Evidence-Based Management of Acute Lung Injury and Acute Respiratory Distress Syndrome

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This report explores the efficacy of existing therapies for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), primarily in terms of clinically important outcomes such as the duration of mechanical ventilation and hospital mortality. Of the 15 therapies reviewed, the strongest evidence suggests that ALI/ARDS should be managed with a low-tidal-volume, pressure-limited approach, with either low or moderately high positive end-expiratory pressure. To date there have been few large, sufficiently powered, randomized controlled clinical trials of ALI/ARDS therapies that addressed patient outcomes. However, there is relatively strong evidence to support conservative fluid management and high-fat, anti-oxidant nutritional formulations. Although most pharmacologic ALI/ARDS therapies have been ineffective, high-dose methylprednisolone is indicated in the subgroups of ALI/ARDS patients who have *Pneumocystis carinii* pneumonia or are at risk of ARDS due to fat embolization. *Key words: acute lung injury, acute respiratory distress syndrome, ARDS, extracorporeal membrane oxygenation, high-frequency ventilation, nitric oxide, nutritional support, liquid ventilation, prone position, surfactant, evidence-based medicine.* [Respir Care 2004;49(7):793–809.

Introduction

Deciding what constitutes effective therapy for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) is difficult because of the inherent complexity of the disease process and a general lack of large, randomized clinical trials to prospectively evaluate therapies. Quite often treatment decisions for a particular patient must be based on either scant evidence or several studies with ambiguous or contradictory results. Under these circumstances there are 2 approaches for arriving at a decision. The traditional approach is called "authority-based" medicine, wherein expert opinion, such as that provided by a venerable clinician or textbook, is sought to inform a decision.[1] However, the authority-based approach has resulted in a wide variety of clinical practices and patient outcomes.[2] Over the past 30 years clinical decision-making has been moving gradually from a model based on a "hierarchy of authority" to one based on a "hierarchy of evidence": hence the term "evidence-based medicine."[3]

Evidence-based medicine uses explicit rules to evaluate evidence and grade recommendations for therapies (Tables 1 and 2).[3,4] In brief, the most reliable evidence (Level I) for clinical practice is data from a large, randomized controlled trial (RCT) with which there is a low risk of either false-positive or false-negative results. In a small RCT (Level II) there is a higher risk of false-positive and/or false-negative results. Less stringent observational study techniques that lack adequate controls provide lower-level evidence (Levels III through V). The lower the evidence level, the more likely the data will suffer bias and a tendency to *overestimate* the therapeutic efficacy of the tested treatment.[4]

The present report discusses the efficacy of ALI/ARDS therapies primarily in terms of improving clinically important outcomes such as the duration of mechanical ventilation and hospital mortality, whereas improvement in such outcomes as gas exchange is considered of lesser importance. Respiratory care for ALI/ARDS traditionally has focused on improving oxygenation, but many epidemiologic studies[5–8] and some clinical trials[9] have found no positive relationship between pulmonary oxygen transfer function and mortality. Thus, the traditional efforts of respiratory care ALI/ARDS practice might not affect outcomes that are relevant to patients.

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Lung-Protective Ventilation

Tidal Volume and Plateau Pressure

The initial evidence that low-tidal-volume, pressure-limited ventilation improves ARDS outcome came from a prospective, uncontrolled study.[10] Fifty-three patients were ventilated with a tidal volume (V_T) between 4 and 7 mL/kg, peak airway pressure of $\leq$ 30 cm H_2O, and permissive hypercapnia. Hospital mortality among those patients was significantly less than that predicted by the Acute Physiology and Chronic Health Evaluation (APACHE II) score (26.4% vs 53.3%, respectively, $p = 0.004$).[10] Since then 5 RCTs[9,11–14] have investigated the role of V_T and end-inspiratory plateau pressure (P_{plat}) on patient outcomes (Table 3). Only the studies by Amato et al[11] and the ARDS Network[9] found that limiting V_T and P_{plat} offered lower mortality than a traditional style of mechanical ventilation. In this report I refer to the Amato et al and ARDS Network studies as the "beneficial studies." In contrast, the studies by Brochard et al,[12] Stewart et al,[13] and Brower et al[14] failed to show benefit from limiting V_T and P_{plat}, so I refer to them as the "nonbeneficial studies." Attempts to reconcile the differences between the beneficial and nonbeneficial studies have produced 2 meta-analyses[15,16] and have been addressed in 3 reviews,[17–19] 2 evidence-based reviews,[3,20] and an editorial.[21]

The first attempt to explain the mortality differences between these RCTs noted that P_{plat} was higher in the control arms of the beneficial studies (37 and 33 cm H_2O) than in the nonbeneficial studies (27, 31, and 32 cm H_2O).[21] The simplicity of that appraisal has persuaded many in the critical care community that low V_T is less important than keeping the $P_{plat} \leq 32$ cm H_2O.

An alternative explanation is that the low V_T used in the negative trials was not low enough.[9,19] The trials have used different methods to calculate the V_T: either by predicted body weight,[9,14] ideal body weight,[13] dry body weight,[12] or measured body weight.[11] Ideal body weight overestimates predicted body weight, so the experimental V_T of 7.0 mL/kg in the study by Stewart et al[13] would translate into 8.0 mL/kg in the ARDS Network study.[9] Likewise, the ARDS Network study found that predicted body weight was 20% lower than the average measured body weight,[9] so the experimental V_T of 7.1 mL/kg used by Brochard et al[12] may have translated to 7.8 mL/kg in the ARDS Network study.[9] In fact, the 6 mL/kg V_T used by Amato et al[11] may have equaled a V_T of approximately 7.2 mL/kg in the ARDS Network study.[9]

Table 1. Evidence Levels

Evidence Level	Description	Advantage or Disadvantage
I	Large randomized clinical trials	Low risk of false-positive or false-negative results
II	Small randomized trials	More risk of false-positive or false-negative results
III	Nonrandomized studies that use a contemporaneous control group	More risk of bias that overestimates the efficacy of the therapy
IV	Nonrandomized studies that rely on historical control groups for comparison; expert opinion	More risk of bias that overestimates the efficacy of the therapy
V	Case study, case series, uncontrolled studies, expert opinion	More risk of bias that overestimates the efficacy of the therapy

It is important to mention that additional factors also may explain why the studies produced different results. A recent review of the pooled data from the nonbeneficial studies found that, after adjusting for baseline differences in covariates, the relative risk of death was lower in the lower-V_T arms of the nonbeneficial studies (Fig. 1).[22] This suggests that there were differences in comorbidities between the treatment groups that favored survival in the traditional-V_T groups of the nonbeneficial studies. Also, differences between the studies in how acidosis was managed may have influenced outcome.[17,20]

Meta-Analysis and the Interpretation of the ARDS Network Study Results

The first meta-analysis of lung-protective ventilation (LPV) was by Eichacker et al.[15] Meta-analysis is a research methodology commonly used in evidence-based medicine. Meta-analysis involves the quantitative analysis of data obtained by combining and synthesizing the results of 2 or more independent (but similar) studies to evaluate the effectiveness of a therapy considered in each of the independent studies.[23] It is important to emphasize that meta-analysis has only been in use since 1976 and its methods are complex, evolving, and controversial.[24]

Because V_T was calculated differently in the various LPV studies, Eichacker et al[15] focused on differences in P_{plat}. They observed that post-randomization P_{plat} in the control arms of the beneficial studies (33–37 cm H_2O) was greater than P_{plat} in the control arms of the nonbeneficial studies (28–32 cm H_2O). Their meta-analysis suggested that:

