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Nonventilatory Treatments for Acute Lung Injury and ARDS*

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Over the past decade, advances in the ventilatory management of acute lung injury (ALI) and ARDS have improved outcomes; however, until recently the search for other therapies has been less fruitful. Recently, the Acute Respiratory Distress Syndrome Network Fluid and Catheter Treatment Trial reported that a conservative fluid management strategy, compared with a fluid liberal strategy, increased the mean (± SE) number of ventilator-free days in patients with ALI (14.6 ± 0.5 vs 12.1 ± 0.5 days, respectively; p < 0.001). In addition to this beneficial effect on outcomes, the study found that the conservative fluid strategy did not increase the incidence of renal failure or the development of shock. Other studies have demonstrated that albumin and furosemide therapy may be beneficial in hypoproteinemic patients with lung injury, though data on outcomes is still lacking. Although several pharmacologic therapies, such as corticosteroids, surfactant, and nitric oxide, have been demonstrated to be ineffective in improving outcomes, several promising new treatments are being investigated in ongoing or upcoming clinical trials. This article reviews these developments and other recent research on the optimal nonventilatory management of patients with ALI. *(CHEST 2007; 131:913–920)*

$\mathbf{A}$dvances in the ventilatory management of acute lung injury (ALI) and ARDS over the past decade have been dramatic. In particular, the use of a low-tidal volume (6 mL/kg predicted body weight), plateau pressure-limited strategy has been demonstrated to reduce mortality from 40 to 31%.[1] Further, a large, multicenter, randomized, controlled trial[2] demonstrated the equivalence of higher and lower levels of positive end-expiratory pressure. Over this time period, a number of nonventilatory therapies for ALI/ARDS have been investigated, many of which have not proven to be effective, while others appear more promising.

This article will review the most recent and relevant evidence regarding nonventilatory treatments for ALI/ARDS, including advances in fluid management and pharmacotherapy. In addition, we will briefly survey promising new and investigational therapies for ALI/ARDS that are the focus of current and upcoming clinical trials.

Fluid Management

Until recently, the optimal strategy for fluid management in patients with ALI/ARDS was unclear. Pulmonary edema, even when noncardiogenic in origin, increases with a rise in hydrostatic pressures. Experimental studies demonstrated that a modest

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decrease in pulmonary vascular pressure could reduce the quantity of pulmonary edema in oleic acid-induced permeability pulmonary edema in dogs.[3] Norman Staub recommended in this journal in 1978 a clinical strategy of lowering microvascular pressures in the setting of increased permeability pulmonary edema (Fig 1).[4] Increased extravascular lung water has been associated with poor outcome in ARDS patients,[5] and likewise, a reduction in pulmonary capillary wedge pressure has been associated with increased survival in ARDS patients.[6] However, balancing the risks of increased edema vs those of decreased vital organ perfusion with a lower intravascular pressure has remained difficult.

Recently, the National Heart, Lung and Blood Institute (NHLBI) Acute Respiratory Distress Syndrome Network published the results of the Fluid And Catheter Treatment Trial (FACTT),[7] a large randomized trial comparing a liberal fluid management strategy to a conservative fluid management strategy in patients with ALI. Fluid and diuretic management were dictated by a highly protocolized regimen, which is described in detail in the original publication, and all patients were managed with a low-tidal volume, plateau pressure-limited ventilation strategy.[1] The fluid management strategies were tested in a factorial design that also evaluated the utility of catheterization with a central venous catheter (CVC) vs a pulmonary artery catheter (PAC)[8]; the two types of catheters were equivalent in terms of clinical outcomes (mortality rate: PAC group,

27.4%; CVC group, 26.3%; p = 0.69; 95% confidence interval for difference, −4.4 to 6.6%). In contrast, there was a clear difference in outcome between the liberal fluid management and conservative fluid management arms of the study. Patients in the conservative fluid management arm had significantly more ventilator-free days than those in the liberal fluid management arm (mean [± SE], 14.6 ± 0.5 vs 12.1 ± 0.5 days, respectively; p < 0.001) and concordant improvements in pulmonary physiology (Table 1).[69] Likewise, patients in the conservative fluid management arm had more ICU-free days than those in the liberal fluid management arm (13.4 ± 0.4 vs 11.2 ± 0.4, respectively; p < 0.001). There was also a 2.9% reduction in the 60-day mortality rate in the conservative fluid management arm compared with the liberal fluid management arm, though the comparison was not statistically significant (25.5% vs 28.4%, respectively; p = 0.30; 95% confidence interval for the difference, −2.6 to 8.4%).

