Nonventilatory strategies for patients with life-threatening 2009 H1N1 influenza and severe respiratory failure

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Severe respiratory failure (including acute lung injury and acute respiratory distress syndrome) caused by 2009 H1N1 influenza infection has been reported worldwide. Refractory hypoxemia is a common finding in these patients and can be challenging to manage. This review focuses on nonventilatory strategies in the advanced treatment of severe respiratory failure and refractory hypoxemia such as that seen in patients with severe acute respiratory distress syndrome attributable to 2009 H1N1 influenza. Specific modalities covered include conservative fluid management, prone positioning, inhaled nitric oxide, and extracorporeal membrane oxygenation and life support. Pharmacologic strategies (including steroids) investigated for the treatment of severe respiratory failure are also reviewed. (Crit Care Med 2010; 38[Suppl.]:S000–S000)

KEY WORDS: ●●●

Severe respiratory failure, including acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (1), in patients with 2009 H1N1 influenza pulmonary infection has been described worldwide (2–9). A common feature of these patients is severe hypoxemia, ARDS, and an inability to achieve adequate oxygenation with conventional ventilation modalities commonly used in the treatment of severe ARDS. In addition, high case fatality rates have been reported, with multiple organ failure as the leading cause of death. Our case series of intensive care unit (ICU) patients with severe 2009 H1N1 influenza virus infection and ARDS in Michigan, reported in June 2009, documented the use of a number of rescue therapies for the treatment of severe hypoxemia in these patients (2).

MATERIALS AND METHODS

Outcomes of Patients With ARDS Attributable to Influenza

A recent retrospective cohort study examined 111 critically ill patients with confirmed influenza virus infection. ARDS complicated the ICU course in 25 (23%) of the patients, with a mortality rate of 52%. Multivariate logistic regression analysis identified the development of ARDS (odds ratio [OR], 7.7; 95% confidence interval [CI], 2.3–29) as an independent risk factor for hospital mortality in critically ill patients with confirmed influenza virus infection (10).

Similarly, a report of children with ARDS attributable to highly pathogenic avian influenza A (H5N1) also documented a significantly higher mortality rate (83%) compared to children with ARDS who were H5N1-negative (48%) (11). The H5N1-positive patients with ARDS also had significantly reduced survival time compared to H5N1-negative ARDS patients (12.3 ± 5.7 days [median, 11 days] vs. 21.5 ± 13.8 days [median, 22 days]), respectively). These observations clearly documented the adverse outcomes associated with influenza A (H5N1)-induced fulminant ARDS.

In contrast to the high reported mortality rates in patients with severe ARDS attributable to influenza infection, over the past decade there has been a significant improvement in survival among patients with ALI treated at ARDS Network centers (Fig. 1), strongly suggesting that advancements in critical care and lung-protective ventilation have accounted for this improvement in mortality (12).

For patients with 2009 H1N1 influenza severe respiratory failure, early initiation of appropriate antiviral treatment is of paramount importance, including oseltamivir or zanamivir (13, 14). In a recent review (15) of the epidemiology of laboratory-confirmed severe and fatal human influenza infections in Thailand, treatment with oseltamivir was associated with survival (OR, 0.11; 95% CI, 0.04–0.30) in hospitalized human influenza pneumonia patients. Additional treatment of ALI and ARDS is supportive care, including optimal mechanical ventilation, nutritional support, manipulation of fluid balance, source control with treatment of sepsis, and prevention of intervening medical complications. Optimal lung-protective ventilatory strategies in these patients, as in those with severe ARDS attributable to other etiologies, focus on limiting end-inspiratory plateau pressure (P_{plat}) to <30 cm H_2O and tidal volumes to <6 mL/kg of predicted body weight, with provision of optimal positive end expiratory pressures for alveolar recruitment.

Mechanical ventilatory support can be injurious and lead to additional lung injury when used at the extremes of pulmonary physiology, a concept that has been termed ventilator-induced lung injury (16). A number of mechanisms can lead to the development of ventilator-induced lung injury, including barotrauma, diffuse alveolar injury attributable to overdistension (volutrauma), injury attributable to repeated cycles of recruitment/derecruitment (atelectrauma), and the most subtle form of injury attributable to the release of local mediators in the lung (biotrauma) (17).

ARDS and ALI are associated with pathologically complex changes in the lung, manifested by an early exudative phase, followed by proliferative and fibrotic phases (18). The acute inflammatory state leads to increased capillary permeability and accumulation of proteinaceous pulmonary edema, leading to hypoxemia. Hypoxia may further aggravate lung injury; therefore, treatment strategies focus on improvement of oxygenation and correction of the underlying problem (19).

Most patients who die of 2009 H1N1 influenza do so as a result of unrelenting hypoxemic respiratory failure. Hypoxemia was iden-

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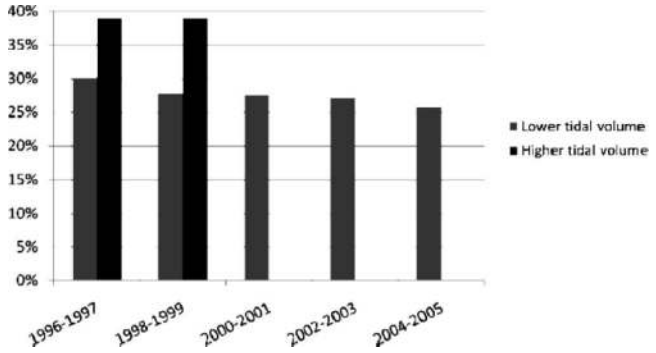

Figure 1. Crude 60-day mortality among acute respiratory distress syndrome (ARDS) Network patients, 1996 to 2005. From: Erickson SE, Martin GS, Davis JL, et al; for the NIH NHLBI ARDS Network: *Crit Care Med* 2009; 37:1574–1579.

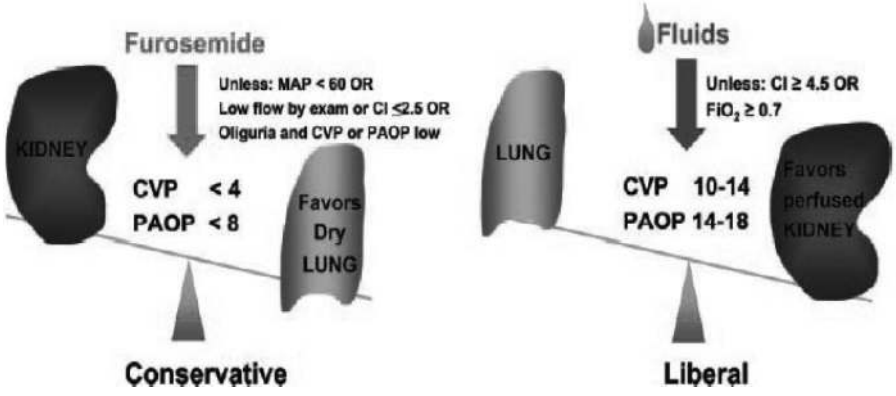

Figure 2. Fluid management strategies in the FACTT trial. *Left,* Fluid-conservative strategy, in which diuretics were administered to a target central venous pressure <4 mm Hg or pulmonary artery occlusion pressure <8 mm Hg. *Right,* Fluid-liberal strategy in which fluids were administered to maintain a central venous pressure between 10 and 14 mm Hg. From: Liu KD, Matthay MA: Advances in critical care for the nephrologists: Acute lung injury/ARDS. *Clin J Am Soc Nephrol* 2008; 3:578–586.

tified as an independent risk factor for mortality in the report from Mexico, documenting a median Pao_2-to-Fio_2 ratio of 164 (range, 87–250) in patients who survived (n = 11) compared to 53 (range, 46–107) in those who died (n = 7), with hazard ratio for death 0.95 (95% CI, 0.91–0.99; $p = .02$). Consideration of rescue therapies for refractory hypoxemia therefore is fully warranted (20). This review focuses on nonventilatory management strategies for the treatment of patients with severe respiratory failure, hypoxemia, and ARDS.

DISCUSSION

Conservative Fluid Management

Diuresis to dry weight is a common strategy used in the treatment of patients with severe hypoxemia attributable to 2009 H1N1 influenza bilateral pneumonia. We utilize continuous infusion furosemide or bumetanide therapy to achieve net negative fluid balance in patients with severe hypoxemia. Evidence supports this simple clinical strategy.