Table 2. Grade System for Recommendations for Therapy, Based on Evidence Level

Grade	Supported By
A	≥ 2 Level I studies
B	1 Level I study
C	Only Level II studies
D	≥ 1 Level III study
E	Level IV or V evidence

1. A lower P_{plat} cannot explain the better survival in the beneficial studies. Rather, the higher P_{plat} in the control arm of the beneficial trials may have increased mortality, thus giving the false impression that very low V_T (< 7 mL/kg) is beneficial.[15]

2. In the nonbeneficial trials there was a trend toward higher mortality in the low-V_T groups, signifying that low-V_T ventilation may be harmful.[15]

3. The control arms of the 2 beneficial trials did not represent "current best practice standards."[15]

4. As long as P_{plat} is ≤ 32 cm H_2O, ALI and ARDS patients should *not* be ventilated with a V_T of 5–7 mL/kg. That claim has been supported by others.[18,25]

The meta-analysis by Eichacker et al[15] has met with several criticisms[22,26–32] of its premises, methods, and conclusions,[15] including:

1. The premise that a world-wide standard for V_T and P_{plat} targets in ALI/ARDS management existed when the ARDS Network study was designed

2. The conclusion that low-V_T ventilation (5–7 mL/kg) may be detrimental

3. The methods used to conduct the meta-analysis

First, the suggestion by Eichacker et al[15] that a universally acknowledged "best clinical practice" existed in the mid-1990s was based on their interpretation of 3 descriptive studies of mechanical ventilation practice.[33–35] Eichacker et al[15] claim that in one study[35] nearly half of the physicians surveyed used a V_T similar to that received by patients in the ARDS Network trial before randomization. However, more than half of the physicians in that survey were using a V_T that equaled or exceeded the V_T used in the control arm of the ARDS Network trial. In fact, the lead author of that study[35] stated that his results did not support the contention by Eichacker et al[15] that there was a standard of care. Furthermore, Stewart,[27] Carmichael,[28] and Petty[29] disagreed with Eichacker et al on the proposition that low V_T is beneficial only when compared against an artificially high V_T. In addition, Brower[19] observed that the V_T used by the ARDS Network was actually 9.9 mL/kg when calculated by measured body weight. That value is similar to the 11.4 and 10.3 mL/kg measured-body-weight V_T used in 2 large RCTs of ARDS during the mid-1990s

Table 3. Synopsis of the 5 Clinical Trials of Traditional Mechanical Ventilation Strategy Versus Lower Tidal Volume and Lower End-Inspiratory Plateau Pressure Ventilation Strategy

Trial, Design, and Subjects	Interventions	Outcomes
NHLBI ARDS Network[9] (2000) Prospective, multi-center, randomized controlled trial Intent to treat 861 patients with ALI/ARDS Enrollment within 36 h of meeting criteria for ALI/ARDS	*Treatment arm:* V_T 4–6 mL/kg of predicted body weight, P_{plat} 25–30 cm H_2O *Control arm:* V_T 4–12 mL/kg of predicted body weight, P_{plat} 45–50 cm H_2O *Both Study Arms:* Ventilation mode: volume-controlled ventilation Fixed relationship of PEEP to F_{IO_2}, to maintain P_{aO_2} of 55–80 mm Hg Promote aggressive treatment of acidosis: f ≤ 35 breaths/min to maintain pH of 7.30–7.45 V_T and P_{plat} targets suspended if pH falls below 7.15 Slow infusion of sodium bicarbonate if pH < 7.15 or pH ≤ 7.25 with P_{aCO_2} ≤ 20 mm Hg Structured, aggressive weaning protocol using pressure-support ventilation Sedation/neuromuscular blockade, nutrition not controlled	*Hospital Mortality* Control arm: 39.8% Treatment arm: 31% (p = 0.005) *Ventilator-Free Days* Control arm: 10 Treatment arm: 12 *Nonpulmonary-Organ-Failure-Free Days* Control arm: 12 Treatment arm: 15 *Ventilation Variables* (treatment arm vs control arm) V_T: 6.2 vs 11.8 mL/kg P_{plat}: 25 vs 33 cm H_2O PEEP: 9.4 vs 8.6 cm H_2O
Amato et al[11] (1998) Prospective, multi-center, randomized controlled trial Intent to treat 53 patients with ARDS and lung-injury score ≥ 2.5	*Treatment arm:* V_T < 6 mL/kg of measured body weight, P_{plat}-PEEP < 20 cm H_2O, PIP < 40 cm H_2O, PEEP set 2 cm H_2O > lower inflection point on pressure-volume curve, or 16 cm H_2O Ventilation modes: pressure-controlled ventilation and pressure-support ventilation; pressure-controlled inverse-ratio ventilation (I:E > 1:1) when F_{IO_2} ≥ 0.50 f < 30 breaths/min Slow infusion of sodium bicarbonate for pH < 7.20 Alveolar recruitment maneuver after ventilator disconnection *Control arm:* Ventilation mode: volume-controlled ventilation Maintain P_{aCO_2} between 35–38 mm Hg by setting f between 12–24 breaths/min and setting V_T at 12 mL/kg measured body weight and then adjusting up to a maximum of 15 mL/kg *regardless of* P_{plat}. Inspiratory flow set between 50–80 L/min to prevent intrinsic PEEP. F_{IO_2} ≤ 0.60 with PEEP adjusted in increments of 3 cm H_2O above a minimum of 5 cm H_2O for S_{aO_2} < 90% *Both Study Arms:* Targeted P_{aO_2} 80 mm Hg Pulmonary artery catheter used for hemodynamic monitoring (pulmonary artery occlusion pressure < 15 mm Hg) Sedation/neuromuscular blockade, ventilator weaning, and nutrition protocols were the same	*28-Day Mortality* Control arm: 71% Treatment arm: 38% (p < 0.001) *Hospital Mortality* Control arm: 71% Treatment arm: 45% (p = 0.37) *Successful Weaning Rate* Control arm: 29% Treatment arm: 66% (p = 0.005) *Incidence of Barotrauma* Control arm: 42% Treatment arm: 7% *Ventilation Variables* (treatment arm vs control arm) V_T: 348 vs 768 mL P_{plat}: 30 vs 37 cm H_2O PEEP: 16 vs 8.7 cm H_2O
Brochard et al[12] (1998) Prospective, multi-center, randomized controlled trial Intent to treat 116 patients with ARDS (lung injury score > 2.5) and *only pulmonary organ failure*	*Treatment arm:* Volume-controlled ventilation with V_T < 10 mL/kg but > 6.0 mL/kg dry body weight, to maintain P_{plat} < 25 cm H_2O, but could increase to 30 cm H_2O if pH < 7.05 or F_{IO_2} > 0.90 *Control arm:* Volume-controlled ventilation with V_T 10–15 mL/kg dry body weight, to achieve P_{aCO_2} 38–42 mm Hg V_T not increased if PIP > 60 cm H_2O f could be increased rather than V_T *Both Study Arms:* PEEP titrated (0–15 cm H_2O) for either best oxygenation improvement or first PEEP level that increased P_{aO_2}/F_{IO_2} to > 200 mm Hg without hemodynamic deterioration Sedation/neuromuscular blockade not controlled Sodium bicarbonate *recommended* when pH < 7.05	*60-Day Mortality* Control arm: 37.9% Treatment arm: 46.6% (p = 0.38) *Ventilation Variables* (treatment arm vs control arm) V_T: 7.1 vs 10.3 mL/kg P_{plat}: 25.7 vs 31.7 cm H_2O PEEP: 10.7 vs 10.7 cm H_2O
Stewart et al[13] (1998) Prospective, multi-center, randomized controlled trial Intent to treat 120 patients at high risk for developing ARDS, with P_{aO_2}/F_{IO_2} < 250 mm Hg	*Treatment arm:* PIP ≤ 30 cm H_2O and V_T ≤ 8 mL/kg of ideal body weight. PIP could be increased in 2-cm H_2O increments up to 40 cm H_2O if pH < 7.0 (respiratory acidosis) *Control arm:* PIP ≤ 50 cm H_2O and V_T 10–15 mL/kg ideal body weight *Both Study Arms:* Ventilation mode: volume-controlled ventilation with decelerating flow pattern or pressure-controlled ventilation. PEEP 5–20 cm H_2O to maintain F_{IO_2} < 0.50 with S_{aO_2} 89–93% f 5–35 breaths/min to maintain P_{aCO_2} of 35–45 mm Hg Sodium bicarbonate infusion if pH < 7.0	*Hospital Mortality* Control arm: 47% Treatment arm: 50% (p = 0.72) *Ventilation Variables* (treatment arm vs control arm) V_T: 7.0 vs 10.7 mL/kg P_{plat}: 22.3 vs 26.8 cm H_2O PEEP: 8.6 vs 7.2 cm H_2O
Brower et al[14] (1999) Prospective, multi-center, randomized controlled trial Intent to treat 52 patients with ARDS	*Treatment arm:* V_T 5–8 mL/kg predicted body weight to keep P_{plat} < 30 cm H_2O *Control arm:* V_T 10–12 mL/kg predicted body weight or less if P_{plat} > 55 cm H_2O *Both Study Arms:* Ventilation mode: volume-controlled ventilation or synchronized intermittent mandatory ventilation with pressure-support of 5 cm H_2O f ≤ 30 breaths/min, adjusted to keep P_{aCO_2} 30–45 mm Hg Sodium bicarbonate permissible if pH < 7.30 and required if pH < 7.20 Fixed relationship of PEEP to F_{IO_2} to maintain P_{aO_2} 55–75 mm Hg	*Hospital Mortality* Control arm: 46% Treatment arm: 50% *Ventilation Variables* (treatment arm vs control arm) V_T: 7.3 vs 10.2 mL/kg P_{plat}: 24.9 vs 30.6 cm H_2O PEEP: 9.8 vs 8.8 cm H_2O

