Update in Mechanical Ventilation, Sedation, and Outcomes 2014

Ewan C. Goligher[1,2,3], Ghislaine Douflé[2], and Eddy Fan[1,2,4]

[1]Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada; [2]Division of Respirology, Department of Medicine, University Health Network, Toronto, Ontario, Canada; and [3]Department of Physiology and [4]Institute for Health Policy, Management, and Evaluation, University of Toronto, Toronto, Ontario, Canada

Abstract

Novel approaches to the management of acute respiratory distress syndrome include strategies to enhance alveolar liquid clearance, promote epithelial cell growth and recovery after acute lung injury, and individualize ventilator care on the basis of physiological responses. The use of extracorporeal membrane oxygenation (ECMO) is growing rapidly, and centers providing ECMO must strive to meet stringent quality standards such as those set out by the ECMONet working group. Prognostic tools such as the RESP score can assist clinicians in predicting outcomes for patients with severe acute respiratory failure but do not predict whether ECMO will enhance survival. Evidence continues to grow that novel modes of mechanical ventilation such as neurally adjusted ventilatory assist are feasible and improve patient physiology and patient–ventilator interaction; data on clinical outcomes are limited but supportive. Critical illness causes long-term psychological and function sequelae: the risk of a new psychiatric diagnosis and severe physical impairment is significantly increased in the months after discharge from the intensive care unit. These long-term effects might be amenable to changes in sedation practice and increased early mobilization. Daily sedation discontinuation enhances the validity of routine delirium assessment. Many critically ill patients merit assessment by palliative care clinicians; the demand for palliative care services among critically ill patients is expected to grow. Future trials to test therapies for critical illness must ensure that study designs are adequately powered to detect benefit using realistic event rates. Integrating "big data" approaches into treatment decisions and trial designs offers a potential means of individualizing care to enhance outcomes for critically ill patients.

Keywords: mechanical ventilation; sedation; sepsis; outcomes; resuscitation

Acute Respiratory Distress Syndrome

The evidence base supporting the management of acute respiratory distress syndrome (ARDS) expanded considerably in 2014. β-Agonists held out benefit for ARDS by reducing fluid transport across the alveolar membrane through activation of basolateral Na^+,K^+-ATPase. However, perioperative β-agonists did not reduce the risk of developing ARDS in high-risk surgical patients (1). Although this therapeutic approach has failed to improve outcome—possibly through unanticipated effects on nonpulmonary organ systems in the presence of severe systemic inflammation—alternative approaches to preventing pulmonary edema may still be of benefit. The lectin-like domain of tumor necrosis factor was shown to directly activate the epithelial sodium channel located on the epithelial surface of type II alveolar cells, thereby mitigating the development of pulmonary edema in response to lung injury (2). This novel mechanism of alveolar liquid clearance may open up new opportunities for therapeutic intervention, but the success of such interventions depends on the as yet uncertain causal role played by pulmonary edema *per se* in the clinical outcome of ARDS.

Statins were known to exert antiinflammatory effects in animal models of sepsis and lung injury (3), and many observational studies found that statin therapy was associated with a reduced risk of mortality in patients with sepsis (4). In 2014, two large randomized trials testing the efficacy of statins for patients with ARDS were published: in one trial, patients with early ARDS were randomized to simvastatin or placebo (5), whereas in the other trial, patients with sepsis-associated ARDS were randomized to rosuvastatin or placebo (6). Both trials found no evidence of mortality reduction from statin therapy; indeed, rosuvastatin was associated with an increased risk of renal and hepatic organ dysfunction. These findings suggest that, despite their putative antiinflammatory

(Received in original form February 18, 2015; accepted in final form April 20, 2015)

Correspondence and requests for reprints should be addressed to Ewan C. Goligher, M.D., Toronto Western Hospital, 399 Bathurst Street, 2MCL-411Q, Toronto, ON, M5T 2S8 Canada. E-mail: ewan.goligher@mail.utoronto.ca

Am J Respir Crit Care Med Vol 191, Iss 12, pp 1367–1373, Jun 15, 2015

DOI: 10.1164/rccm.201502-0346UP
Internet address: www.atsjournals.org

effects, statins do not significantly modulate the mechanisms leading from pulmonary inflammation to death from ARDS.