The National Heart, Lung, and Blood Institute ARDS Network prospective, randomized, clinical trial (Prospective, Randomized, Multicentered Trial of Fluid Conservative vs. Fluid Liberal Management of ALI and ARDS, FACCT) that evaluated the use of a liberal vs. conservative fluid strategy (using diuretics to target a central venous pressure <4 mm Hg or pulmonary artery occlusion pressure <8 mm Hg) in patients with ALI documented that a fluid-conservative strategy resulted in a significant increase in ventilator-free days and a nonsignificant decrease in mortality by 3% (Fig. 2) (21). The same clinical trial found no additional benefit to the use of a pulmonary artery catheter rather than a central venous catheter in fluid management (22). No significant difference in the need for hemodialysis was identified in the conservative vs. liberal fluid management strategies in this clinical trial (14% vs. 10%; $p = .06$), but the indications for initiation of hemodialysis were not controlled, making comparison difficult. A secondary analysis of the National Heart, Lung, and Blood Institute ARDS Network tidal volume study cohort documented that cumulative negative fluid balance on day 4 of the study was associated with significantly lower hospital mortality (OR, 0.50; 95% CI, 0.28–0.89; $p < .001$) and more ventilator-free and ICU-free days (23). Similarly, a *post hoc* subgroup analysis of 1000 surgical patients enrolled in the FACTT trial documented that a conservative fluid-administration strategy resulted in more ventilator-free and ICU-free days, and no difference in mortality or renal failure (24).

A small (n = 40) double-blind, placebo-controlled, multicenter trial randomized patients with ALI/ARDS and hypoproteinemia (serum total protein concentrations <6 g/dL) to receive furosemide with albumin or furosemide with placebo for 72 hrs, titrated to fluid loss and normalization of serum total protein concentration. Albumin-treated patients had greater increase in oxygenation (mean change in Pao_2/Fio_2, +43 vs. −24 mm Hg at 24 hrs and +49 vs. −13 mm Hg at day 3), with greater net negative fluid balance (−5480 mL vs. −1490 mL at day 3) and better maintenance of hemodynamic stability (25). Additional larger definitive clinical trials are warranted to confirm these preliminary findings.

It should be noted, however, that many patients with severe ARDS attributable to 2009 H1N1 influenza pneumonia present with acute kidney injury and multiple organ dysfunction and/or failure. In these patients, early initiation of continuous renal replacement therapy may facilitate optimal management of fluid balance with the ability to titrate fluid removal and achieve goals for net negative fluid balance on an hourly basis. In the recent report of 722 patients admitted to ICUs in Australia and New Zealand with confirmed infection with the 2009 H1N1 virus, 506 patients (70.1%) required renal replacement therapy, and 498 (69.0%) required vasopressor drugs during their ICU stay (26).

Prone Positioning

Changes in patient positioning can have a dramatic effect on oxygenation and ventilation in severe ARDS. Changing the patient position to prone or a steep lateral decubitus position can improve the distribution of perfusion to

ventilated lung regions, decreasing intrapulmonary shunt and improving oxygenation (27).

The use of intermittent prone positioning can significantly improve oxygenation in 60% to 70% of patients (28, 29). A multicenter, randomized trial of conventional treatment vs. placing patients in a prone position for ≥6 hrs daily for 10 days was conducted on patients 16 yrs or older with ALI or ARDS (30). No differences were identified between the groups in mortality or complications at any time point during the study, with up to 6 mos follow-up. The mean increase in the Pao_2-to-Fio_2 ratio was greater in the prone than in the supine group (63 ± 67 vs. 45 ± 68; $p = .02$). Of note is that the mean Pao_2 of 85 to 88 mm Hg and mean Pao_2-to-Fio_2 ratio of 125 to 129 are still high for patients with severe ARDS; therefore, these patients may not have been likely to benefit considerably by the prone intervention with regard to mortality. A retrospective analysis of patients in the prone position arm of this study revealed that ALI/ARDS patients who responded to prone positioning with a reduction in their $Paco_2$ ≥1 mm Hg showed an increase in survival at 28 days, with a decrease in the mortality rate from 52% to 35% (31).

A multicentered, randomized, controlled clinical trial of supine versus prone positioning in 102 pediatric patients failed to demonstrate a significant difference in the main outcome measure, which was ventilator-free days to day 28. There were also no differences in the secondary end points study conducted, including proportion alive and ventilator-free on day 28, mortality, time to recovery from lung injury, organ-failure-free days, and functional health (32).

A prospective, randomized study (n = 136), with guidelines established for ventilator settings and weaning, examined the efficacy of the prolonged prone position (continuous prone position for 20 hrs daily) in severe ARDS patients with 48 hrs of tracheal intubation. Multivariate analysis documented that randomization to the supine position was an independent risk factor for mortality (OR, 2.53; $p = .03$). These authors concluded that prone ventilation is feasible and safe and may reduce mortality in patients with severe ARDS when it is initiated early and applied for most of the day (33).

An open, randomized, controlled trial in 17 medical–surgical ICUs enrolled 40 mechanically ventilated patients with early and refractory ARDS despite protective ventilation in the supine position. Patients were randomized to remain supine or to be moved to early (within 48 hrs) and continuous (≥20 hrs/day) prone position until recovery or death. The trial was prematurely stopped because of a low patient recruitment rate. Pao_2/Fio_2 tended to be higher in prone than in supine patients after 6 hrs (202 ± 78 mm Hg vs. 165 ± 70 mm Hg); this difference reached statistical significance on day 3 (234 ± 85 vs. 159 ± 78). Prone-related side effects were minimal and reversible. Sixty-day survival reached the targeted 15% absolute increase in prone patients (62% vs. 47%) but failed to reach significance because of the small sample. This study adds data to reinforce the potential beneficial effect of early continuous prone positioning on survival in ARDS patients (34).

The most recent systematic review of the effect of prone mechanical ventilation on clinical outcomes in patients with acute hypoxemic respiratory failure reported that it does not reduce mortality or duration of ventilation, despite improved oxygenation and a decreased risk of pneumonia (Figs. 3, 4) (35). However, despite no significant effect on mortality reduction, these data do confirm a significant improvement in oxygenation and support the use of prone position ventilation as a rescue strategy in patients with severe hypoxemia. Additional systematic reviews and meta-analyses have confirmed similar findings. Interestingly, the pooled OR for ICU mortality in the selected group of the more severely ill patients favored prone positioning (OR, 0.29; 95% CI, 01.12–0.70) (36–40).

Prone positioning may be labor-intensive with associated risks, including inadvertent extubation and pressure sores, and requires the use of appropriate cushioning of the dependent portions of the body to avoid pressure ulcerations. However, the technique can be performed safely by trained and dedicated critical care staff aware of its potential benefits in critically ill patients with severe respiratory failure and hypoxemia. Interestingly, prone positioning was used in 42% of patients in the conventional management group (control arm) of the conventional ventilation or extracorporeal membrane oxygenation (ECMO) for severe adult respiratory failure (CESAR) trial, compared to only 4% in the ECMO group.

Extended prone position ventilation in severe ARDS has been confirmed in a

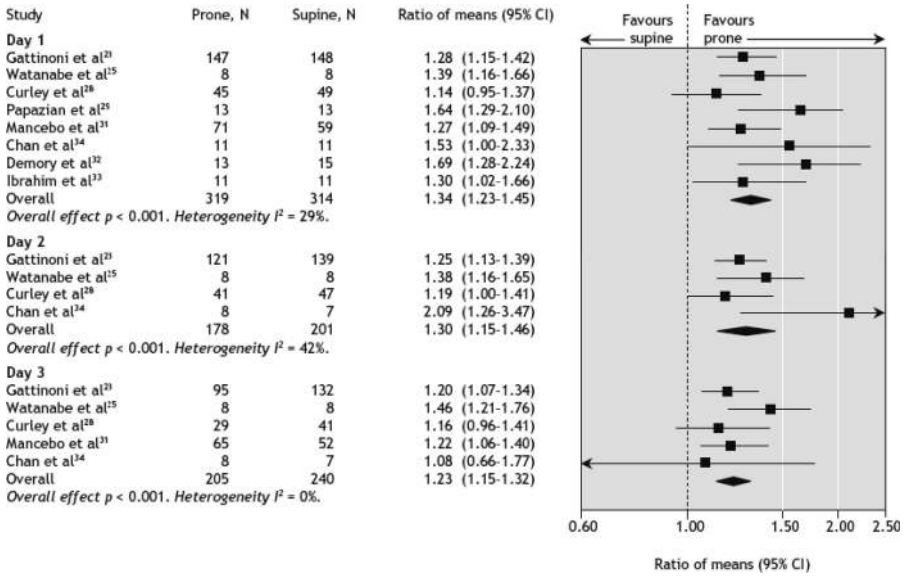

Figure 3. Effect of ventilation in the prone position on daily ratio of partial pressure of oxygen to inspired fraction of oxygen. A random-effects model was used in the analysis. Values were recorded at the end of the period of prone positioning (prone group) and simultaneously in the supine group. Ratio of means indicates mean ratio of partial pressure of oxygen to inspired fraction of oxygen in the prone group divided by that in the supine group. I^2 indicates percentage of total variation across studies owing to between-study heterogeneity rather than chance. CI, confidence interval. From: Sud S, Sud M, Friedrich JO, et al: Effect of mechanical ventilation in the prone position on clinical outcomes in patients with acute hypoxemic respiratory failure: A systematic review and meta-analysis. *CMAJ* 2008; 178:1153–1161.