NHLBI = National Heart, Lung, and Blood Institute
ARDS = acute respiratory distress syndrome
ALI = acute lung injury
F_{IO_2} = fraction of inspired oxygen
V_T = tidal volume
P_{plat} = plateau pressure
PEEP = positive end-expiratory pressure
I:E = inspiratory-expiratory ratio
f = respiratory frequency
S_{aO_2} = arterial oxygen saturation
P_{aO_2}/F_{IO_2} = ratio of arterial partial pressure of oxygen to F_{IO_2}
PIP = peak inspiratory pressure

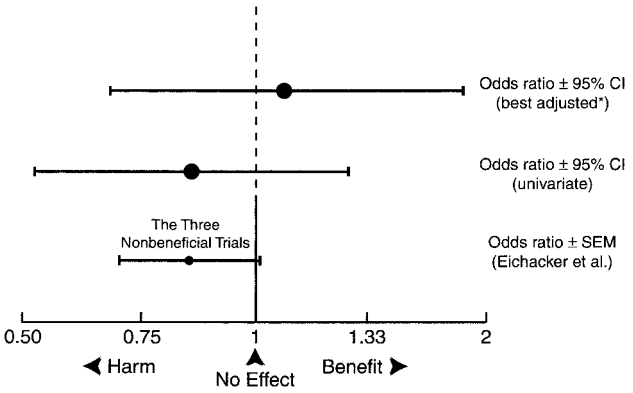

Fig. 1. Pooled odds ratio ± 95% confidence intervals (CIs, represented by the horizontal lines) from the 3 studies that found no benefit from lung-protective ventilation (the nonbeneficial trials). After model adjustments for baseline differences between the treatment groups in certain variables, such as the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen and Acute Physiology and Chronic Health Evaluation score, the best adjusted odds ratio of this meta-analysis suggests a survival benefit from lung-protective ventilation (odds ratio = 1.10). Thus, the negative findings in the 3 nonbeneficial studies were probably due to the between-group differences in baseline variables that favored outcomes in the traditional-ventilation group. (From Reference 22, with permission.)

(the Ibuprofen[36] and Exosurf[37] studies, respectively), in which the clinicians retained control of ventilator settings.

Second, the interpretation by Eichacker et al[15] that low-V_T ventilation may be detrimental was based on a nonsignificant trend toward a higher mortality in the 3 nonbeneficial studies. The ARDS Network countered that all 3 studies did not have sufficient statistical power to show lack of efficacy, and even if the studies were combined, the mortality difference between the treatment groups would remain insignificant.[26] As mentioned above, a thorough meta-analysis based on the pooled raw data from the nonbeneficial studies demonstrated that the apparent negative effects of low-V_T ventilation were probably due to an uneven distribution of comorbid factors that favored survival in the traditional V_T ventilation group.[22]

Third, the methodology used by Eichacker et al[15] to construct their meta-analysis has been criticized.[22,26,27,30–32] A major controversy in meta-analysis involves determining how and under what circumstances data from studies with different methodologies can be combined. Using summary statistics from the published literature (as was done by Eichacker et al[15]) rather than obtaining the raw data from each study yields less reliable results and a more biased estimate of effect size (ie, the degree to which a phenomenon, such as mortality, actually exists in a population).[24] As an example, baseline differences in the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (P_{aO_2}/F_{IO_2}), APACHE II score, and comorbidities between treatment groups and across the studies made questionable the decision to combine those studies for meta-analysis.[30]

Testing for heterogeneity among the studies included in the meta-analysis was done improperly; simply grouping studies together as beneficial and nonbeneficial was inappropriate.[31] In deciding whether studies can be grouped together, it is crucial to examine between-study differences in such factors as how V_T was set, how P_{plat} was managed, differences in time points at which mortality was assessed, and how co-interventions such as acidosis management were controlled. As an example, Meade and Herridge[20] found these differences between the studies to be sufficiently large as to prevent the pooling of data for quantitative assessment. Eichacker et al[15] attempted to assess mortality risk without considering that these studies used different end points (ie, 28-d mortality[11] vs 60-d mortality[12] vs hospital mortality[9,13,14]). For instance, Amato et al[11] reported significantly lower mortality with LPV at study-day 28, yet hospital mortality was not different between the groups. In fact, the hospital mortality rate in the LPV group was similar to the nonbeneficial trials (45%).[11]

Another important aspect of meta-analysis methodology relates to how studies with disparate sample sizes are weighted for statistical analysis.[24] Eichacker et al[15] failed to account for the fact that large differences in sample size influence the overall estimate of treatment effects.[17,26,31] When the data from all 5 studies were analyzed with proper weighting by sample size, the combined relative risk of mortality in the LPV treatment groups was 0.84, with a 95% confidence interval of 0.73 to 0.97 (Fig. 2).[17] In addition, 4 of the 5 studies were stopped early (either for efficacy or futility), which may have influenced the estimated treatment effect among the studies.[26] When clinical trials are stopped early, the resulting estimated treatment effects tend to be biased by the stoppage rules. For example, in studies that are stopped early because of futility the estimated mortality effects are biased toward overestimating the harmful effects of the experimental treatment, whereas when a study is stopped early for efficacy, the estimated mortality effects are biased toward overestimating the beneficial effects of the experimental treatment.[17]