Statins and β-agonists join a long list of failed pharmacological therapies for ARDS. These negative results, obtained despite a sound basic rationale for therapeutic effectiveness (7), suggest that the causal pathway leading to death from ARDS requires further careful delineation. Discrepancies between the results obtained from early basic and clinical studies versus the findings of adequately powered clinical trials of these therapies reinforce the notion that surrogate outcome measures based on organ function cannot reliably predict clinical benefit. This fact is particularly relevant to the study of ARDS prevention, given that ARDS itself constitutes a type of organ function surrogate outcome (8). ARDS prevention strategies need to be evaluated in terms of their impact on patient-centered clinical outcomes rather than their effect on the development of the physiological and clinical features that constitute ARDS (9).

Keratinocyte growth factor is a potent, fibroblast-produced stimulant of epithelial cell growth that exerts a range of theoretically beneficial effects in the injured lung (10, 11), and holds promise as a pharmacological therapy for ARDS. In humans challenged with inhaled lipopolysaccharide after pretreatment with palifermin (modified human keratinocyte growth factor) versus control, bronchoalveolar lavage fluid showed increased type II alveolar cell proliferation and increased levels of antiinflammatory and proreparative cytokines—a pattern consistent with enhanced epithelial repair. Palifermin was well tolerated. Questions about the effective dose and route of delivery and effectiveness of the agent in patients with clinically significant lung injury and pulmonary inflammation remain (10), but further study is clearly warranted.

The incidence of a number of common acute and chronic lung diseases—including ARDS, chronic obstructive pulmonary disease, and idiopathic pulmonary fibrosis—rises significantly with age, particularly above 40 years of age (12, 13). This may arise in part because of age-related changes in the function of bone marrow–derived mesenchymal stem cells (MSCs). Epithelial repair after lung injury is critically dependent on MSCs, which mobilize a potent antiinflammatory response to pulmonary injury. Observations suggest that aged MSCs exhibit lower expression levels of genes for several key cytokine and chemokine receptors, impairing MSC activation and migration in response to pulmonary inflammation (14). Age-related changes in tissue elastic properties and in the immune response to injury can also increase the risk of lung injury in older patients (15). These considerations suggest that limiting tidal volume and plateau pressure to prevent ventilator-induced lung injury (VILI) is particularly important in older patients. On the other hand, although there are no randomized trials of lung-protective ventilation strategies in children, observational studies in pediatric patients suggest a benefit from the use of lower tidal volumes (15). Given the current evidence, lung-protective ventilation strategies are therefore probably advisable in all mechanically ventilated patients, regardless of age.

VILI can result from intraoperative mechanical ventilation and may impact perioperative outcomes (16). However, the PROVHILO (Protective Ventilation Using High versus Low PEEP) trial found no difference in the rate of postoperative pulmonary complications with higher (12 cm H_2O) versus lower positive end-expiratory pressure (PEEP) ($\leq$2 cm H_2O) titration strategies applied during general anesthesia (17). This finding adds to the list of well-designed randomized trials failing to demonstrate benefit from ventilation with higher levels of PEEP. One explanation for the apparent lack of benefit—in the face of a strong biological rationale for benefit—is that patients vary considerably in how they respond to PEEP. For example, the improvement in oxygenation after an increase in PEEP varies widely across patients with ARDS (18); patients with significant improvement in oxygenation after an increase in PEEP had lower mortality than patients without improvement in a secondary analysis of two randomized trials of higher versus lower PEEP (18). Although improved oxygenation *per se* is unlikely to explain the difference in mortality, the oxygenation response may reflect the degree of lung recruitment and favorable changes in stress and strain at the alveolar level. In some patients, PEEP recruits collapsed alveoli and improves the homogeneity of ventilation (19). Local ventilation inhomogeneities can amplify alveolar stress, propagating VILI (20). The magnitude of such inhomogeneity was linked to disease severity and outcome in ARDS (19). Moreover, lung recruitability was associated with greater reductions in inhomogeneity. These insights support the critical importance of evaluating the impact of PEEP in individual patients at the bedside to assess its effect on VILI.