The study found no differences between the two fluid strategies in the incidence or prevalence of shock or in the need for renal replacement therapy, although there was a strong trend in the latter toward a benefit in the conservative fluid management arm (10% required dialysis; liberal fluid management arm, 14%; p = 0.06). Similarly, the mean number of days of renal support required did not differ between the two groups (conservative fluid management group 11.0 ± 1.7 days; liberal fluid management group, 10.9 ± 1.4 days; p = 0.96). These data provide reassurance that the conservative fluid management strategy did not negatively impact renal function.

Translation to Clinical Practice

When considering how to translate the results of the FACTT into clinical practice, several factors should be considered. First, only patients who were not experiencing cardiopulmonary shock were managed by the protocol. If the mean arterial pressure was < 60 mm Hg or the patient required therapy with vasopressors (other than dopamine at a dose of < 5 μg/kg/min), fluid management was left to the judgment of the managing physician. Thus, the finding that a conservative fluid management strategy was associated with better outcomes in this study does not imply that patients who are in shock ought to have fluids restricted. Second, the mean time from ICU admission to protocol implementation was approximately 43 h. Therefore, as pointed out by Rivers in the editorial accompanying the trial,[9] the results of the FACTT do not conflict with the finding that early goal-directed therapy in patients with sepsis (with its

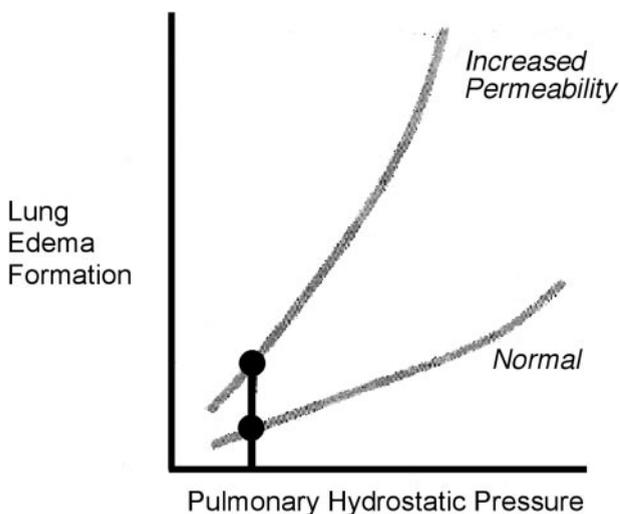FIGURE 1. Relationship between pulmonary hydrostatic pressure and lung edema formation under normal conditions and increased permeability. Even under normal conditions, an increase in pulmonary hydrostatic pressure results in increased lung edema formation. This relationship, however, is dramatically accentuated under conditions of increased lung permeability. Adapted with permission from Staub.[4]

Table 1—*Pulmonary Outcomes and Physiologic Variables in the FACTT**

| Variables | Fluid Management | | p Value† |
	Conservative Group	Liberal Group	
Ventilator-free days, No.	14.6 ± 0.5	12.1 ± 0.5	< 0.001
PEEP, cm H_2O	7.5 ± 0.3	8.2 ± 0.2	0.008
Plateau pressure, cm H_2O	24.2 ± 0.6	25.7 ± 0.5	0.002
PaO_2/FIO_2	198 ± 8	183 ± 6	0.07
Oxygenation index‡	10.1 ± 0.8	11.8 ± 0.7	0.003
Lung injury score§	2.03 ± 0.07	2.27 ± 0.06	< 0.001