A second meta-analysis, by Petrucci and Iacovelli,[16] used both fixed and random effects models for determining treatment effect size and assessed mortality risk based on comparable end points (mortality at study-day 28 vs hospital mortality). When the appropriate combination of studies[9,11,12] were examined based on mortality at study-day 28, the point estimate of mortality was significantly lower with LPV (relative risk 0.74, absolute risk difference −10%). When the appropriate combination of studies[9,11,13,14] was examined based on hospital mortality, the point estimate of mortality—although not statistically different—favored LPV (relative risk 0.82, absolute risk difference −8%). Petrucci and Iacovelli[16] concluded that LPV

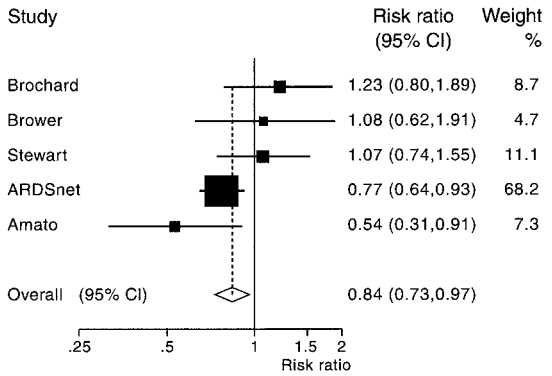

Fig. 2. Risk ratios ± 95% confidence intervals (CIs, represented by the horizontal lines) of mortality in the 5 clinical trials of lung-protective ventilation with patients suffering acute lung injury. The size of the squares indicates the weighting of the studies (according to sample size) in the meta-analysis. When the appropriate weighting is used the overall mortality risk with lung-protective ventilation is < 1, which suggests better outcomes with lung-protective ventilation than with a conventional ventilation strategy, with patients suffering acute lung injury. ARDSnet = Acute Respiratory Distress Syndrome Network. (From Reference 17, with permission.)

reduced mortality at study-day 28 and that the combined data strongly suggest that LPV may reduce hospital mortality. However, they also interpreted their meta-analysis as *cautiously* supportive of the contention that as long as P_{plat} is ≤ 32 cm H_2O, further V_T reduction *may* not offer additional mortality benefit.

The opinion that V_T reduction may not be necessary with ALI/ARDS patients as long as P_{plat} is ≤ 32 cm H_2O was recently addressed by the ARDS Network[38] in a post hoc analysis of mortality, by quartiles of P_{plat}. Among patients randomized to receive V_T of 12 mL/kg predicted body weight, the P_{plat} in the first and second quartiles was < 32 cm H_2O, compared to a P_{plat} of < 26 cm H_2O in the first and second quartiles of patients randomized to receive V_T of 6 mL/kg predicted body weight. However, there was a consistent trend toward lower mortality in each quartile of patients randomized to the low-V_T group, which suggests a possible mortality benefit if P_{plat} is reduced below 30 cm H_2O.

In conclusion, the RCTs regarding V_T and P_{plat} have led to disparate opinions regarding the regulation of V_T and P_{plat} with ALI/ARDS patients. Some believe that an intermediate V_T of 8–10 mL/kg is safe as long as P_{plat} is ≤ 32 cm H_2O;[15,18,25] others believe that either the ARDS Network trial currently provides the best evidence to guide clinical practice[19,26–29] or that there is sufficient evidence to support the use of low-V_T, pressure-limited ventilation.[3] However, the belief that an intermediate V_T of 8–10 mL/kg in conjunction with a P_{plat} ≤ 32 cm H_2O is relatively safe is not supported by credible evidence. Attempts to support that position by meta-analysis are unconvincing, as illustrated by the deeply flawed methodology of Eichacker et al[15] and the very cautious statements made by Petrucci and Iacovelli.[16] Therefore, the ARDS Network trial provides Level I evidence in support of using a V_T of 6 mL/kg predicted body weight and a P_{plat} of ≤ 30 cm H_2O in ALI/ARDS patients.

Open-Lung Strategy

An early approach to LPV for ARDS proposed (1) brief application (5–10 min) of high-pressure ventilation (peak airway pressure of 55 cm H_2O and positive end-expiratory pressure [PEEP] of 16 cm H_2O) to recruit and stabilize collapsed lung regions, and (2) low-amplitude pressure ventilation (≤ 20 cm H_2O) with a very brief expiratory time that induces intrinsic PEEP at approximately the same level used during the recruitment maneuver.[39] An alternative LPV approach is to set PEEP and V_T, respectively, according to the lower and upper inflection points of the inflation pressure-volume curve to prevent or ameliorate ventilator-associated lung injury from repetitive shear-stress and over-distention.[40,41] Those 2 LPV approaches, which were partially incorporated into the study by Amato et al,[11] require several different ventilator manipulations (pressure-controlled inverse-ratio ventilation, recruitment maneuvers, and high-level PEEP), each of which can, separately or in concert, promote lung-protection, so the interpretation of the relative benefit of any of these manipulations is uncertain.

Positive End-Expiratory Pressure

As mentioned above, it is difficult to assess the role of PEEP in improving mortality during LPV, based on the study by Amato et al.[11] Although mortality at study-day 28 was significantly lower with the open-lung approach, hospital mortality was not different from conventional ventilation. However, Amato et al[11] reported a significantly higher rate of successful weaning among patients managed with the open-lung approach. Recently, the ARDS Network announced the results of a study that compared low-V_T ventilation with the relatively-low-PEEP strategy used in the original ventilator trial with a higher-PEEP strategy.[42] The study was stopped early because of futility, but the overall hospital mortality rate was only 26%.[42] Although that study was negative, it provided Level I evidence that higher PEEP levels do not negatively impact a low-V_T strategy.

Recruitment Maneuvers

In animal models of ALI, tidal collapse and recruitment of alveoli potentiates lung injury by repetitive shear-stresses that develop both at the margins between areas of normal

and collapsed lung tissue[39] and with the sequential reopening of collapsed bronchioles and alveolar ducts.[43] Because this is believed to contribute to ventilator-associated lung injury in humans, periodic recruitment of atelectatic lung tissue has been recommended for ARDS patients.[44] The evidence for applying recruitment maneuvers to ARDS patients is ambiguous for several reasons. First, recruitment can be achieved with several different techniques, such as sustained (30–40 s) high-level continuous positive airway pressure (CPAP),[11] traditional sighs,[45] extended sighs,[46] intermittent high-level PEEP,[47] and brief periods (2 min) of super-PEEP (20–40 cm H_2O) with pressure-controlled ventilation.[48] Second, recruitment and derecruitment is a variable, temporally-mediated phenomenon that is not well understood.[49–51] This uncertainty was recently manifested by the acknowledgment that higher PEEP may be required to maintain lung volume after a recruitment maneuver.[44] Third, the underlying etiology of ARDS (ie, direct pulmonary injury vs indirect, blood-borne sources of lung injury) may strongly influence the efficacy of a recruitment maneuver, according to the degree of derangement in chest wall mechanics.[45,52] Fourth, the effectiveness of a recruitment maneuver may be linked to an interaction between the P_{plat} and PEEP achieved during a recruitment maneuver.[53]

Because lung injury is unevenly distributed in ARDS, a recruitment maneuver may potentiate injury by causing excessive regional end-inspiratory lung volume. Applying 30 cm H_2O of transpulmonary pressure (the pressure needed to fully recruit a normal, collapsed lung) may produce shear pressures of 140 cm H_2O at the margins between normal and collapsed lung tissue.[39] Although this argument is made by proponents of the recruitment maneuver, paradoxically it also raises the question of whether the *repetitive* use of the recruitment maneuver promotes lung injury. These issues must be clarified before an RCT can be done to test whether the addition of a recruitment maneuver to LPV either hastens ARDS recovery or improves mortality.