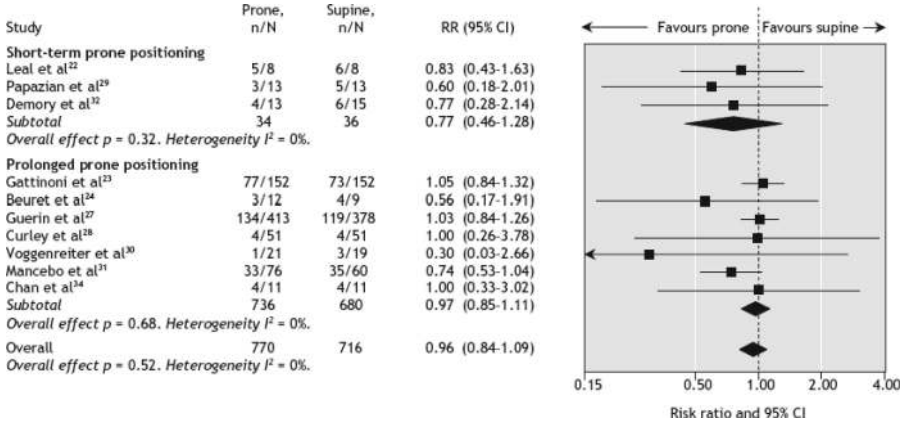

Figure 4. Effect of ventilation in the prone position on mortality. A random-effects model was used for analysis. The duration of prone positioning was up to 24 hrs for 1 to 2 days in the short-term trials and up to 24 hrs daily for >2 days in the prolonged-duration trials. The trial by Gattinoni et al (24) included data only for patients with acute hypoxemic respiratory failure. Including all patients from this trial (7 of 25 deaths in the prone group and 14 of 28 deaths in the supine group) did not change the result (risk ratio [RR], 0.95; 95% CI, 0.83–1.08; $p = .41$). I^2 indicates percentage of total variation across studies owing to between-study heterogeneity rather than chance. From: Sud S, Sud M, Friedrich JO, et al. Effect of mechanical ventilation in the prone position on clinical outcomes in patients with acute hypoxemic respiratory failure: A systematic review and meta-analysis. *CMAJ* 2008; 178:1153–1161.

recent pilot feasibility study. Extended prone position ventilation was defined as prone position ventilation for 48 hrs or until the oxygenation index was ≤10. A prospective interventional study in 15 patients confirmed that there was a statistically significant improvement in oxygenation (Pao_2/Fio_2 92 ± 12 vs. 227 ± 43; $p < .0001$) and oxygenation index (22 ± 5 vs. 8 ± 2; $p < .0001$), reduction of $Paco_2$ (54 ± 9 vs. 39 ± 4; $p < .0001$) and P_{plat} (32 ± 2 vs. 27 ± 3; $p < .0001$), and improved static compliance (21 ± 3 vs. 37 ± 6; $p < .0001$) with extended prone position ventilation. All the parameters continued to improve significantly while the subjects remained in the prone position and did not change on returning the patients to the supine position. The results obtained suggest that extended prone position ventilation is safe and effective in patients with severe ARDS when it is performed by a trained staff and within an established protocol. Extended prone position ventilation is emerging as an effective rescue therapy for patients with severe ARDS and severe hypoxemia (41).

In our experience, prone positioning is a useful tool for treatment of hypoxemia, can sometimes prevent the need for extracorporeal life support (ECLS), and is used for lung recruitment in patients on ECLS. One technique involves alternating prone with supine positioning every 6 hrs. Patients will often experience an initial worsening in their respiratory status with each change in position, but this passes quickly in the first 15 to 30 mins, followed by eventual improvement in oxygenation and ventilation. Prone positioning, although not associated with a significant survival advantage, may serve a role as rescue therapy for patients with ARDS and refractory life-threatening hypoxemia.

Nitric Oxide

Nitric oxide (NO), a naturally occurring product identical to endothelial-derived relaxing factor (42–44), is an important endogenous mediator in several physiologic processes *in vivo*. One of its most important cardiovascular actions is potent vasodilation, which results from decreased calcium in smooth muscle cell cytoplasm after NO-dependent increase in cyclic-guanosine monophosphate. The activity of NO can be pharmacologic as well as physiologic. Inhaled NO (INO) has the advantage of selective delivery to ventilated alveolar units. The impact of INO depends on the relative contribution of hypoxic vasoconstriction and ventilation/perfusion mismatch to the hypoxemia.

INO affects gas exchange by increasing blood flow in ventilated areas to improve $ventilation_A/perfusion_c$ matching. Because of its high affinity for hemoglobin, INO is active principally in ventilated lung regions, with relatively little diffusion into neighboring nonventilated tissues. A major established therapeutic use of INO is in pulmonary hypertension of the newborn (45–48). INO has also been shown to reduce pulmonary artery pressures and/or pulmonary vascular resistance in a number of animal models of acute pulmonary injury (49–54), making it relevant for patients with ALI/ARDS.

Two small single-center studies and four multicenter, randomized, placebo-controlled trials have failed to determine the therapeutic role of INO in patients with acute respiratory failure. Low-dose INO in ALI and ARDS has been associated with improved short-term oxygenation but has had no substantial impact on the duration of mechanical ventilatory support or on mortality (55–59).

The Cochrane Database systematic review of INO for acute hypoxemic respiratory failure in children and adults included five randomized, controlled, clinical trials assessing 535 patients with acute hypoxemic respiratory failure. There was no significant difference in mortality with the use of NO in trials without crossover (risk ratio [RR], 0.98; 95% CI, 0.66–0.44). Published evidence from one study demonstrated that NO transiently improved oxygenation in the first 72 hrs of treatment. Limited data demonstrated no significant difference in ventilator-free days between treatment and placebo groups, and no specific dose of NO was significantly advantageous over another. Other clinical indicators of effectiveness, such as duration of stays in the hospital and ICU, were inconsistently reported. No significant complications were directly attributable to this treatment. NO did not demonstrate any statistically significant effect on mortality and transiently improved oxygenation in patients with hypoxemic respiratory failure (60). The authors conclude that if further trials comparing INO with an inhaled placebo are to proceed, then they should be stratified for primary disease, should assess the impact of other combined treatment modalities for respiratory failure, and must specifically evaluate clinically relevant outcomes before any benefit of INO for respiratory failure can be excluded.

A more recent systematic review and meta-analysis of the effect of NO on oxygenation and mortality in ALI included 12 trials randomly assigning 1237 patients. Overall methodologic quality was good. On day 1 of treatment, NO increased oxygenation as measured by the

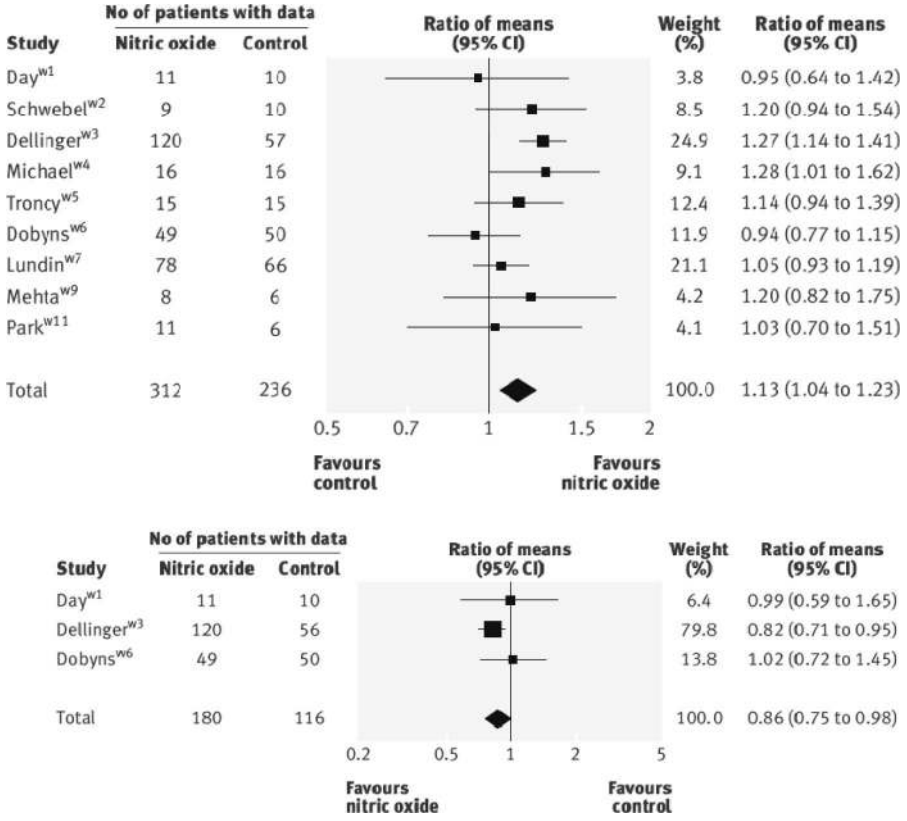

Figure 5. Effect of nitric oxide (NO) on Pao_2/Fio_2 ratio and oxygenation index at 24 hrs. Weight is the relative contribution of each study to overall estimate of treatment effect (ratio of means, NO relative to control) on log scale assuming a random effects model. For some trials, number of patients with data are less than number randomized. From: Adhikari NKJ, Burns KEA, Friedrich JO, et al: Effect of nitric oxide on oxygenation and mortality in acute lung injury: Systematic review and meta-analysis. *BMJ* 2007; 334:779.