*Values are given as the mean $\pm$ SE, unless otherwise indicated. FIO_2 = fraction of inspired oxygen; PEEP = positive end-expiratory pressure.
†p Values for the physiologic variables are for comparison of trends over time using repeated-measures analysis of variance, though only day 7 values are shown for simplicity.
‡Oxygenation index was calculated as (mean airway pressure $\times$ FIO_2/PaO_2) $\times$ 100, with a lower number indicating better gas exchange.
§Lung injury score was calculated as previously described by Murray et al.[69]

concomitant aggressive resuscitation) improves outcomes.[10] In the trial that first established the benefits of early goal-directed therapy,[10] patients with early severe sepsis or septic shock were enrolled on average 1.5 h after arrival in the emergency department and were treated for at least 6 h with aggressive crystalloid resuscitation, using central venous pressure monitoring, and optimization of oxygen delivery using vasopressors, RBC transfusions, and inotropes as necessary. This strategy decreased the in-hospital mortality rate in that single-center study from 46.5 to 30.5% (p = 0.009) and is now widely accepted as appropriate initial management of early severe sepsis. Third, the liberal fluid management strategy

would be more accurately called a usual fluid management strategy, since the average daily fluid gain of approximately 1 L in this group is quite similar to that observed in prior studies[1,2] from the Acute Respiratory Distress Syndrome Network in which fluid management was not protocolized (Fig 2). In contrast, the conservative fluid management group had a net fluid balance of approximately zero over the first 7 days of the protocol. These data may provide useful benchmarks to guide the fluid management of critically ill patients in the real world, with the important caveats that electrolytes must be closely monitored and the many safety features of the FACTT (like holding back therapy with diuretics
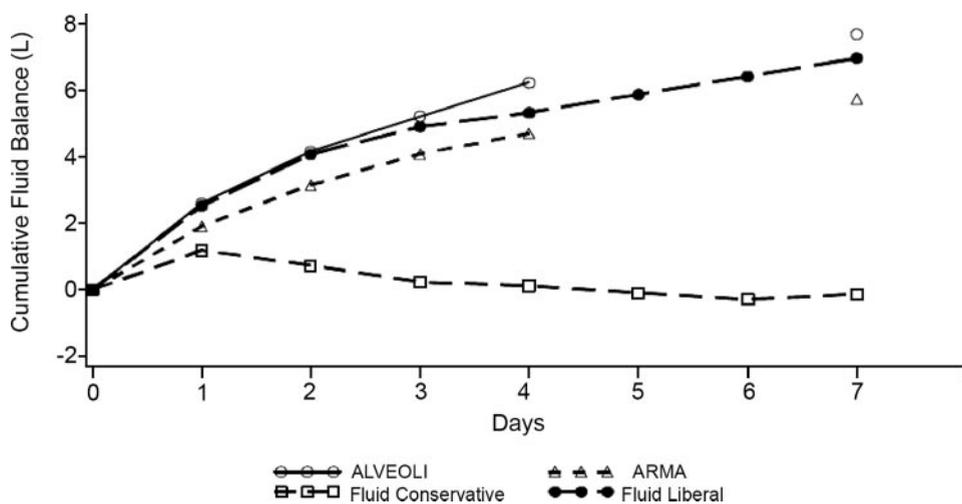
FIGURE 2. Cumulative fluid balance in patients enrolled in the FACTT compared to patients in prior Acute Respiratory Distress Syndrome Network studies. Fluid administration in the liberal fluid management arm of the FACTT mimicked that in two prior Acute Respiratory Distress Syndrome Network studies of ventilator management strategy and resulted in a gain of approximately 1 L/d. In contrast, fluid administration in the conservative fluid management arm resulted in a net even fluid balance. ARMA = Acute Respiratory Distress Syndrome Network trial of 6 vs 12 mL/kg tidal volume ventilation[1]; ALVEOLI = Acute Respiratory Distress Syndrome Network trial of low vs high positive end-expiratory pressure.[2] Adapted with permission from the Acute Respiratory Distress Syndrome Network.[7] Copyright 2006 Massachusetts Medical Society. All rights reserved.

until patients had been out of shock for at least 12 h) must be noted. Finally, patients with an established need for dialysis were excluded from the trial, and it remains unclear what volume management strategy should be followed in this population.

The Acute Respiratory Distress Syndrome Network has generated a simplified version of the conservative fluid management protocol that will be used for future trials (Table 2). This more practical version of the protocol is greatly simplified from the one used in the FACTT and published with the original study; however, it provides useful targets for the monitoring of intravascular pressure and urine output, and suggests therapies to help reach those goals once the patient has been out of shock for at least 12 h. Although the FACTT demonstrated the equivalence of CVCs and PACs, the protocol includes guidelines for use with a PAC for those physicians who remain more comfortable with this type of monitoring or for situations in which a PAC is needed for another purpose. In addition, suggested guidelines for continuous furosemide infusion are provided, as some authorities have suggested that this method of administration provides equivalent or superior diuresis with lower doses of medication,[11] though this approach was not specifically evaluated in the Acute Respiratory Distress Syndrome Network trial.