Virtually all of the clinical evidence on the efficacy of recruitment maneuvers comes from small, nonrandomized trials and case reports, the majority of which have reported only short-term improvement (from 20 min to 4 h) in oxygenation and pulmonary mechanics,[45,46,48,54–57] whereas other reports have found no discernable oxygenation improvement.[58] To date the only prospective RCT on the efficacy of recruitment maneuvers on oxygenation has been reported by the ARDS Network.[59] In that study 72 patients enrolled into the higher-PEEP arm of a recent LPV trial[42] were randomized to receive either CPAP of 35–40 cm H_2O for 30 s or a sham recruitment maneuver (ie, no intervention during the designated 30 s). The efficacy of the recruitment maneuver was assessed by changes in oxygen saturation measured via pulse oximetry (S_{pO_2}) as well as PEEP and F_{IO_2} requirements (which were strictly controlled by protocol) 8 h after the recruitment maneuver or sham recruitment maneuver. There was no difference between the groups in PEEP or F_{IO_2} requirement. Change in S_{pO_2} following a recruitment maneuver was highly variable, and the greatest incremental change in S_{pO_2} occurred within 10 min of the recruitment maneuver.[59] In conclusion, there is Level V evidence to support the use of recruitment maneuvers to provide at least short-term improvement in oxygenation and pulmonary mechanics and Level II evidence that brief periods of high CPAP are ineffective in producing sustained oxygenation improvement.

Use of the Pressure-Volume Curve to Set V_T and PEEP

It is commonly believed that the lower inflection point on the inflation limb of the pressure-volume curve represents the reopening of closed peripheral airways and the recruitment of collapsed alveoli.[60] Some studies have demonstrated marked improvement in end-expiratory lung volume, reduced hysteresis (signifying lung recruitment), and improved oxygenation when PEEP was set above the lower inflection point.[40,61,62] The presence of an upper inflection point on the inflation limb of the pressure-volume curve may signify lung overdistention, so tidal ventilation above the upper inflection point theoretically may increase the risk of ventilator-associated lung injury.[41] There are numerous ambiguities related to the measurement and interpretation of the pressure-volume curve that make its application to clinical practice uncertain.[63] As with recruitment maneuvers, studies of the pressure-volume curve necessarily have focused on basic issues such as oxygenation and pulmonary mechanics. To date, there is no high-level evidence that setting PEEP and V_T according to the characteristics of the pressure-volume curve reduces mortality to the level achieved by simply reducing V_T and P_{plat} to the levels suggested by the ARDS Network study.[9]

High-Frequency Oscillatory Ventilation

Several small, uncontrolled studies of patients with severe ARDS (lung injury scores of 3.2– 3.8) managed with high-frequency oscillatory ventilation (HFOV) have demonstrated improved oxygenation[64–67] and study-day-30 mortality rates of 43–67%. However, the importance of those results is difficult to judge, because the studies were small and uncontrolled and HFOV was used as rescue therapy with extremely ill patients.[64,65]

In one RCT 148 patients were randomized to receive either conventional mechanical ventilation (V_T 6–10 mL/kg measured body weight and PEEP 10–18 cm H_2O) or HFOV (initiated at 5 Hz, bias flow of 40 L/min with a mean

airway pressure 5 cm H_2O greater than that used during conventional mechanical ventilation).[68] Despite an initial oxygenation improvement in the HFOV group there was no difference between the groups at 24 h. Although there was insufficient statistical power to detect a mortality difference, there was a trend toward lower mortality in the HFOV group both at study-day 30 (37% vs 52%, respectively, $p = 0.102$) and at 6 months (47% vs 59%, respectively, $p = 0.143$).[68] Thus, there is Level I evidence showing only transient oxygenation improvement and no mortality benefit. Further study of HFOV for ARDS will be required, and several limitations of current HFOV therapy need to be addressed, including the power capacity of the high-frequency ventilator, the availability of a wider range of frequencies for adult patients, and the use of recruitment maneuvers prior to initiating HFOV.[69]

Prone Positioning

Prone positioning may promote lung protection in ARDS by restoring functional residual capacity and decreasing the vertical transpulmonary pressure gradient so that alveoli are more uniform in size.[70] This may lessen cyclic opening/closing of unstable alveolar units in the dependent regions and may lessen overdistention at end-inspiration in nondependent regions.[70] A recent evidence-based review[71] of 25 uncontrolled studies and 1 RCT found at least some oxygenation improvement in 75% of patients.

In a large RCT of prone positioning, which included 340 ALI/ARDS patients,[72] mortality was not different between prone-positioned patients and controls, either at the end of the 10-day course of therapy (21% vs 25%, respectively), at discharge from the intensive care unit (ICU) (51% vs 48%, respectively), or at 6-month follow-up (63% vs 59%, respectively). However, a post hoc analysis revealed that mortality at study-day 10 and at ICU discharge at significantly lower among prone-position patients who were in the lowest quartile of P_{aO_2}/F_{IO_2} (< 88 mm Hg), the lowest quartile of APACHE II scores, or the highest quartile of V_T (> 12 mL/kg predicted body weight).[72] Three potential limitations to that study were (1) the duration of prone positioning may have been insufficient (7 h/d), (2) the mechanical ventilation strategy was not standardized, and (3) there was a 27% incidence of noncompliance with the prone positioning protocol. Unfortunately, the trial was stopped early due to low enrollment; the study was inadequately powered to assess an impact on mortality.[73]

In a preliminary report[74] from another RCT, ICU mortality was 58.6% among patients managed with conventional positioning and 44.4% among patients managed with prone positioning. In that study both ventilator and weaning management were standardized by protocol, and prone positioning was started within 48 h of ARDS diagnosis and sustained for 20 h/d. Unfortunately, that study also was underpowered and the results were not statistically significant.[74] In conclusion, there is Level I evidence that prone positioning improves oxygenation and that it might improve mortality among the most severely ill ALI/ARDS patients.

Partial Liquid Ventilation

During partial liquid ventilation the lungs are filled to functional residual capacity with perfluorocarbon, a liquid that is twice as dense as water and allows the free diffusion of oxygen and carbon dioxide.[75] Partial liquid ventilation may promote lung protection by 2 mechanisms: (1) recruitment and stabilization of surfactant-deficient alveoli by reducing surface tension forces and (2) cleansing the alveolar environment of inflammatory mediators.[76] To date there have been 5 published clinical trials of partial liquid ventilation with adults suffering ALI/ARDS. Early uncontrolled studies by Hirschl et al,[77,78] with 19 severe-ARDS patients found that oxygenation improved over the first 48–72 h of therapy. In an RCT with 16 trauma patients with ARDS[75] neither oxygenation nor hospital mortality (13%) were different between patients receiving partial liquid ventilation and those receiving conventional mechanical ventilation, but the inflammatory response was less among the patients who received partial liquid ventilation.

Recently, 90 patients were enrolled into an RCT that compared partial liquid ventilation to conventional mechanical ventilation.[79] Patients randomized to partial liquid ventilation had significantly less progression of lung injury (defined as the progression from ALI to ARDS) than the conventional mechanical ventilation group (39% vs 82%, respectively, $p = 0.03$).[79] However, mortality was not different (42% in the partial-liquid-ventilation group vs 36% in the conventional-ventilation group) nor was the number of ventilator-free days.[79] In conclusion, Level II evidence indicates that partial liquid ventilation reduces inflammatory response and helps prevent the progression of lung injury, but those benefits do not appear to translate into shorter mechanical ventilation or lower mortality.

