lung, as with surfactant therapy.

Fluorocarbons have been used in animals with total liquid ventilation.[193] This approach requires a liquid ventilator-gas exchange device to oxygenate the liquid, deliver the tidal volume, and remove carbon dioxide. An alternative approach is partial liquid ventilation, in which the lungs are filled approximately to functional residual capacity. Gas ventilation is then continued with a conventional ventilator.[194–198] In these various animal models of lung injury, total and partial liquid ventilation improved gas exchange when compared to conventional ventilation. The improvement in gas exchange is probably explained by alveolar recruitment. Studies[199,200] in humans with ARDS also showed promising improvements in gas exchange. Atelectasis and alveolar filling are frequently worse in dependent lung regions,[14] and the dense fluorocarbon tends to "gravitate" to these regions, where it is of potentially greatest value for alveolar recruitment. Moreover, the weight and resulting pressure of the liquid in dependent regions may divert blood flow to nondependent, better-ventilated regions.

The use of mechanical ventilation with high airway pressures may still be injurious to the lung parenchyma during liquid ventilation, as during gas ventilation. In total liquid ventilation, there is also the risk of mechanical interference with venous return. There was minimal hemodynamic instability with partial liquid ventilation at a dose of 20 mL/kg.[194] Instillation of greater volumes of fluorocarbon may decrease cardiac output by a similar mechanism as high PEEP.[198] There are some encouraging reports of the safety and efficacy of partial liquid ventilation in adults[199] and pediatric patients[200] with ARDS, as well as in neonates with respiratory distress.[201] However, more investigation is needed to demonstrate improvements in key clinical outcomes before this novel technique can be adopted for routine clinical use in ALI/ARDS patients.

Anti-inflammatory Strategies

The inflammatory response in ALI is associated with recruitment of large numbers of neutrophils and monocytes to the distal airspaces of the lung and the release of proinflammatory molecules, including cytokines, oxygen radicals, and proteases.[202] Excessive inflammation may worsen ALI/ARDS. As discussed below, some recent studies suggested that important clinical outcomes in ALI/ARDS patients would improve with modulation of lung inflammation. Other studies were disappointing.

Therapeutic Strategies to Reduce Sepsis-Induced ARDS: Patients with ALI/ARDS from sepsis have higher mortality than patients with ALI/ARDS from most other causes.[10,73] Treatment of sepsis before or in the early phase of ALI/ARDS could improve outcomes in these patients. Unfortunately, the results of trials of high doses of glucocorticoids,[203–205] antiendotoxin monoclonal antibody, anti–TNF-α therapy, and anti–interleukin (IL)-1 therapy were disappointing. However, recently, activated protein C has been shown to reduce mortality in sepsis patients[206] by novel anti-inflammatory and anticoagulent mechanisms.[207]

Glucocorticoid Therapy: As discussed in the preceding section, high doses of glucocorticoids do not prevent the development of ARDS in patients with sepsis. In addition, randomized, controlled clinical trials[203–205] did not show beneficial effects when high doses of glucocorticoids were administered to ALI/ARDS patients early in their course. Interestingly, in one of these studies,[204] serum complement levels were not lowered in patients with sepsis-induced ARDS who were treated with high-dose methylprednisolone. Since some patients with late-phase ALI/ARDS have persistent inflammation, fibroproliferation, and inflammatory cytokine release in the airspaces of the lung, glucocorticoids at this late stage could modulate these processes and facilitate recovery. However, glucocorticoids could also increase risks of nosocomial infections, which would diminish chances for recovery. Several case series reports[208,209] suggested that glucocorticoids could lower mortality in some patients with severe ALI/ARDS when administered several days after ALI/ARDS onset. In a small, randomized, placebo-controlled trial,[210] important clinical outcomes were better in patients randomized to receive methylprednisolone in the late phase of ALI/ARDS. This was a small trial (16 patients randomized to receive methylprednisolone and 8 patients to receive placebo), and several patients crossed over between study groups. The NIH ARDS Network is conducting a larger prospective, randomized, double-blind trial to confirm these results.