Other Fluid Management Strategies

The debate over whether to resuscitate critically ill patients with crystalloid or colloid solutions has been ongoing in the critical care literature for years. Early metaanalyses[12] suggested that albumin resuscitation was associated with increased mortality in critically ill patients, although these results were called into question by later metaanalyses.[13] More recently, a large randomized controlled trial[14] in a mixed population of 7,000 critically ill patients (the Saline versus Albumin Fluid Evaluation trial) reported that albumin resuscitation was equivalent to saline solution resuscitation, and a similar trial[15] of crystalloid vs other colloids is ongoing. Addressing this controversy, a 2004 consensus panel convened by the American Thoracic Society[16] concluded that the use of colloids should generally be reserved for specific conditions in which there was clear evidence of benefit. The subset of lung injury patients with hypoproteinemia was included in this consensus statement as one in which the judicious use of albumin (with furosemide) may be beneficial. Hypoproteinemia is a documented risk factor for the development of ALI and for poor outcome in critical illness in general.[17,18] Martin and colleagues[19] randomized 37 patients with ALI and a serum protein concentration of < 5.0 mg/dL to receive either furosemide and albumin every 8 h for 5 days or double placebo. The intervention group had improved oxygenation, fluid balance, and hemodynamics; no differences in mortality were seen, although the study was not powered to assess this outcome. In a follow-up study[20] comparing the administration of furosemide with albumin to that of furosemide without albumin, the combination of the two agents again proved to be superior, using similar end points. Thus, in the particular setting of hypoproteinemia and ALI, the combination of furosemide and albumin may be useful in improving pulmonary physiology; whether outcomes will be improved by this therapy remains to be seen.

Continuous hemofiltration with a zero fluid balance has been proposed as a potential therapy for ALI patients due to the theoretical benefits of removing humoral mediators of lung injury from the

Table 2—*Simplified Algorithm for Conservative Management of Fluids in Patients With ALI, Based on Protocol Used in the FACTT**

CVP, mm Hg (Recommended)	PAOP, mm Hg (Optional)	MAP ≥ 60 mm Hg and Not Receiving Vasopressors for ≥ 12 h	
		Average Urine Output < 0.5 mL/kg/h	Average Urine Output ≥ 0.5 mL/kg/h
> 8	> 12	Furosemide†; reassess in 1 h	Furosemide; reassess in 4 h
4–8	8–12	Fluid bolus as fast as possible‡; reassess in 1 h	Furosemide; reassess in 4 h
< 4	< 8	Fluid bolus as fast as possible‡; reassess in 1 h	No intervention; reassess in 4 h

*CVP = central venous pressure; PAOP = pulmonary artery occlusion pressure; MAP = mean arterial pressure. Reprinted with the courtesy of the NHLBI Acute Respiratory Distress Syndrome Network. Patients must have had a MAP of > 60 mm Hg without requiring vasopressors for at least 12 h before this protocol is initiated.

†Furosemide dosing: begin with a 20-mg bolus, 3 mg/h infusion, or last known effective dose. Double each subsequent dose until the goal is achieved (oliguria reversal or intravascular pressure target), with a maximal dose of 160-mg bolus or 24 mg/h. Do not exceed 620 mg/d. If the patient has heart failure, treatment with dobutamine may be considered. Diuretic therapy should be withheld for patients with renal failure, which is defined as dialysis dependence, oliguria with a serum creatinine level of > 2 mg/dL, or oliguria with a serum creatinine level of < 2 mg/dL but with urinary indices indicative of acute renal failure.

‡Fluid bolus: 15 mL/kg crystalloid (round to nearest 250 mL) or 1 unit of packed RBCs or 25 g of albumin.

circulation and reducing lung vascular pressures. In an animal model[21] of oleic acid-induced lung injury, continuous hemofiltration reduced pulmonary edema by reducing both lung vascular pressures and epithelial permeability to protein, with the latter apparently achieved in part by decreasing plasma levels of the inflammatory cytokines interleukin-6 and interleukin-8. Similar results have been reported in other animal models[22–24]; however, studies in humans have reported conflicting results. One single-center trial[25] administered continuous venovenous hemodiafiltration to 10 pediatric oncology patients with ARDS and found that 9 of the children were successfully extubated. In contrast, another observational trial[26] of 37 adult patients with acute renal failure and ALI found that the therapy had little beneficial impact on pulmonary physiology end points. Further clinical trials on this subject are needed.