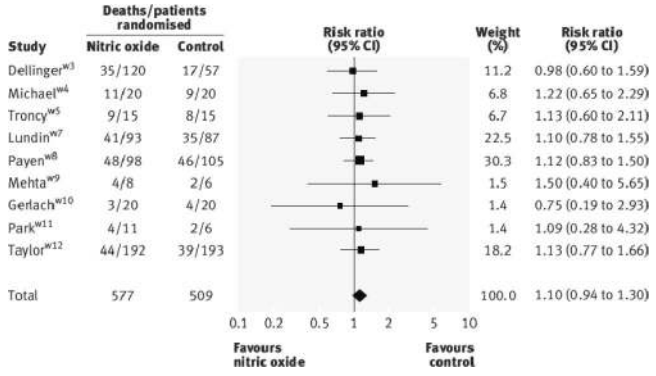

Figure 6. Effect of NO on mortality. Weight is the relative contribution of each study to the overall estimate of treatment effect on a log scale assuming a random effects model. Two trials with ≥50% of control patients crossing-over to NO also reported mortality date (w2 w6). Inclusion of these trials did not alter summary mortality estimate (RR, 1.09; CI, 0.94–1.27). From: Adhikari NKJ, Burns KEA, Friedrich JO, et al: Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. *BMJ* 2007; 334:779.

Pao_2/Fio_2 ratio (13%; range, 4%–23%) and decreased the oxygenation index (14%; range, 2%–25%; Fig. 5). Evidence suggested that improvements in oxygenation persisted until day 4. Using random effects models, they found no significant effect of NO on hospital mortality (RR, 1.10; 95% CI, 0.94–1.30), duration of ventilation, or ventilator-free days (Fig. 6). There was no effect on mean pulmonary arterial pressure. Interestingly, patients receiving NO had an increased risk of developing renal dysfunction (1.50; range, 1.11–2.02) (61).

The improvement in oxygenation associated with INO in ALI and ARDS has not been translated into improved clinical outcome. Variable response to INO may be related to increased blood flow in nonventilated areas in the setting of disordered pulmonary vasoregulation in ALI/ARDS. INO may improve oxygenation by decreasing intrapulmonary shunt, or it may worsen oxygenation by reversing hypoxemic pulmonary vasoconstriction, thereby increasing ventilation/perfusion mismatch. This may also be related to the fact that ARDS is a heterogeneous condition with multiple causes (pulmonary and extrapulmonary), and that only a small minority of patients with ARDS die of respiratory failure; the majority die of multiple organ dysfunction and failure. These data do not support the routine use of INO in the treatment of ALI or ARDS, but it should be considered as a salvage or rescue therapy in patients who continue to have life-threatening hypoxemia despite optimization of all other treatment strategies.

It can be challenging to wean INO in ALI/ARDS patients who are responders to INO. Some have advocated the use of enteral off-label sildenafil, a selective and potent inhibitor of phosphodiesterase type 5, particularly to ameliorate the effect of INO withdrawal (62). Furthermore, some data suggest that sildenafil may augment and prolong the pulmonary vasodilatory effects of INO, allowing successful weaning and discontinuation of INO in patients in whom INO withdrawal had previously failed (63).

In patients with severe ARDS attributable to 2009 H1N1 influenza, INO has been used as a rescue strategy in some patients. We also use it in a strategy to stabilize ECMO evaluation patients with severe hypoxemia for transfer to our facility. Variable efficacy has been observed, and no formal recommendation can yet be made. Organized data collection efforts are needed regarding treatment strategies used in these critically ill patients with severe ARDS attributable to 2009 H1N1 influenza to assess the efficacy of these rescue therapies for the treatment of severe hypoxemia.

Prostacyclin and Other Vasodilatory Prostaglandins

Prostacyclin is a microcirculatory vasodilator and inhibitor of platelet aggregation used for several indications in neonatal and adult medicine. When

Table 1. Adult respiratory failure ECLS Criteria

Indications	Contraindications
Duration of mechanical ventilation < 5–7 days 7–10 days only if mechanically ventilated with high pressures for <7 days	There is no absolute contraindication to ECLS, because each patient is considered individually with respect to risks and benefits. There are conditions, however, that are known to be associated with a poor outcome despite ECLS and can be considered as relative contraindications.
Pulmonary compliance <0.5 mL/cm H_2O/kg	Mechanical ventilation at high settings (F_{IO_2} >0.9, P-plat >30) for ≥7 days
Oxygenation PaO_2/F_{IO_2} <100 and no response to standard therapies for severe ARDS Shunt >30%	Major pharmacologic immunosuppression (absolute neutrophil count <400 cells/mm^3) CNS hemorrhage that is recent or expanding Contraindication to systemic anticoagulation

ECLS, extracorporeal life support; CNS, central nervous system.

aerosolized, its vasodilatory action in ventilated areas should be similar to that of INO in improving $ventilation_A$/$perfusion_c$ matching without promoting systemic hypotension. Consistent with this, aerosolized prostacyclin improved acute respiratory function to the same degree as INO in several studies in patients with ARDS (64–66). Observational studies have documented that prostacyclin is an efficacious selective pulmonary vasodilator, with significant dose-related improvements in oxygenation, no demonstrable effect on systemic arterial pressures over the dose range of 0 to 50 ng/kg/min, and no demonstrable platelet function defect despite significant systemic levels of prostacyclin metabolite (67, 68).

Inhaled iloprost is the stable carbacyclin analog of prostacyclin. In contrast to prostacyclin, iloprost is stable at room temperature, has physiologic pH, and has normal light conditions. Whereas prostacyclin has a half-life of only 3 mins, iloprost has a half-life of 20 to 30 mins and exerts its pulmonary vasodilating effects for 30 to 90 mins. Clinical studies have shown that inhaled iloprost has comparable pulmonary hemodynamic effects to INO and inhaled prostacyclin (69). It was approved by the U.S. Food and Drug Administration in 2004 for pulmonary hypertension with New York Heart Association class III or IV symptoms. We currently use INO and inhaled iloprost as rescue therapies for patients with severe ARDS and hypoxemia.

Another vasodilatory prostaglandin, alprostadil, has also been shown to allow improvements similar to those of INO when delivered by aerosol to patients with ARDS (70, 71). These results suggest that aerosolized prostacyclin or similar drugs could be viable therapeutic alternatives to INO. Additionally prostacyclin may have some advantages over NO because it is easier to administer and has harmless metabolites; however, it is more expensive and has not shown any survival benefit in human trials.

Extracorporeal Life Support

In patients with acute and severe respiratory failure and ARDS that do not respond to any advanced modes of mechanical ventilation, the use of ECLS or ECMO is an option. ECLS is a proven modality for treatment of severe respiratory failure in the neonate (72, 73) and use has increased since its inception (74). For infants, children, and adults with severe ARDS, ECLS therapy has produced survival rates of 85%, 74%, and 52%, respectively (75). The indications for ECLS for adult respiratory failure are listed in Table 1. Referral to an ECLS center should occur early if need for this technology is suspected. This will allow safe patient transport and avoidance of the "crash on," with all of its inherent complications.

The technique of ECLS for patients with severe respiratory failure involves a veno-venous or veno-arterial life support circuit with a membrane oxygenator to temporarily take over the lung functions. Mechanical ventilator settings are adjusted to minimize ventilator-induced lung injury and to maximize the recruitment to functional residual capacity. The treatment program for adults involves an algorithm that aims to normalize body physiology, aggressively recruit functional residual capacity, and minimize barotrauma. This algorithm, used in 141 patients with respiratory failure referred for consideration of ECLS, yielded a survival rate of 62% in patients with severe ARDS (median initial Pa_{O_2}/F_{IO_2} ratio, 66) (76).

The primary indication for ECLS in patients with severe respiratory failure is when the risk of dying of ARDS is considered >80% despite optimal ventilator and medical management. This translates to an alveolar–arterial oxygen gradient >600 mm Hg or a Pa_{O_2}-to-F_{IO_2} ratio of <70 on 100% oxygen.

The majority of patients with severe ARDS are managed with veno-venous ECMO. Adult patients are typically cannulated percutaneously with 21-F to 23-F catheters for drainage and infusion of blood. Veno-arterial access is used to provide respiratory and hemodynamic support for patients in shock (as may be the case in some H1N1 patients). Anticoagulation is necessary and is titrated by measurement of whole blood activated clotting time and/or serial partial thromboplastin time. ECLS allows for a decrease in mechanical ventilator settings to nondamaging "rest" levels while maintaining functional residual capacity recruitment measures. Once the patient's native lung function has improved, a trial off ECLS is attempted at moderate ventilatory settings that allow for potential increases in therapy (e.g., F_{IO_2}, 0.5–0.6). If the trial of ECLS is successful, the cannulae are removed and the recovery continues.