Antioxidant Therapy: There is convincing evidence that reactive oxygen species play a major role in mediating injury to the endothelial barrier of the lung in the presence of endotoxin, bacterial sepsis, or hyperoxic lung injury. Antioxidant therapy has been useful in the prevention and the treatment of ALI in some animal models.[211] Patients with ALI/ARDS experience oxidative stress from neutrophil activation and from high levels of inspired oxygen.[212] Work by Quinlan et al[213] indicates that patients who do not survive ARDS sustain much greater levels of oxidative molecular damage, suggesting that their antioxidant defense mechanisms are weakened.

N-acetylcysteine and procysteine, oxygen free-radical scavengers and precursors for glutathione, were efficacious in some experimental studies.[211] In phase II clinical studies[214,215] in ALI/ARDS and sepsis, there were encouraging trends in important clinical outcomes in patients who received these agents. However, the results of a large, randomized, placebo-controlled trial failed to show beneficial effects of procysteine in patients with ALI/ARDS.[2]

Prostaglandin Agonists/Inhibitors: Prostaglandin E_1 is a vasodilator that blocks platelet aggregation and decreases neutrophil activation. This agent showed promise in experimental and preliminary clinical studies of lung injury.[98] However, a multicenter study[99] of 100 ALI/ARDS patients reported no evidence of reduced mortality in those treated with IV prostaglandin E_1. Liposomal delivery of prostaglandin E_1 was also not beneficial in a phase II study.[216]

The synthesis of cyclooxygenase products of the prostaglandin pathway, particularly thromboxane,

has been linked with abnormal airway mechanics, hypoxemia, systemic hypotension, and multiple organ dysfunction in animal models of lung injury. Therefore, a prospective, double-blind, randomized trial[207] tested the ability of ibuprofen, an inhibitor of the cyclooxygenase pathway, to reduce morbidity and mortality in 455 patients with sepsis who were at risk of multiple organ failure, including ARDS. Despite an 89% reduction in prostanoid levels, mortality rates in the placebo group (40%) and the ibuprofen group (37%) were similar, and there were no significant effects on the duration of shock or in organ failure-free days.[207]

Ketoconazole, a potent inhibitor of thromboxane and leukotriene synthesis,[217] was reported to prevent the development of ALI/ARDS in high-risk surgical patients.[218] However, when this agent was studied in an NIH-sponsored multicenter phase III trial[219] to test its efficacy for decreasing mortality and the duration of assisted ventilation in 234 patients with ALI/ARDS, there was no decrease in mortality for ketoconazole treatment (35%) vs the placebo group (34%), and the median number of ventilator-free days was 9 in the placebo group vs 10 days in the ketoconazole group.

Lisofylline and Pentoxifylline: Pentoxifylline is a phosphodiesterase inhibitor that inhibits neutrophil chemotaxis and activation in animal models of ARDS.[220–222] Limited clinical experience in humans suggests some beneficial effects,[223] but there is not enough information to allow definite recommendations for clinical use. Lisofylline is chemically related to pentoxifylline, but its anti-inflammatory mechanism is through inhibition of the release of free-fatty acids from cell membranes under oxidative stress.[224,225] In animal studies,[226] lisofylline inhibited release of TNF, IL-1, and IL-6, attenuated shock-induced lung injury in mice, and had favorable effects on the course of murine endotoxin shock. Unfortunately, a recently completed phase III trial[227] by the NIH ARDS Network in 220 ALI/ARDS patients showed no beneficial effects of lisofylline.