Extracorporeal membrane oxygenation (ECMO) is growing rapidly in its worldwide application and availability for patients with severe acute respiratory failure. Given the complex infrastructure and clinical services required to safely and effectively provide ECMO, there is increasing concern to ensure that ECMO care is centralized in tertiary centers with adequate experience and resources. In 2014, a global consortium of leaders in ECMO (ECMONet) released a consensus statement recommending that ECMO be provided in high-volume regional or national centers of excellence (21). The statement specified that ECMO programs must have adequate access to complex clinical support services, sufficient staffing, and established plans for certifying and maintaining staff training and conducting quality assurance. Increasing the homogeneity of care delivered to patients with severe acute respiratory failure will also facilitate critical research into the impact of ECMO on clinical and economic outcomes.

Deciding whether to initiate ECMO for patients with severe ARDS remains a challenging decision balancing the probability of achieving a good outcome in a severely ill patient against the costs associated with employing a scarce and resource-intensive intervention. A prognostic instrument, the RESP score, might assist in clinical decision-making. The RESP (Respiratory ECMO Survival Prediction) score was developed from data in the Extracorporeal Life Support Organization registry and externally validated to predict the probability of survival after initiation of ECMO for severe ARDS (22) with excellent calibration and reasonable discrimination (available at www.respscore.com). The actual clinical usefulness of the score remains uncertain—the score predicts the probability of survival in patients in whom ECMO is initiated but does not predict whether ECMO initiation will significantly alter the probability of

survival (23). Furthermore, the decision to initiate ECMO incorporates many additional factors including the trajectory of illness and the patient's wishes and values. Clinicians will continue to rely heavily on clinical experience and personal judgment in making these complex and time-pressured decisions.

Modes of Mechanical Ventilation

Lung-protective ventilation is widely accepted as the most important aspect of providing safe and effective mechanical ventilation, but it has proven difficult to consistently apply lung-protective ventilation strategies, particularly with respect to accepted limits on tidal volume (24). Studies of mechanical ventilation have therefore largely focused on optimizing ventilator modes, rather than comparing different modes of ventilation. For example, although pressure-targeted and volume-cycled modes of ventilation are both widely employed in clinical practice around the world (25), there is considerable uncertainty about the superiority of one approach over the other. Of interest, a meta-analysis of randomized trials found that pressure-targeted ventilation was associated with a significant reduction in intensive care unit (ICU) mortality (but not hospital mortality or 28-d mortality) compared with volume-cycled ventilation (26); the quality of the evidence was downgraded because effect estimates varied widely between trials. Although no definitive conclusions can be drawn on the basis of this meta-analysis, further attention to the comparative effects of these two common modes of ventilation on VILI and patient outcome is strongly warranted.

Most of the more recent studies comparing different modes of ventilation originate from the pediatric literature. The impact of high-frequency oscillatory ventilation appears to be similar in the pediatric and adult populations; studies consistently demonstrate a lack of benefit (27–29). Newer modes of ventilation such as neurally adjusted ventilatory assist (NAVA) and proportional assist ventilation (PAV) are generating interest as treatment options for pediatric respiratory failure. Despite being conceptually attractive, the NAVA mode has not yet gained widespread clinical use, perhaps because of a persistent lack of evidence of improved outcome. NAVA undeniably enhances patient–ventilatory synchrony (30); although dyssynchrony has been linked to prolonged duration of ventilation (31), it is not clear whether dyssynchrony actually causes prolonged ventilation or merely reflects sicker and more complex cases of acute respiratory failure. A number of studies have found that the newer modes of ventilation are feasible in pediatric patients and improve physiological parameters. In pediatric patients transitioned from high-frequency oscillatory ventilation to partially assisted ventilation, NAVA was associated with shorter duration of mechanical ventilation, improved patient–ventilator interactions, and decreased work of breathing when compared with pressure support ventilation (32). In a randomized trial of 170 pediatric patients, the use of NAVA was associated with reduced sedative requirements in the subset of patients who required a longer period of mechanical ventilation (33).