In a series of 255 adult patients who were placed on ECLS for severe ARDS refractory to all other treatment strategies, 67% were weaned off ECLS, and 52% survived to hospital discharge (77). Multivariate analysis identified the following pre-ECLS variables as significant independent predictors of survival: (1) age; (2) gender; (3) arterial blood pH ≤7.10; (4) Pa_{O_2}-to-F_{IO_2} ratio; and (5) days of mechanical ventilation. None of the patients who survived ECLS required permanent mechanical ventilation or supplemental oxygen therapy. Those who can be successfully decannulated from ECLS had a 77% chance of being discharged from the hospital and of complete recovery.

An analysis of 1473 adult ECMO patients with respiratory failure from the Extracorporeal Life Support Organization (ELSO) registry during 1986 to 2006 was recently reported (Table 2) (78). Median Pa_{O_2}-to-F_{IO_2} ratio pre-ECMO was 57, with

Table 2. ECMO in adult patients with acute respiratory failure: Clinical features and outcomes over two decades

Pre-ECMO Variable	1986–1991	1992–1996	1997–2001	2002–2006	*p*
n	52	304	517	600	—
Survival, n (%)	19 (40)	153 (50)	268 (52)	301 (50)	<.001
Age (yr), median (IQR)	25 (19–35)	31 (21–43)	36 (22–49)	37 (23–51)	.001
Weight (kg)	60 (56–77)	61 (50–75)	74 (60–90)	75 (63–90)	.001
Hours of ventilation, median (IQR)	72 (12–192)	120 (30–192)	55 (18–143)	42 (17–139)	.02
Cardiac arrest, n (%)	0	5 (2)	43 (8)	60 (11)	<.001
SaO_2 (%)	87 (52–98)	87 (76–91)	87 (77–92)	86 (77–92)	.62
F_{IO_2}	100	100	100	100	.49
INO	0	2 (1)	71 (14)	118 (20)	<.001
High-frequency ventilation	0	4 (1)	16 (5)	50 (9)	.09
VV mode, n (%)	4 (44)	29 (69)	301 (72)	419 (72)	.32
ECMO duration (hr), median (IQR)	192 (84–323)	150 (86–319)	166 (86–301)	144 (67–259)	.94

ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; SaO^2, arterial oxygen saturation; INO, inhaled nitric oxide; VV, veno-venous.

Modified from Brogan et al (78).

interquartile range (IQR) of 46 to 75. Survival among this cohort of adults was 50%, and most patients (78%) were supported with veno-venous ECMO. Advanced age, increased duration of mechanical ventilation before ECMO, diagnosis, and complications while on ECMO were associated with increased mortality. This report identified some interesting trends with the use of ECMO in adults with respiratory failure over the past 20 yrs. These include increased age, reduced hours of ventilation pre-ECMO, increased use of high-frequency ventilation and INO before ECMO, and increased use of veno-venous ECMO. Survival has remained at approximately 50% since 1992. Interestingly, ECMO use has been increasing for broader indications, including the use of veno-venous ECMO for respiratory support as a bridge to lung transplantation, documented by some centers with a 1-yr survival of 68% (79).

A long-term (>1 yr) follow-up study reporting on pulmonary morphology, function, and health-related quality of life in 21 survivors of severe ARDS and ECMO was recently published (80). Most patients had residual lung parenchymal changes suggestive of fibrosis on high-resolution computed tomography of the lungs. However, the extension of morphologic abnormalities were limited and without the typical anterior localization, and were presumed to indicate ventilator-associated lung injury. Pulmonary function tests confirmed low-normal values, with some subclinical obstruction noted. Most patients had reduced quality of life but had fewer respiratory symptoms compared to conventionally treated patients with ARDS, as reported in previous studies. The majority were integrated back into normal work and physical and social functioning.

The CESAR Trial

The CESAR trial was a multicentered, prospective, randomized trial performed in the United Kingdom in adults (n = 180) with severe, but potentially reversible, acute respiratory failure, defined as Murray score >3 or pH <7.20 (81). Exclusion criteria were high pressure (>30 cm H_2O of peak inspiratory pressure) or high F_{IO_2} (>0.8) ventilation for >7 days, intracranial bleeding, any other contraindication to limited heparinization, or any contraindication to continuation of active treatment. The primary outcome measures included death or severe disability 6 mos after randomization or before discharge from hospital.

The study was planned to enroll 300 patients randomly allocated to consideration for treatment by an algorithm that could include ECMO or conventional management. The conventional mechanical ventilation arm of the trial was managed as follows: "Conventional ventilatory support can include any treatment modality thought appropriate by the patient's intensivist (excluding ECMO). Intensivists had full discretion to treat patients as they thought appropriate, but it was recommended that they adopt a low tidal volume ventilation strategy." Details of compliance with lung protective ventilation in the control cohort were not reported. Patients in the ECMO arm were transferred to the ECMO center at Leicester for protocol management and ECMO if needed. Analysis was by intention to treat. The study was stopped by the Data Safety Monitoring Board for effectiveness after 180 patients. Of the 90 conventional treatment patients, 41 survived. Of the 90 ECMO patients, five died before or during transport to the ECMO center, 17 improved on the management algorithm, and 68 patients required ECMO. Six-month survival without disability was 63% (57 of 90) in the ECMO group compared to 47% (41 of 90) in the conventional management group (RR, 0.69; 95% CI, 0.05–0.97; $p = .03$). The conclusion of the CESAR trial was that management of ARDS with a standardized algorithm including ECMO in an expert center resulted in better survival than the best care in other centers in the United Kingdom.

ECMO and 2009 H1N1 Influenza Severe ARDS

ECMO support has been used as a treatment for severe respiratory failure attributable to 2009 H1N1 influenza in the United States (2) and worldwide, but U.S. multicentered data on its efficacy are not yet available. The Australian and New Zealand Intensive Care (ANZIC) study on critical care services and 2009 H1N1 influenza in Australia and New Zealand reported the clinical characteristics and outcome of 722 patients with confirmed H1N1 infection who were admitted to an ICU. Data on the use of mechanical ventilation in the ICU were available for 706 patients; of these, 456 (64%) underwent mechanical ventilation for a median of 8 days, and 53 (11.6%) of these patients were subsequently treated with ECMO, representing 2.1 patients per one million inhabitants (82). Overall mortality rate was 14.3% (103 of 722 patients), with median treatment of 7.0 days (IQR, 2.7–13.4) in the ICU.

The recent case series report of all patients (n = 68) with 2009 H1N1 influenza-associated ARDS treated with ECMO in 15 ICU in Australia and New Zealand between June 1 and August 31, 2009 documented a 21% mortality rate (83). During the study period, 194 patients with either confirmed 2009 H1N1 influenza or influenza A not subtyped were admitted to the participating ICU requiring mechanical ventilation, and 61 patients

(31.4%) were treated with ECMO. Before ECMO, patients had severe hypoxemia despite advanced mechanical ventilatory support, with a median Pao_2-to-Fio_2 ratio of 56 (IQR, 48–63), positive end-expiratory pressure of 18 cm H_2O (IQR, 15–20), and an ALI Murray score of 3.8 (IQR, 3.5–4.0). All patients fulfilled the ARDS severity criteria for enrollment in the CESAR trial of ECMO treatment. Interestingly, approximately 15% of these patients were pregnant or postpartum, the largest case series of such patients in the literature. Median (IQR) duration of mechanical ventilation before initiation of ECMO was 2 (1–5) days. The initial mode of ECMO was veno-venous in 93% and veno-arterial in 7% of patients. Median (IQR) duration of ECMO support was 10 (7–15) days. Hemorrhagic complications occurred in 54% of patients, most commonly at the ECMO cannulation sites. At the time of reporting, 48 of the 68 patients (71%; 95% CI, 60%–82%) survived to ICU discharge, of whom 32 survived to hospital discharge. Fourteen patients (21%; 95% CI, 11%–30%) died and six remained in the ICU, two of whom were still receiving ECMO. The patients treated with ECMO had longer duration of mechanical ventilation (median [IQR], 18 [9–27] vs. 8 [4–14] days; $p = .001$), ICU stay (median [IQR], 22 [13–32] vs. 12 [7–18] days; $p = .001$), and greater ICU mortality (14 [23%] vs. 12 [9%]; $p = .01$).

The ELSO has collected data on ECMO patients from international centers since 1986 and thus represents a cross-section of ECMO practice. Because of the overwhelming request for information on H1N1 patients who go on to receive ECLS for severe hypoxemia and ARDS, the ELSO has developed a method to track these cases (H1N1 ECLS Registry). The form is brief with a minimal data set to capture critical ECLS information and outcome. The case report form and additional information can be found at the ELSO website (http://www.elso.med.umich.edu/H1N1.htm). ELSO has initiated an open call for submission of ECMO cases and welcome the participation of all participating ELSO centers and non-ELSO centers in this important effort. We aim to subsequently examine the ELSO data registry for adult patients with respiratory failure attributable to 2009 H1N1 influenza to describe the population and determine factors associated with hospital survival.