Anti–IL-8 Therapy and Other Potential Anti-inflammatory Strategies: Other anti-inflammatory strategies could be effective in attenuating lung injury or preventing its development in high-risk patients. One approach is to reduce the number of neutrophils that migrate into the extravascular space of the lung by interfering with neutrophil adhesion to the lung endothelium, or by reducing the release of chemotactic factors in the extravascular space. There is strong experimental evidence for inhibiting the release of IL-8, an important chemotactic stimulus for migration of neutrophils from an intravascular to an extravascular location. Monoclonal antibodies that neutralize IL-8 reduced acid-induced lung injury in rabbits.[228] Several clinical studies[229–233] indicate that substantial quantities of IL-8 are present in the BAL fluid or the pulmonary edema fluid of patients in the early phase of ARDS. Additional studies are needed, especially because of a concern for increased risk of infection with anti–IL-8 therapy. Clinical trials of anti–IL-8 therapy for prevention in high-risk patients or in early ALI/ARDS may soon be warranted.

Other potentially useful strategies for modulating inflammation in patients with ALI/ARDS include platelet-activating factor inhibitors, antiproteases, anticytokine therapies, and agents designed to inhibit the coagulation cascade. To our knowledge none of these strategies have been tested in clinical trials in patients with established ALI/ARDS.

Enhanced Resolution of Alveolar Edema: Until recently, attention was focused on pulmonary endothelial function during ALI/ARDS. It is now clear that the structure and function of the alveolar epithelium are also important determinants of lung injury.[234,235] The epithelium is the site of alveolar fluid reabsorption,[236] an essential step in the resolution of ALI/ARDS. Alveolar fluid clearance depends primarily on active sodium transport across the alveolar epithelium.[235] Substantial experimental work has elucidated the mechanisms that modulate sodium transport and water movement.

Several pharmacologic agents have been identified that can increase alveolar fluid clearance experimentally either by acting on the epithelial sodium channel or the sodium/potassium adenosine triphosphatase pumps. β_2-Adrenergic stimulation markedly increases alveolar fluid clearance in the normal lung of several species[236] and in the *ex vivo* human lung.[237] In most of these studies, the β_2-agonist was administered into the airspaces. β_2-Agonists administered IV and endogenous epinephrine released from the adrenal gland also markedly increase alveolar epithelial sodium and fluid clearance.[236] Data from a 1997 study[237] indicate that salmeterol, a lipid-soluble β_2-agonist, can maximally upregulate alveolar fluid clearance in the *ex vivo* human lung at a dose of only 10^{-6} mol/L. This is the same concentration that was achieved in the alveolar compartment in sheep studies in which salmeterol was aerosolized in a clinically relevant dosage of 5 mg/h.[238] These studies suggest that β_2-agonists can be delivered by aerosol in intubated patients receiving mechanical ventilation and can achieve concentrations in the distal airspaces of the lung that will enhance alveolar fluid clearance.

Can sodium and fluid transport be stimulated with β_2-agonists in the presence of lung injury? In three

recent studies[239–241] in hyperoxic lung injury models in rats, intra-alveolar terbutaline administration markedly increased alveolar fluid clearance. In these studies, the edema was probably confined predominantly to the interstitium. However, the results established that exogenous β_2-agonist therapy could increase alveolar and lung fluid clearance in the injured lung. In other studies,[236] alveolar fluid clearance was markedly increased by endogenous epinephrine release in the presence of endotoxemia or bacteremia. However, following prolonged hemorrhagic shock in rats, oxidant mechanisms decreased the response of the alveolar epithelium to β_2-agonist stimulation.[242] Thus, under some circumstances, the epithelium may not respond to β_2-agonist stimulation because of extensive injury and loss of alveolar type II cells or because of downregulation of the response to β_2-agonists. Controlled clinical trials are needed to evaluate aerosolized β-adrenergic agonist therapy in patients with ALI/ARDS.