The benefit of noninvasive ventilation for patients with acute exacerbations of chronic obstructive pulmonary disease is well established. However, patient–ventilator dyssynchrony is common during noninvasive ventilation, resulting in frequent ineffective ("wasted") efforts that may contribute to the risk of failure of noninvasive ventilation. Noninvasive NAVA was shown to improve synchrony and reduce the frequency of ineffective efforts in patients with chronic obstructive pulmonary disease exacerbation compared with standard noninvasive ventilation (34). It remains unclear whether routine use of noninvasive NAVA would reduce the risk of intubation in this patient population.

One of the key advantages of NAVA is the ready access to information on patient inspiratory effort. Monitoring patient inspiratory effort has been largely overlooked during mechanical ventilation to date. Data in pediatric patients suggest that inspiratory effort levels are often well below normal during routine mechanical ventilation (35). This might increase the risk of disuse atrophy of the diaphragm, theoretically leading to diaphragm dysfunction and prolonged mechanical ventilation. The use of proportional assist modes such as NAVA and PAV can ensure that reasonable levels of inspiratory effort are maintained (36). NAVA increases the diaphragmatic contribution to inspiratory muscle activity compared with pressure support and may therefore help to maintain diaphragm activity and strength (37).

Maintaining normal levels of inspiratory effort may also prevent VILI. In an experimental study, higher levels of spontaneous breathing were associated with improved oxygenation, lower transpulmonary pressures, a more homogeneous distribution of ventilation, and lower pulmonary inflammatory cytokine levels (38). Because inspiratory muscle activity has been shown to propagate lung injury in more severe ARDS (39), the severity of lung injury may be a critical determinant of the relative risk and benefit of spontaneous breathing (40).

Long-Term Outcomes

Critical illness and ICU exposure have profound effects on the quality of life and functional status of patients. Functional disability persists well beyond ICU discharge, as significant deficits in physical function have been documented at 12 months after ICU admission (41). Importantly, the severity of physical impairment is related to potentially modifiable factors such as the duration of ICU stay, corticosteroid dosage, and the duration of immobilization (41, 42). Critical illness also has a deleterious effect on mental health, as the rate of new psychiatric diagnoses and the use of psychoactive medication increase in the months after ICU exposure (43).

Many patients develop profound axial skeletal weakness during the early phase of critical illness: in one study 55% of patients who remained on mechanical ventilation for 8 days or longer had significant muscle weakness (Medical Research Council score below 48) (44). This weakness was associated with prolonged ventilator dependence and hospitalization, significant increases in health care costs, and a higher 1-year mortality rate (44). The extent of the true causal effect of ICU-acquired weakness on long-term clinical outcomes remains unclear: the observed association is subject to the limitations of matching based on propensity scores (45). Moreover, functional independence is contingent on many factors beyond muscle function (46). Further work is required to understand how to prevent and treat ICU-acquired

weakness, as emphasized in a clinical practice guideline (47). Of note, diaphragm atrophy and contractile dysfunction were documented in living critically ill patients (48). The mechanisms responsible for atrophy and contractile dysfunction in critically ill patients (including the role of mechanical ventilation) are currently the subject of intense study. Diaphragm dysfunction may prolong mechanical ventilation (49) and increase the risk of mortality (50).

Sedation and Analgesia

Evidence strongly implicates excessive sedation as a cause of significant morbidity and mortality in critical illness. Sedation delays liberation from ventilation and increases the risk of delirium and long-term cognitive impairment (51). At the bedside, certain clinical conditions sometimes make it necessary and appropriate to sedate patients; in such situations, the choice of agent may have an important effect on outcome. The most recent ICU sedation guideline recommends the use of a nonbenzodiazepine sedative over benzodiazepines (52): consistent with previous studies (53), an observational study found that propofol is associated with accelerated liberation from mechanical ventilation and lower hospital mortality (54). Propofol use should nevertheless be judicious, and clinicians must continue efforts to limit sedation exposure (55).