ECMO guidelines (general and patient-specific) are available from the ELSO web site and contain important and complete information regarding initiation and maintenance of ECMO support through decannulation and discontinuation of ECMO (http://www.elso.med.umich.edu/guide.htm).

Advances in ECMO

There have been a number of significant advances in ECMO support over the past few years. Traditional cannulation for veno-venous ECMO has been a two-cannulae system, with venous drainage from the right femoral vein and return to the right atrium via a right internal jugular vein cannula. A single bicaval dual-lumen cannula placed in the internal jugular position (Avalon Elite; Avalon Laboratories, Rancho Dominguez, CA) is now available. This is placed percutaneously in the right internal jugular vein and allows simultaneous removal of blood from the superior and inferior vena cavae with return of blood into the right atrium with minimal recirculation.

In most adults, a 27-Fr to 31-Fr Avalon catheter is inserted with a Seldinger technique using an extended length guidewire (100 cm or 210 cm length) to ensure that the distal port tip of the catheter is positioned in the inferior vena cava for venous drainage to the ECMO circuit with the oxygenator. The proximal drainage port drains blood from the superior vena cava. A uniquely designed medial infusion port returns blood to the right atrium for concentrated oxygen delivery. Optimal orientation of this medial infusion port is critical, and we have used transesophageal echocardiography in some cases to ensure adequacy of support.

For decades the standard ECMO circuit was based on a high-resistance, thrombogenic membrane lung that required a servo-regulated roller pump and continuous anticoagulation. Continuous attendance by the ICU nurse and an ECMO specialist was required to manage anticoagulation and manage emergencies. In the past few years, low-resistance, high-flow, hollow fiber membrane lungs have become available (Quadrox PLS Diffusion Membrane oxygenator; Maquet; and Novalung; Novalung GmbH). These devices are less thrombogenic and can be used with safer centrifugal pumps (Biomedicus, Medtronic Inc; Centrimag, Levitronix; and Maquet; Medos), leading to longer life, increased reliability, and reduction in the incidence of device-related adverse events. These features permit safe automatic perfusion for many days. The patient and the circuit can be managed by a trained ICU nurse, thus decreasing the expense of ECMO.

The development of mobile ECMO programs in critical care began years ago, and a number of centers in the United States have provided mobile ECMO, including the University of Michigan and C. S. Mott Children's Hospital in Ann Arbor, MI; the Arkansas Children's Hospital in Little Rock, AR; the Miami Children's Hospital in Miami, FL; and Wilford Hall Medical Center in San Antonio, TX (84).

Selective CO_2 removal can be accomplished with low blood flow rates (10 mL/kg/min) with the device attached with arteriovenous access (arterial cannula inserted into femoral artery, membrane oxygenator with venous cannula return to femoral vein, driving force is patient's blood pressure) (85–88). This technology is effective as an arteriovenous CO_2 removal device (effective treatment for status asthmaticus) but has significant limitations in providing oxygenation support.

In H1N1 severe ARDS cases, native lung function is usually so compromised with resultant severe hypoxemia that full oxygenation, and therefore high blood flow (60 mL/kg/min), is required. Additionally, the combination of extracorporeal carbon dioxide removal and limitation of tidal volume to <6 mL/kg was associated with improved markers of lung protection and the reduction of pulmonary cytokines concentration (89). Prospective, randomized trials are warranted to examine the efficacy of this new technology.

Pharmacologic Strategies

Multiple pharmacologic interventions (including prostaglandins, prostacyclin, lisofylline, ketoconazole, N-acetylcysteine, corticosteroids, and NO) have been investigated in the treatment of ALI and ARDS, but none yet has demonstrated improved survival (90, 91). Two pharmacologic strategies (ketoconazole and lisofylline) were investigated by the ARDS Clinical Trials Network, and both studies were stopped by the Data Safety and Monitoring Boards for futility at interim analyses (92, 93).

A Cochrane Database Systematic Review of pharmacologic therapy for adults with ALI and ARDS reviewed 33 trials randomizing 3272 patients and con-

cluded that two interventions were beneficial in single small trials: corticosteroids administered for late-phase ARDS reduced hospital mortality (n = 24) and pentoxifylline reduced 1-month mortality (n = 30). Individual trials of nine additional pharmacologic interventions failed to show a beneficial effect, concluding that effective pharmacotherapy for ALI and ARDS is extremely limited, with insufficient evidence to support any specific intervention (94).

Corticosteroids

Because ARDS is associated with persistent inflammation and excessive fibroproliferation, previous studies have investigated the use of corticosteroids. Four clinical trials of high-dose, short-course corticosteroids for early ARDS failed to show any improvements in survival (95–98). In contrast, several small case series (99–104) and a single-center randomized trial (n = 24) (105) reported improved lung function and survival with moderate-dose corticosteroids in patients with persistent (≥7 days) ARDS.

The multicenter trial (n = 180) from the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network (www.ardsnet.org) randomized patients with ARDS of at least 7 days' duration to receive either methylprednisolone or placebo in a double-blind manner (106). Methylprednisolone therapy was not associated with a survival benefit (29.2% vs. 28.6% mortality) despite increased ventilator-free and shock-free days, improved oxygenation, and improved pulmonary compliance during the first 28 days. Compared with a placebo, methylprednisolone was associated with significantly increased 60- and 180-day mortality rates in patients enrolled at least 14 days after the onset of ARDS. A higher rate of neuromuscular weakness and increased blood glucose concentrations, with no increase in infectious complications, were also identified. These results do not support the routine use of methylprednisolone for persistent ARDS.

A recent *post hoc* secondary analysis of this trial examined 128 study patients who survived 60 days to hospital discharge. Forty-three patients (34%) had evidence of ICU-acquired neuromyopathy associated with prolonged mechanical ventilation and therefore delayed discharge after the critical illness. However, treatment with methylprednisolone was not significantly associated with an increased risk of neuromyopathy (OR, 1.5; 95% CI, 0.7–0.32). This study documented that ICU-acquired neuromyopathy is common in ARDS survivors but is not associated with steroid treatment (107). Similar results were found with early, but prolonged, administration of low-dose methylprednisolone (1 mg/kg/d) in a recent randomized, controlled trial by Meduri et al (108).

A meta-analysis reported in 2008 showed that prolonged administration of systemic steroids is associated with favorable outcomes and survival benefit when administered before day 14 of ARDS (109). The latter finding stood particularly true when subgroups from the ARDS were reanalyzed based on the time of treatment initiation.

The most recent meta-analysis (110) included both cohort studies with significant limitations and randomized, controlled trials, and concluded that the use of low-dose corticosteroids was associated with improved mortality and morbidity without an increase in adverse reactions or improved oxygenation (Fig. 7). The authors concluded that the consistency of results in both study designs suggested that steroids are an effective treatment for ALI or ARDS. An additional meta-analysis of just eight controlled studies (n = 628) confirmed that reduction in mortality was substantial for all patients (RR, 0.75; 95% CI, 0.63–0.89; $p < .001$; I^2, 43%) and for those treated before day 14 (RR, 0.71; 95% CI, 0.59–0.85; $p < .001$; I^2, 40%) (111).

The use of steroids in ALI and ARDS clearly remains controversial. The potential mortality benefits of steroids in ARDS will be confirmed only by an adequately powered large randomized trial (112, 113). Additional questions regarding the efficacy of steroids arise when ARDS patients also manifest refractory septic shock requiring vasopressor therapy and receive low-dose corticosteroid therapy (114, 115).

Steroids and 2009 H1N1 Influenza ARDS

No clear data are available regarding the potential efficacy of steroids in the treatment of severe ARDS attributable to 2009 H1N1 influenza at this present time. In animal studies, the use of dexamethasone in a murine ARDS model induced by H5N1 viral infection did not improve mortality. There was no significant amelioration of the hypoxemia and ARDS-associated pathologic changes in dexamethasone-treated mice. Furthermore, dexamethasone therapy did not inhibit inflammatory cellular infiltration and cytokine release (interleukin-6 and tumor necrosis factor-alpha) in bronchoalveolar lavage fluid induced by the H5N1 infection (116). In contrast, low-dose dexamethasone was documented to significantly reduce pulmonary inflammation and fibrosis after lipopolysaccharide-induced ALI in a rat model, and was associated with elevation of glucocorticoid receptor expression in the lung, likely through up-regulation of glucocorticoid receptor levels and promotion of the nuclear translocation of glucocorticoid receptor protein (117).

Steroids have been useful as adjunctive therapy to suppress inflammatory responses in certain serious infections (118), including *Pneumocystis carinii* pneumonia (119). In contrast, steroids may be detrimental in some infections, particularly acute viral hepatitis (120). Steroid-based immunosuppression has been implicated in the increased severity of recurrent hepatitis C virus infection in liver transplant patients. Evidence suggests that steroid boluses used to treat acute rejection are associated with an increase in hepatitis C virus viral load and the severity of recurrence. Two possible mechanisms for a steroid-mediated effect on hepatitis C virus viral loads are postulation: a direct effect of steroids on the virus by enhancing its replication and an indirect effect attributable to the suppression of the hepatitis C virus immune response, allowing unrestricted hepatitis C virus replication (121).