Surfactant Replacement Therapy

Surfactant, a lipid-protein complex, lowers alveolar surface tension and thus increases pulmonary compliance.[80] In animal models of ALI, exudation of serum protein into the alveolar environment deactivates surfactant, which increases surface tension, decreases lung volume, and decreases compliance.[80] Pulmonary lavage fluid from ARDS patients has diminished levels of phospholipids and decreased surface-tension-reducing properties.[81] Early case reports[82–85] found that instilling synthetic, bovine, or por-

cine surfactant into the lungs usually resulted in a sustained oxygenation improvement in severe ARDS.

Eight prospective studies[37,86–92] have investigated various types of surfactant for treating ARDS: 5 of the studies were RCTs[37,86,87,89,92] and 3 were uncontrolled single-arm studies.[88,90,91] Among the RCTs, Spragg et al[86] reported that instillation of a single-dose of porcine surfactant produced a modest, transitory oxygenation improvement, whereas Gregory et al[89] found a significant sustained improvement in P_{aO_2}/F_{IO_2} when Survanta was instilled into the endotracheal tube. The Exosurf ARDS Sepsis Study Group[37] enrolled 725 patients and found no difference in mortality (40% in each group), P_{aO_2}/F_{IO_2}, days of mechanical ventilation, or days in the ICU. A more recent RCT[92] compared instilled recombinant surfactant protein to standard care with 40 patients and found no difference in oxygenation or ventilator-free days, but there was a dose-dependent trend toward better mortality at study-day 28 (20–33% vs 38%, respectively).

Judging the efficacy of surfactant therapy in ARDS is difficult for 3 reasons. First, much larger amounts of surfactant may be needed to improve pulmonary function, because of the large surface area of adult lungs, and also to counter the effects of alveolar exudates, which convert surfactant to a nonfunctional form.[93] By extension, it may be necessary to cleanse the alveolar environment of exudates by bronchoalveolar lavage prior to instilling surfactant.[93] Second, the type of surfactant preparation may impact efficacy:[86,94] synthetic surfactants, which lack key apoproteins, are more susceptible to inactivation by plasma proteins in the alveolar exudate than are natural sources such as bovine surfactant.[93] Third, the timing of surfactant therapy relative to the evolution of ARDS may be crucial to efficacy.[94] In conclusion, there is Level I evidence that aerosolized surfactant does not improve oxygenation, and Level II evidence indicates that surfactant does not improve oxygenation, ventilator-free days, or mortality.

Inhaled Nitric Oxide

Nitric oxide is an endothelial-derived, vascular, relaxing factor that causes smooth-muscle relaxation and vasodilation.[95] In a small, repeated-measures study design[96] that compared inhaled nitric oxide (INO) to intravenous administration of prostacyclin with ARDS patients INO reduced pulmonary artery pressure and improved oxygenation without causing systemic vasodilation. Four RCTs[97–100] compared INO to either an inhaled placebo gas or routine practice and found no mortality benefit from INO. All trials showed an initial improvement in oxygenation that typically did not persist more than 24 h. Mean pulmonary arterial pressure was significantly lower with INO, but the effect did not persist beyond 48 h. Morbidity indices such as reversal of ALI or ventilator-free days were not different. A recent meta-analysis[101] determined that INO may be useful as short-term rescue therapy—a conclusion shared by others who have reviewed the data.[102–104] In conclusion, there is Level I evidence that INO provides short-term oxygenation improvement and reduces pulmonary arterial pressure.

Extracorporeal Membrane Oxygenation and Extracorporeal Carbon Dioxide Removal

During the early 1970s patients with refractory hypoxemia were often treated with extracorporeal membrane oxygenation (ECMO) in an attempt to support systemic oxygen delivery and allow reduced airway pressure and F_{IO_2}. Despite an impressive initial case study[105] the reported mortality among 150 patients treated with ECMO was greater than 85%.[106] The only RCT of ECMO enrolled 90 patients with severe hypoxemia (either a $P_{aO_2} < 50$ mm Hg and $F_{IO_2} = 1.0$ for > 2 h, or a $P_{aO_2} < 50$ mm Hg and $F_{IO_2} = 0.60$ for > 12 h).[107] Although ARDS was not specifically mentioned, the majority of patients had severe pneumonia, septicemia, inhalation injury, or trauma. Patients were randomized to receive either mechanical ventilation alone, or in conjunction with ECMO. Mortality of both groups was in excess of 90%.[107] The relevance of that study is limited because the primary focus of mechanical ventilation in the 1970s was to reduce F_{IO_2} rather than to limit airway pressure and V_T.

Shortly after publication of the ECMO trial[107] a new method of extracorporeal support emphasized lung-protection through "motionless lungs."[108] Low-frequency positive-pressure ventilation with extracorporeal carbon dioxide removal (LFPPV-$ECCO_2R$) incorporated venovenous bypass for carbon dioxide removal and apneic oxygenation. Three to five sigh breaths were used to maintain functional residual capacity, and tracheal gas insufflation was used to maintain PEEP of 15–25 cm H_2O during prolonged expiration.[109] Early uncontrolled studies of LFPPV-$ECCO_2R$[108,109] and LFPPV-$ECCO_2R$ with pressure-controlled inverse ratio ventilation[110] reported markedly lower mortality (23–37%) among patients who had met ECMO oxygenation criteria (compared to the historical ECMO mortality rate of $> 85\%$). An uncontrolled study of LFPPV-$ECCO_2R$ with 43 patients reported a mortality of 48.8%.[111] An RCT that compared LFPPV-$ECCO_2R$ to conventional mechanical ventilation found no difference in mortality (67% vs 58%, respectively),[112] but the overall mortality rate was higher than in previous uncontrolled studies.[110,111] In conclusion, there is Level II evidence that LFPPV-$ECCO_2R$ offers no benefit to severe-ARDS patients.

Pharmacologic Therapy

The common pathologic feature of ALI/ARDS is an inflammatory process involving a complex interaction between platelets, leukocytes, mononuclear cells, macro-

phages, and endothelial cells.[76] Dysregulation of cellular responses often occurs, and diffuse lung injury causes spillover of cytokines and other inflammatory and thrombotic mediators into the bloodstream, which can lead to multi-organ system dysfunction.[113] This has led to the opinion that ALI/ARDS is almost always a systemic syndrome.[113] Pharmacologic treatment focuses on attenuating the inflammatory response.

Ibuprofen

In both animal models of ALI and in humans with sepsis, arachidonic acid metabolites such as thromboxane, leukotrienes, and prostaglandins have been linked to abnormal pulmonary mechanics, pulmonary hypertension, hypoxemia, shock, and multi-organ system dysfunction.[77,114] Animal models of sepsis demonstrated that nonsteroidal anti-inflammatory agents improved survival and attenuated pathophysiologic disturbances.[115] However, in a large RCT[36] intravenous administration of ibuprofen to 455 patients with early sepsis did not reduce the incidence or duration of shock or ARDS. Mortality at study-day 28 was not different between patients treated with ibuprofen or placebo (37% vs 40%, respectively). In conclusion, there is Level I evidence that nonsteroidal anti-inflammatories do not ameliorate the inflammatory response in sepsis. By extension, it is unlikely that nonsteroidal anti-inflammatory agents would be useful in treating ARDS.