In addition to aerosolized β_2-agonists, alveolar epithelial fluid clearance could be increased with systemically delivered β_2-agonists. Dobutamine, a commonly used β_2-adrenergic agonist, markedly increased alveolar and lung fluid clearance in an experimental rat model of pulmonary edema when administered IV at a clinically relevant dosage of at 5 μg/kg/min.[243] Dopamine, when administered at 5 μg/kg/min IV, increased alveolar fluid clearance in an isolated perfused rat model by increasing the activity of sodium/potassium adenosine triphosphatase pumps.[244] Thus, clinically available vasoactive agents could be useful in some patients with pulmonary edema to increase rates of alveolar fluid clearance.

Enhanced Repair of the Alveolar Epithelial Barrier: One of the hallmarks of ALI/ARDS is disruption of the alveolar epithelium with necrosis or apoptosis of alveolar type I cells. Effective recovery of lung function depends on reconstitution of the alveolar structure in the injured lung areas. As part of the repair process, alveolar epithelial type II cells proliferate and provide a provisional new epithelial barrier.[245] Ideally, alveolar epithelial proliferation would occur with a minimal fibrotic response. However, in some patients, activated myofibroblasts from the interstitium migrate into the alveoli through gaps in the basement membrane and attach to the luminal surface of damaged alveolar membranes. Myofibroblast replication at the air-lung interface may cause fibrosing alveolitis and obliteration of gas exchange units.[246,247] This process is controlled by endogenous mediators such as platelet-derived growth factor and other peptides.[247,248] Clinical evidence[249] suggests that collagen synthesis occurs in the early phase of ALI/ARDS. Thus, the severe fibroproliferative response in some patients in the late-phase of ALI/ARDS may be determined early in the course of lung injury.

The provision of a new epithelial barrier with type II cells may have beneficial effects in addition to restoration of the air-liquid interface. For example, re-epithelialization of the air-lung interface is associated with a gradual regression of intra-alveolar granulation tissue.[247] Also, the rate of alveolar epithelial fluid clearance in the subacute phase of bleomycin-induced ALI in rats was increased by $> 100\%$ over baseline levels.[250] Enhanced alveolar fluid clearance depends in part on extensive proliferation of alveolar epithelial type II cells.

Studies[251–253] suggest that hepatocyte growth factor and keratinocyte growth factor are major mitogens for alveolar epithelial type II cells, and intratracheal pretreatment of rats with keratinocyte growth factor (5 mg/kg) prior to induction of lung injury with hyperoxia, acid instillation, bleomycin, or radiation decreased severity of injury. The mechanism of protection may be due to increased alveolar fluid transport secondary to the increased numbers of alveolar type II cells and by other mechanisms, including increased release of surface-active material or more resistance of the alveolar epithelium to injury.

Conclusion

The decrease in ALI/ARDS mortality reported since 1991[254,255] is attributable to improvements in many aspects of care, such as ventilator management, diagnosis and treatment of infections, and nutritional support. However, mortality is still high, and some survivors suffer with various sequelae for months after recovery from critical illness.[256,257] Thus, further improvements in treatment are needed.

Improved understanding of the pathogenesis of ALI/ARDS has led to important advances in the treatment of ALI/ARDS, particularly in the area of ventilator-associated lung injury.[2] Standard supportive care for patients with ALI/ARDS should now include a protective ventilatory strategy with low tidal volume ventilation by the protocol developed by the NIH ARDS Network.[30] Further refinements of the protocol for mechanical ventilation will occur as additional clinical trials are completed. In addition, novel modes of mechanical ventilation are being studied and may augment standard therapy in the future. Although most anti-inflammatory strategies have been disappointing in clinical trials, further trials are underway to test the efficacy of late corti-

costeroids and other approaches to modulation of inflammation in ALI/ARDS. Furthermore, the recent success of activated protein C therapy for severe sepsis[206,207] makes it likely that the severity of sepsis associated with ALI/ARDS will be attenuated by this new therapy. In addition, basic research continues to drive the development of new treatment strategies. An exciting new area of research is the modulation of alveolar epithelial function and healing that may provide an important new direction for treatment of ALI/ARDS.

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