Steroid use has been reported in some case reports of H1N1-associated ARDS without any adverse outcome (122). Some have advocated that the rationale for using steroids in the treatment of severe cases of H5N1 avian influenza, related to cytokine storm, may also be applicable in cases of severe 2009 H1N1 influenza ALI and ARDS (123, 124). In northern Vietnam, mortality was 59% among 29 recipients of steroids compared with 24% among 38 patients who did not receive steroids ($p = .004$) (125).

A retrospective case series studied patients (n = 29) with influenza A (H5N1) admitted to the National Institute of Infectious and Tropical Diseases in Hanoi, Vietnam, from January 2004 through July 2005, with symptoms of acute respi-

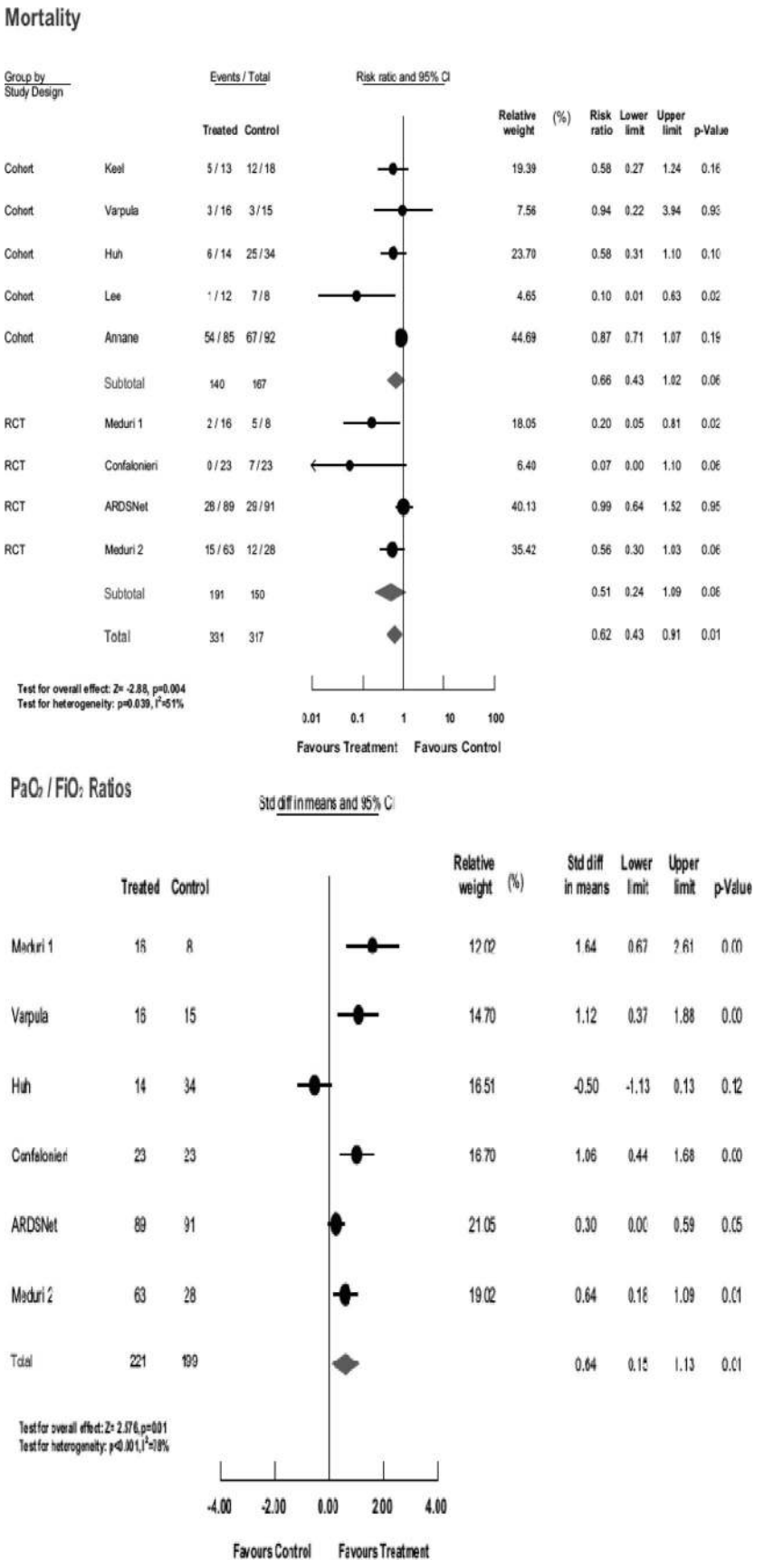

Figure 7. Effect of steroid treatment on mortality and oxygenation in ALI and ARDS. From: Tang BMP, Craig JC, Eslick GD, et al: Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: A systematic review and meta-analysis. *Crit Care Med* 2009; 37:1594–1603.

ratory tract infection and positive findings for A/H5 viral RNA by reverse-transcription polymerase chain reaction. The mean age was 35 yrs and seven patients (24.1%) died. Mortality rates were 20% (5 of 25) and 50% (2 of 4) among patients treated with or without oseltamivir ($p = .24$), respectively. Additionally the mortality rates were 33.3% (5 of 15) and 14.2% (2 of 14) among patients treated with and without methylprednisolone ($p = .39$), respectively. After logistic regression analysis was adjusted for variation in severity, no significant effectiveness for survival was observed among patients treated with oseltamivir or methylprednisolone (126).

The World Health Organization, in their update on avian influenza A (H5N1) virus infection in humans, stated that corticosteroids should not be used routinely because they have not been shown to be effective and may result in serious adverse events. Interestingly, in the recent ANZIC publication of 722 patients admitted to ICU with confirmed infection with the 2009 H1N1 virus, 494 (68.4%) received steroids. The overall mortality rate was reported as 14.3% in this case series (26).

Exogenous Surfactant Therapy

The rationale for exogenous surfactant therapy in ALI/ARDS is primarily to reverse surfactant dysfunction (inhibition), although surfactant deficiency is also treated by this intervention. Regardless of the cause, a common pathophysiologic feature of patients with ARDS is a dysfunction of the endogenous surfactant system. Exogenous surfactant therapy is an effective standard of care in neonates with ARDS (127, 128), but no similar effect is seen for adults. Ongoing and future research efforts suggest that this may eventually be feasible (129, 130).

Abnormalities in surfactant in lung lavage from patients with ALI/ARDS are well-documented (131–138). Exogenous surfactant therapy has a strong scientific rationale based on extensive biophysical research showing that increasing surfactant concentration can overcome inhibition by endogenous compounds present in injured lungs (91). In addition, the ability of exogenous surfactants to improve pulmonary mechanics and function has been established in multiple animal models of ALI/ARDS including acid aspiration, meconium aspiration, anti-lung serum, bacterial or endotoxin injury, va-

gotomy, hyperoxia, *in vivo* lung lavage, N-nitroso-N-methylurethane injury, and viral pneumonia.

In addition to its essential biophysical actions in lowering surface tension and stabilizing alveolar inflation–deflation, surfactant is known to play a role in host defense against infection through the biological activity of the two hydrophilic surfactant proteins A and D. These proteins have been shown to influence the opsonization, phagocytosis, and agglutination of microorganisms within the respiratory tract (139–142). The localization of surfactant protein A/surfactant protein D in the alveolar hypophase ideally positions these proteins (and other components of the surfactant system) to act as "first responders" to inhaled pathogens. More recent data indicate that the pulmonary surfactant directly affects *Mycobacterium tuberculosis* gene transcription in ways that suggest a preconditioning of the *Mycobacterium* for interactions with macrophages, evoking a multitude of transcriptional responses (143).

Consistent with these laboratory findings, surfactant therapy has been shown to be successful in infants with ARDS-related lung injury associated with meconium aspiration or pneumonia (144–147), as well as in children and young adults with ALI/ARDS (148–151). Particularly impressive is the recent double-blind, placebo-controlled trial (152) of calfactant (a natural lung surfactant containing high levels of surfactant-specific protein B) compared with placebo in 153 infants, children, and adolescents (up to age 21 yrs) with respiratory failure from ALI. Improved oxygenation and significantly decreased mortality were seen after treatment with the bovine-derived surfactant Infasurf (calfactant; Forest Pharmaceuticals, New York, NY). Interestingly, no significant decrease in the course of respiratory failure (duration of ventilation, ICU, or hospital stay) was observed. Aside from low tidal volume ventilation, this is one of the few controlled studies to show substantive survival improvement in patients with ALI/ARDS.