Ketaconazole

Ketoconazole is a synthetic anti-fungal imidazole with anti-inflammatory properties[116] that works by inhibiting the production of thromboxane.[117] A large RCT of ketaconazole, with 234 patients with early ALI/ARDS, found no difference between the ketaconazole group and the placebo group with regard to hospital mortality (35.2% vs 34.1%, respectively), ventilator-free days, or organ-failure-free days.[118] In conclusion, there is Level I evidence that ketaconazole does not benefit patients with early ALI/ARDS.

Pentoxifylline and Lisofylline

Neutrophils are integral to the inflammatory process, and much experimental and clinical evidence suggests that neutrophils play a major role in the evolution of ALI/ARDS.[119] The cytokine tumor necrosis factor plays a crucial role in both stimulating neutrophil adherence to the capillary endothelium and in neutrophil activation.[76] Pentoxifylline, a phosphodiesterase inhibitor, and its derivative lisofylline have anti-inflammatory properties such as inhibition of both neutrophil activation and platelet aggregation, and reduction of tumor necrosis factor release. However, a small uncontrolled study of high-dose pentoxifylline, with 6 ARDS patients, failed to show improvement in either gas exchange or hemodynamic function.[120] A large RCT of lisofylline versus placebo, with 235 patients with early ALI/ARDS, reported no difference in mortality at study-day 28 (31.9% vs 24.7%, respectively, $p = 0.215$) and no difference in either ventilator-free days or resolution of organ failure.[121] In conclusion, there is Level V evidence that pentoxifylline does not benefit ALI/ARDS and Level I evidence that lisofylline does not benefit early ALI/ARDS.

N-acetylcysteine and Procysteine

An important source of lung injury are the radical oxygen species (superoxide, hydroxyl, hydrogen peroxide, and hypochlorus acid) that are produced by activated neutrophils, macrophages, and stimulated pulmonary endothelial cells.[76,122] Radical oxygen species cause cellular damage, including breakdown of deoxyribonucleic acid, lipid peroxidation of cell membranes, and protein degradation.[76,122] Major antioxidants such as superoxide dismutase, catalase, and glutathione neutralize free radicals and limit cellular damage.[122] An initial RCT of intravenous N-acetylcysteine versus placebo in 66 ARDS patients found no mortality difference at study-day 60 (53% vs 50%, respectively), oxygenation, or time required to ameliorate lung injury.[123] A small RCT with 46 ARDS patients compared N-acetylcysteine and procysteine to placebo and found no difference in mortality at study-day 30 (36%, 35%, and 40%, respectively),[122] though the anti-oxidants group had significantly fewer ALI days. Another small RCT[124] that compared N-acetylcysteine to placebo, with 42 patients with early ARDS, also found no mortality difference (32% vs 25%, respectively). However, by study-day 3 lung injury score was significantly lower among patients who received N-acetylcysteine (1.76 ± 0.17 vs 2.23 ± 0.62, respectively, $p < 0.05$).[124] In conclusion, Level II evidence indicates that anti-oxidants offer no mortality benefit for patients with early ALI/ARDS. However, there is Level II evidence that anti-oxidants reduce the number of ALI days and/or improve lung injury score.

High-Dose Methylprednisolone

ARDS has 2 distinct phases: an acute exudative phase characterized by inflammation and a subacute phase characterized by fibrosing alveolitis.[119] Corticosteroids, which inhibit the inflammatory process at virtually all levels,[125] have been employed in the treatment of ARDS since the syndrome was first described over 35 years ago[126] and have been used in both the acute and subacute phases. Two RCTs have tested the efficacy of high-dose intravenous corticosteroids versus placebo in patients either at risk for ARDS[127] or with early ARDS.[128] High-dose methylprednisolone did not lessen the incidence of ARDS among

patients at high risk,[127] did not reverse lung injury in patients with early ARDS,[128] and had no effect on mortality.[127,128] However, it did significantly increase the incidence of infectious complications.[127] Those studies supported the findings of the first RCT of high-dose methylprednisolone versus placebo with sepsis patients at high risk for developing ARDS,[129] in which there was no difference in the incidence of ARDS (34% vs 38%, respectively) or hospital mortality (58% vs 54%, respectively).

However, a recent evidence-based review[130] of corticosteroids for ARDS found that certain subgroups with early ALI/ARDS do benefit from corticosteroids. In an RCT that compared methylprednisolone to placebo in patients with orthopedic fractures and at risk for developing pulmonary fat embolism, those treated with methylprednisolone did not develop ARDS, whereas 22% of the patients randomized to placebo did ($p < 0.05$).[131] Three RCTs found that patients with *Pneumocystis carinii* pneumonia treated with methylprednisolone had substantially lower incidence of deterioration in pulmonary function,[132] lower risk of respiratory failure,[133] and lower mortality.[133,134]

Fibroproliferation is a prominent feature of the subacute phase of ARDS, and high-dose corticosteroid therapy may be particularly effective in reversing fibrosis and improving outcomes of subacute ARDS.[135] In 3 uncontrolled studies[136–138] high-dose methylprednisolone was administered to a total of 45 patients in the subacute phase of ARDS, and mortality was 20–24%. To date, only one small RCT has compared high-dose methylprednisolone to placebo; that study found markedly lower hospital mortality with high-dose methylprednisolone (12% vs 62%, respectively).[139]

The ARDS Network recently completed a large RCT in which 180 patients with subacute ARDS were randomized to receive either high-dose methylprednisolone or placebo (see http://www.ardsnet.org/). Until that study is published, the highest available evidence on this subject is Level II evidence, which supports high-dose corticosteroid therapy for patients with unresolved ARDS of $\geq$ 7 days duration. In contrast, there is both Level I and Level II evidence showing lack of efficacy and higher risk of infection with high-dose corticosteroid therapy for early ARDS. The exceptions to that finding are (1) Level I evidence that high-dose corticosteroids benefit patients suffering *P. carinii* pneumonia and (2) Level II evidence that corticosteroids benefit patients at risk of developing ARDS from fat embolization.

Fluid Management

In ALI, damage to the capillary endothelium and alveolar epithelium increases permeability, leading to pulmonary edema from the leakage of protein-rich plasma into the interstitial and alveolar spaces.[140] Because the protein osmotic pressure gradient that opposes edema formation is reduced, the magnitude of the pulmonary edema depends on the pressure gradient between the microvascular and peri-microvascular space,[141] so pulmonary edema forms despite normal microvascular hydrostatic pressure.[142] In addition, a recent observational study of ALI/ARDS patients reported that hospital mortality was higher, and duration of mechanical ventilation was longer, among patients who suffered impaired alveolar fluid clearance ($< 3\%$/h).[143] Furthermore, experimental evidence suggests that high pulmonary microvascular pressures (a common consequence of aggressive fluid management) can result in pulmonary capillary stress-failure and increased production of procollagens, fibronectins, and other mediators of lung fibrosis.[144]

Four studies have examined the role of fluid management in critically ill patients. In an observational study with 40 ARDS patients Humphrey et al[145] reported significantly lower hospital mortality among patients whose pulmonary artery occlusion pressure was reduced by $> 25\%$ than among those whose pulmonary artery occlusion pressure was not reduced or only marginally reduced (mortality 25% vs 71%, respectively). In an RCT of fluid management that emphasized fluid restriction and diuresis, 101 patients with pulmonary edema were randomized to have either fluid management based on clinical pulmonary artery occlusion pressure monitoring or protocol-driven management based on reducing extravascular lung water.[146] The patients managed with the extravascular-lung-water-reduction protocol had significantly lower fluid balance (0.142 ± 3.632 vs 2.239 ± 3.695 L, respectively, $p = 0.001$), significantly fewer ventilator days, and shorter ICU stay. In the subgroup of 52 ARDS patients, those managed with the extravascular-lung-water-reduction protocol had significantly lower fluid balance and a trend toward fewer days of mechanical ventilation.[146] For the entire group there was an insignificant trend toward lower mortality among the patients managed with the extravascular-lung-water-reduction protocol (56% vs 65%, respectively, $p = 0.327$).[146]