Pharmacotherapy

The search for an effective pharmacologic therapy for ALI/ARDS has continued over the past decade without major success; to date, no pharmacologic agent has been demonstrated to reduce mortality among patients with this condition.[27] Several treatments, however, merit brief discussion due to historical interest as a therapy for ALI, conclusive evidence of lack of benefit, or potentially intriguing analyses of subgroups or secondary outcomes. In addition, we will cover several promising new therapies that are the focus of ongoing or upcoming clinical trials.

Pharmacologic therapies recently investigated[27] as possible treatments for ALI include surfactant, inhaled nitric oxide (NO), corticosteroids, antifungal drugs, and phosphodiesterase inhibitors (Table 3).[28–33,35–40,42–48,51,70–73] Exogenous surfactant administration was first administered as a therapy for lung injury in the late 1980s.[28] Several phase I and II trials in humans showed promising trends in outcomes,[29,30] but a larger randomized controlled trial[31] of aerosolized synthetic surfactant in patients with sepsis-related lung injury did not demonstrate a benefit. Since then, further trials[32,33] of endotracheal delivery of natural or recombinant surfactants have also found no benefit in adult populations. One randomized controlled trial[34] in a pediatric population, however, found that exogenous surfactant improved both oxygenation and mortality in children with ALI.

Inhaled NO has been considered a promising therapy for lung injury due to its ability to provide selective pulmonary vasodilatation and improve ventilation-perfusion mismatch. Unfortunately, although several trials[35–40] have now demonstrated some improvements in oxygenation and pulmonary hemodynamics with the use of NO, the lack of mortality benefit has been just as consistent. Further, while nearly 60% of patients who receive inhaled NO will respond clinically with improved oxygenation, these benefits are typically short-lived, fading after the first 1 to 2 days of administration.[41] Thus, although the use of NO may be considered as a rescue therapy in patients who are exceptionally difficult to oxygenate, it has no role in standard therapy for ALI.

Similarly, corticosteroids seemed to be an ideal therapy for lung injury, given their potent antiinflammatory and antifibrotic properties. Clinical trials have evaluated the utility of corticosteroids in preventing ALI/ARDS[42–45] and in treating either early-stage (inflammatory) or late-stage (fibrotic) ALI/ARDS[46–48]; none have demonstrated a mortality benefit. In addition, the use of corticosteroids has been limited by concerns over their contributions to neuromuscular disorders associated with critical illness, particularly when combined with neuromuscular blocking agents.[49,50]

Most recently, the NHLBI Acute Respiratory Distress Syndrome Network published the results of a randomized controlled trial[51] of methylprednisolone in ARDS patients of at least 7 days duration. Although therapy with methylprednisolone in-

Table 3—*Pharmacotherapies Investigated as Possible Treatment for ALI/ARDS*

Therapy	Outcomes	References
Surfactant	No significant mortality benefit (adult populations)	28–33
NO	Improves oxygenation but no mortality benefit	35–40
Corticosteroids (preventative)	Not effective in preventing ALI/ARDS	42–45
Corticosteroids (therapeutic)	No mortality benefit; may increase risk in patients with ARDS of ≥ 14 d duration	46–48,51
Antifungal agents (-azoles)	No mortality benefit in treating established ARDS; may help prevent development of ARDS	70–72
Phosphodiesterase inhibitors (*eg*, lisofylline and pentoxifylline)	No mortality benefit in ALI/ARDS	73