Several small pilot studies have also documented improved respiratory function (oxygenation) in adults with ALI/ARDS (153–157). However, larger controlled, clinical trials in adults have been less successful. By far, the largest prospective, controlled study of surfactant therapy in adults with ARDS was definitively negative. Anzueto et al (158) administered nebulized Exosurf (colfosceril; Glaxo Wellcome, New York, NY) vs. placebo to 725 adults with ARDS secondary to sepsis and found no improvement in any measure of oxygenation and no effect on morbidity or mortality. However, interpretation of these negative results is confounded because laboratory and clinical studies have documented that Exosurf has low activity compared to animal-derived surfactants. Furthermore, Exosurf is no longer marketed in the U.S. In addition, aerosolization has not been shown to be as effective as airway instillation in delivering surfactant.

Gregory et al (159) reported only small benefits in oxygenation in a controlled trial in adults with ARDS who received four 100-mg/kg doses of Survanta (beractant; Abbott Laboratories, Abbott Park, IL), but with no overall advantage in survival in the 43 surfactant-treated patients studied. However, this exogenous surfactant contains only very small amounts of surfactant protein B (160), which is known to be the most active apoprotein in native surfactant (161).

A more recent study (162) using recombinant surfactant protein C (Venticute; Altana Pharma, Atlanta, GA) in adults with ARDS showed immediate improvements in oxygenation, but no improvement in duration of mechanical ventilation, lengths of stay, or mortality. *Post hoc* analysis did suggest, however, that the response in the subgroup of patients with ARDS attributable to "direct lung injury" was positive (163). A follow-up prospective phase III study in this category of patients (Venticute in Patients with Pneumonia or Aspiration of Gastric Contents and Intubation/Ventilation/Oxygenation Impairment; NCT00074906) was recently halted because of futility.

Exogenous surfactant therapy in ALI/ARDS requires the use of the most active clinical surfactant drugs plus effective delivery methods. In addition to animal-derived surfactants such as Infasurf, highly active new synthetic lipid/peptide lung surfactants are being developed that have significant potential advantages in manufacturing, economy, and purity compared to biological products (164–166). Such synthetic surfactants include preparations with novel physicochemical properties like phospholipase-resistance, which may be of particular importance in ALI/ARDS when these lytic enzymes can be elaborated in high concentrations in the interstitium and alveoli (167).

Most recently, an international, multicenter, stratified, randomized, controlled, open, parallel group study (n = 418 adult patients) examined the efficacy of exogenous natural porcine surfactant HL 10 instilled as a large bolus. No difference in 28-day mortality was identified (24.5% in the usual care group vs. 28.8% in the HL 10 group). The estimated OR for death at day 28 in the usual care group vs. the HL 10 group was 0.75 (95% CI, 0.48–1.18; $p = .220$. The most common adverse events related to HL 10 administration were temporary hypoxemia defined as oxygen saturation <88% (51.9% in HL 10 group vs. 25.2% in usual care) and hypotension defined as mean arterial blood pressure <60 mm Hg (341% in HL 10 group vs. 17.1% in usual care). In this study, large bolus of exogenous natural porcine surfactant HL 10 in patients with ALI/ARDS did not improve outcome and showed a trend toward increased mortality and adverse effects (168).

In summary, because of the results of these randomized, clinical trials, exogenous surfactant therapy is not a strategy that can be used in adult patients with ARDS. In the future, other surfactants with different compositions may show beneficial effects and warrant continued investigation.

Future Pharmacologic Strategies

Most recently, alterations in coagulation and fibrinolysis in the pathogenesis of ALI and ARDS have been examined, particularly related to alveolar fibrin deposition. Increased local tissue factor-mediated thrombin generation and depression of local fibrinolysis related to increased plasminogen activator inhibitors have been reported (169). Pulmonary coagulopathy may be a prominent feature of ARDS and ventilator-induced lung injury, just as microvascular thrombosis is a common feature of sepsis. Plasma protein C was found to be decreased in patients with nonseptic ALI and was associated with higher mortality and fewer ventilator-free days (170).

Recent studies have documented that intravenous infusion and inhalation of aerosolized recombinant human-activated protein C attenuated ovine lipopolysaccharide-induced lung injury by preventing a decline in the volume of aerated lung tissue and improving oxygenation

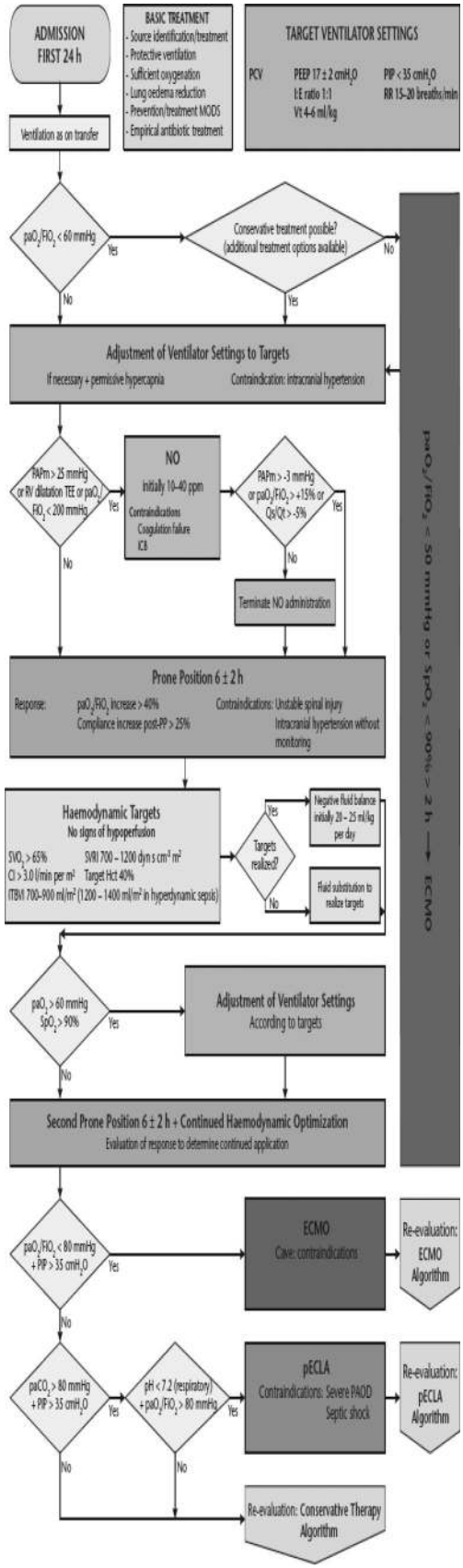

Figure 8. Treatment algorithm for ARDS. This "admission algorithm" applies to the first 24 hrs of treatment and uses all advanced treatment options for patients with ARDS discussed in this review. From: Deja M, Hommel M, Weber-Carstens S, et al: Evidence-based therapy of severe acute respiratory distress syndrome: an algorithm-guided approach. *J Int Med Res* 2008; 36:211–221.

(171–173). A recent randomized, placebo-controlled trial failed to show a beneficial effect (no difference in ventilator-free days or 60-day mortality) of activated protein C vs. placebo treatment in patients with ALI without sepsis (174). Additional studies in this important area are warranted.

Novel pharmacologic therapies specifically for the prevention and treatment of influenza infection are also needed. Recent reports (175–177) suggest that statins (administered either therapeutically or prophylactically) might also have beneficial effects on influenza outcomes. A recent study documented that a statin/caffeine combination (50 μg statin/200 μg caffeine) effectively ameliorated lung damage, inhibited viral replication, and was at least as effective as traditional antiviral agents in a murine model of H5N1, H3N2, and H1N1 infection (178).

Developing optimal single-agent and combination therapies for ALI/ARDS clearly requires integrated basic science and clinical research. Detailed testing of putative agents for their activity alone and in mechanistically complementary combinations in cell and animal models is essential, because it is not feasible to examine all relevant agents and combinations in human studies. This is particularly true for ALI/ARDS, for which clinical trials are complicated by the heterogeneity of associated patient populations and the multiple etiologies and broad pathology of lung injury. A rational approach to developmental pharmacotherapy that integrates findings on mechanistic activity and agent efficacy in basic research to facilitate the design and analysis of focused clinical trials is crucial for defining optimal therapeutic strategies for ALI/ARDS-related lung injury in patients of all ages.

CONCLUSION

Incremental Approach to the Management of Patients With Severe ARDS

In patients with severe refractory hypoxemia and ARDS attributable to 2009 H1N1 influenza, there is potential utility in the incremental approach to ARDS management (Fig. 8). Implementation of the specific strategies discussed here may result in improved oxygenation, improved pulmonary compliance, and, ultimately, survival in individual patients.

There is also the possibility that some of these interventional strategies may have additive effects. We also have used these treatment strategies in stabilization of patients with severe ARDS before transport to our institution to enable safer transport (179).

It is important to have full knowledge of the results of prospective, randomized trials that have carefully assessed the impact of these treatment strategies on patient outcome in ALI and ARDS. Nevertheless, appropriate bedside implementation of these potential treatment strategies may provide life-saving salvage in individual patients with refractory hypoxemia attributable due to severe ARDS and 2009 H1N1 influenza infection.

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