In another RCT that compared an extravascular-lung-water-reduction protocol to routine management, with 47 critically ill patients, hospital mortality was significantly lower in the subset of patients with ARDS or sepsis who were managed with the protocol (33% vs 100%, respectively, $p < 0.05$).[147] For all study patients hospital mortality was substantially higher among those who had initially high extravascular lung water (> 14 mL/kg ideal body weight) than those whose extravascular lung water was lower (87% vs 41%, respectively, $p < 0.05$).[147]

In a recent RCT[148] 37 ALI patients with hypoproteinemia (serum protein < 5 g/dL) were randomized to receive a protocol regimen of 25 g of human serum albumin every 8 h and continuous furosemide infusion or dual placebo. Patients who experienced diuresis and weight loss over the

Table 4. Current Evidence-Based Therapy Recommendations for Patients With Acute Lung Injury or Acute Respiratory Distress Syndrome

ALI/ARDS Therapy	Outcome	Recommendation	Highest Evidence Level	Grade
Low-V_T, low-P_{plat} ventilation	↓ Mortality	Yes	I	B
	↑ Ventilator-free days	Yes	I	B
Open-lung approach	↓ Mortality	Yes	II	C
	↑ Ventilator-free days	Yes	II	C
Alveolar recruitment maneuver: high-level CPAP	↑ Oxygenation	No	II	C
Alveolar recruitment maneuver: non-CPAP	↑ Oxygenation	Yes	V	E
High-frequency oscillatory ventilation	↓ Mortality	No	I	B
	↑ Oxygenation	Yes	I	B
Prone positioning	↓ Mortality	No	I	A
	↑ Oxygenation	Yes	I	B
Partial liquid ventilation	↓ Mortality	No	II	C
	↑ Ventilator-free days	No	II	C
Surfactant replacement via aerosol	↓ Mortality	No	I	B
	↑ Ventilator-free days	No	I	B
Surfactant replacement via instillation	↓ Mortality	No	II	C
	↑ Ventilator-free days	No	II	C
Inhaled nitric oxide	↓ Mortality	No	I	A
	↑ Oxygenation	Yes	I	B
Low-frequency positive-pressure ventilation with extracorporeal carbon dioxide removal	↓ Mortality	No	II	C
Ibuprofen	↓ Mortality	No	I	B
Ketaconazole	↓ Mortality	No	I	B
	↑ Ventilator-free days	No	I	B
Lisofylline	↓ Mortality	No	I	B
	↑ Ventilator-free days	No	I	B
N-acetylcysteine	↓ Mortality	No	II	C
	↓ Severity of lung injury	Yes	II	C
High-dose methylprednisolone for early ARDS	↓ Mortality	No	II	C
	↓ Severity of lung injury	No	II	C
High-dose methylprednisolone for patients at-risk for ARDS due to fat embolism	↓ Incidence of ARDS	Yes	II	C
High-dose methylprednisolone for patients with *Pneumocystis carinii* pneumonia	↓ Mortality	Yes	II	C
	↓ Severity of lung injury	Yes	II	C
High-dose methylprednisolone for subacute phase of ARDS	↓ Mortality	Yes	II	C
Fluid-conservative management	↓ Mortality	Yes	II	C
	↑ Ventilator-free days	Yes	II	C
Nutritional support containing eicosapentaenoic acid and gamma-linoleic acid	↑ Oxygenation	Yes	I	B
	↑ Ventilator-free days	Yes	I	B

ALI = acute lung injury
ARDS = acute respiratory distress syndrome
V_T = tidal volume
P_{plat} = plateau pressure
CPAP = continuous positive airway pressure

5 days of study had better P_{aO_2}/F_{IO_2}, more ventilator-free days, and a trend toward shorter ICU stay.[148] Interestingly, regardless of therapy assignment, patients who experienced weight loss had better oxygenation and were less likely to have died during subsequent follow-up than were the patients who experienced weight gain.[148]

As of this writing, the ARDS Network is conducting a study of fluid management of ALI/ARDS patients

(see: http://www.ardsnet.org/). The study plans to enroll 1,000 patients and will have 90% power to detect a 10% difference in mortality. Until that study is completed, the highest available evidence on this subject is Level II evidence, which suggests that a fluid-conservative management strategy geared toward reducing extravascular lung water improves oxygenation and reduces morbidity and mortality for ALI/ARDS patients.

Nutritional Support

Critically ill, mechanically ventilated patients typically have elevated metabolic rates (up to 126% of predicted).[149] With those patients the goal of nutritional support is to provide sufficient caloric intake both to account for basal metabolic rate and to meet the demands for synthesis of new lean body tissue.[150] A case report,[150] a small uncontrolled study,[151] and a small RCT[152] all reported that high levels of carbohydrate in nutritional support increase the respiratory quotient and minute production of carbon dioxide, which increases minute ventilation demand. Therefore, to reduce minute ventilation in critically ill patients who are either hypermetabolic or nutritionally-depleted, typically 50% of the nonprotein portion of caloric intake consists of lipid. During LPV it is important to limit carbon dioxide production and minute ventilation to minimize V_T and P_{plat}.

Recent interest in nutritional support of ALI/ARDS patients has focused on the anti-inflammatory role of a low-carbohydrate, high-fat diet. In particular, polyunsaturated fatty acids such as eicosapentaenoic acid (EPA) and gamma-linoleic acid (GLA) are believed to play an important role in cell membrane function, modulate vascular endothelial permeability and platelet aggregation, and reduce the production of pro-inflammatory arachidonic acid metabolites.[153] A large RCT[153] reported that patients who received a 4–7-d course of enteral feeding of formulations containing both EPA and GLA had significantly better oxygenation, fewer mechanical ventilation days, and shorter ICU stay than patients fed a control diet. A post-hoc analysis[154] of those ARDS patients found fewer neutrophils and less total protein, leukotriene B_4, interleukin-8, and ceruloplasmin in bronchoalveolar lavage fluid from the patients who received the EPA/GLA diet than from the controls. Those results suggest that dietary supplements that combine EPA and GLA reduce inflammation and alveolar-capillary permeability in ARDS patients. Thus, there is Level I evidence supporting the use of EPA and GLA in nutritional support of ALI/ARDS patients.

Summary

Table 4 summarizes the 15 therapies discussed in the present report. In brief, there is strong evidence to suggest that ALI/ARDS patients should be managed with a low-V_T, pressure-limited approach, with either low or moderately high PEEP. When necessary to reverse severe hypoxemia, a recruitment maneuver probably should be performed with some other technique than brief periods of high-level CPAP. Alternatively, prone positioning and HFOV can be used to improve oxygenation. INO should be restricted to short-term rescue therapy for severely hypoxemic patients. Of the pharmacologic therapies only high-dose methylprednisolone has been shown to reduce mortality in patients with *P. carinii* pneumonia, and it also can reduce the risk of ALI due to fat embolism. There is some preliminary evidence that high-dose methylprednisolone may also reduce mortality in patients with subacute ARDS. A fluid-conservative approach to fluid management of ARDS patients may improve survival and reduce the duration of mechanical ventilatory support. Likewise, there is evidence that antioxidants, particularly in high-fat nutritional support formulations, may shorten the duration of mechanical ventilation for ARDS patients.

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