creased the number of ventilator-free days, shock-free days, and ICU-free days during the first month, it was associated with a significant increase in 60-day and 180-day mortality rates among patients enrolled > 13 days after the onset of ARDS. This discrepancy may be related to the finding that patients who were treated with methylprednisolone were more likely to return to assisted ventilation after extubation than those treated with placebo (28% vs 9%, respectively; p = 0.006). Methylprednisolone did, however, reduce the 60-day mortality rate in patients with elevated BAL fluid levels of procollagen peptide III, which is a biological marker of collagen synthesis in the lung previously demonstrated to have prognostic value in ARDS.[52] Although the overall rate of neuromyopathy at 180 days did not differ between the corticosteroid and placebo groups, all nine reports of serious adverse events associated with neuromyopathy were in the methylprednisolone group (p = 0.001). Of note, the subgroup interaction analyses of outcomes up to day 60 were defined *a priori* per the study investigators, while those analyses focusing on 180-day outcomes were *post hoc*. Thus, although the results of this large, randomized, controlled trial are complex, on balance the evidence still argues against treating ALI/ARDS with corticosteroids, particularly in patients with ALI/ARDS of > 13 days duration, given the lack of beneficial effect on long-term outcomes and concerns about neuromuscular side effects.

Novel Potential Therapies for ALI

Though none of the aforementioned agents have proved to be effective in improving ALI-related mortality, several promising new therapies are being evaluated in ongoing or upcoming clinical trials. Activated protein C, available commercially as drotrecogin alfa, has been demonstrated to significantly reduce mortality in patients with severe sepsis.[53] Recognition of the potential role of disordered coagulation and fibrinolysis in the pathogenesis of lung injury is growing.[54,55] In patients with lung injury, lower levels of endogenous protein C are associated with poor clinical outcomes.[56] Furthermore, studies[57,58] in healthy human subjects have demonstrated that the administration of activated protein C decreases lung inflammation and inhibits coagulation after endotoxin exposure. These discoveries prompted the design of a multicenter phase II trial of activated protein C in patients with ALI, which is expected to finish enrollment in 2008.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is another novel therapy currently being evaluated as a possible therapy for lung injury. GM-CSF plays an important role in the development and homeostasis of alveolar macrophages as well as in the prevention of apoptosis in the alveolar epithelium.[59] Animal models[60] first suggested a benefit from GM-CSF therapy in experimentally induced lung injury, and a randomized controlled phase II trial[61] of GM-CSF in 10 human patients with lung injury found an improvement in oxygenation over a 5-day period. A randomized controlled trial is ongoing now at the University of Michigan to determine whether a 14-day course of GM-CSF improves clinical outcomes, including ventilator-free days and mortality, in patients with ALI/ARDS.

Alveolar fluid clearance is a critical component of the resolution of lung injury.[62] β-agonists accelerate alveolar fluid clearance in isolated human lung models[63] and in rat models of lung injury,[64] and salmeterol has been demonstrated to decrease the incidence of high-altitude pulmonary edema in an at-risk population.[65] β-agonists may also decrease lung inflammation, as demonstrated by both *in vivo* experiments[66] and *in vitro* experiments.[67] A small, single-center, randomized, controlled trial[68] recently demonstrated that therapy with IV salbutamol (albuterol) reduced the amount of extravascular lung water, though there was a trend toward a higher incidence of arrhythmias in the treatment group. As a result of these findings, the NHLBI Acute Respiratory Distress Syndrome Network is initiating a large, multicenter, randomized, controlled trial of the efficacy and safety of aerosolized β-agonist therapy in ALI/ARDS patients.

Conclusions

New evidence strongly suggests that we should follow a conservative fluid management strategy for most patients with established ALI/ARDS who are not in shock, with the goal of keeping the patient's fluid balance net even. Managing fluids with this approach increases the number of ventilator-free days in patients with ALI with no increase in the rates of shock or renal failure. Electrolyte values must be closely monitored when following this strategy, and patients in shock should still receive aggressive volume resuscitation. Therapy with albumin and furosemide may be beneficial in selected patients with hypoproteinemia and ALI, although conclusive data are still lacking on patient outcomes.

Although there have been no dramatic advances in the pharmacologic treatment of ALI/ARDS over the past decade, several new and promising treatments, including activated protein C, GM-CSF, and inhaled β-agonists, are currently being evaluated in clinical trials. Notably, the latest advances in the treatment of ALI, such as ventilation with lower tidal volumes

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and conservative management of fluids, constitute major improvements in supportive care. Assiduous attention to other elements of the supportive care of critically ill patients such as the prevention of ventilator-associated pneumonia and adequate nutritional support should also be provided to ALI patients in hopes of further improving outcomes.

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