Given the prevalence and long-term sequelae of ICU delirium, it is important to monitor for its development. Sedation critically confounds the diagnosis of ICU delirium; delirium persisting for 2 hours beyond sedation interruption portends a much worse prognosis than the apparent delirium that rapidly reverses after sedation interruption (56). Delirium assessment should therefore be performed off sedation and careful attention should be paid to modifiable delirium risk factors in patients with persistent delirium (51). Pharmacological therapies for delirium (as opposed to merely agitation) are limited. Data suggest that statins might prevent delirium (57); the results of an ongoing randomized trial are awaited.

Physical pain is a common and distressing problem for critically ill patients predisposing to psychological distress and increased sedation and analgesia requirements (58); given the barriers to communication for patients (especially those receiving invasive mechanical ventilation), it can be challenging to accurately assess and adequately treat pain. A range of factors predict the risk of physical pain associated with common ICU procedures including specific types of procedures (i.e., chest tube removal, arterial line insertion), and preprocedural pain intensity and distress (59). Identifying these risk factors and carefully monitoring for physical pain during ICU procedures may help to prevent physical pain—an absolute ethical and professional obligation.

Organization of Care

Reductions in resident duty hours have prompted concerns about medical errors arising from more frequent hand-over and cross-coverage. In light of these concerns, Kajdacsy-Balla Amaral and colleagues examined the decisions and patient outcomes associated with night-time cross-coverage (60). Surprisingly, cross-coverage was associated with improved clinical outcomes, raising the possibility that an independent "second look" might lead to beneficial changes in management. The exact mechanism by which cross-coverage might confer mortality reduction remains unclear: the regular day-time team may be subject to cognitive biases and heuristic assumptions leading to missed diagnoses or mismanagement. Alternatively, cross-covering fellows may be less likely to initiate end-of-life discussions (61). The cognitive biases to which intensivists are prone as raised by this study merit further detailed examination.

Medical emergency teams are widely deployed with a presumptive goal of preventing ICU admission through early assessment and resuscitation. Such efforts are critically contingent on accurate identification of hospitalized patients at high risk of critical illness; monitoring and nursing resources can then be allocated accordingly. A number of prognostic tools are available, including a risk stratification tool (the eCART [electronic Cardiac Arrest Risk Triage] score) that exhibited excellent discrimination (62). Of course, accurate early identification is helpful to patients insofar as increased medical attention improves clinical outcomes—studies to date on the impact of medical emergency teams do not support such a benefit (63).

Although critical care is primarily aimed at resuscitating severely ill patients and saving patients' lives, intensivists frequently care for patients at the end of life. Quality end-of-life care requires a special set of clinical and interpersonal skills and a careful focus on issues unique to the dying (64). In fact, approximately 20% of patients admitted to ICUs in the United States merit palliative care consultation according to usual clinical criteria (65). Palliative care services are currently insufficient to meet this demand and future workforce shortages are projected (66). Although it remains unclear whether routine standardized palliative care interventions affect the dying process in the ICU, intensivists should advocate for increased access for their patients to palliative care services, and they must ensure that they are adequately trained to care for the dying.

Future Directions

It has proven difficult to demonstrate the efficacy of many critical care interventions in randomized trials; this may in part be due to the challenges of testing therapies in the context of critical illness, where many factors aside from the treatment or causal pathway under study compete to determine outcome. Methodological flaws may also account for the infrequent success: for example, many trials are inadequately powered to detect realistic benefit (67), a problem compounded by frequent overestimation of baseline event rates (67). Outcome definitions vary widely between studies, complicating synthesis and meta-analysis (67, 68). Standardizing trial design, outcomes, and reporting may enhance interpretation and application of results, providing more definitive "yes" or "no" answers to the important clinical questions under study.

The marked heterogeneity in treatment response between individual critically ill patients also significantly limits the overall effectiveness of potential therapies. Several authors have proposed that harnessing the massive volume of patient- and disease-related clinical and physiological data now available to clinicians might enhance our ability to tailor therapy to individual patients—a form of "personalized

medicine" in the critically ill (69). For example, computational approaches such as machine learning permit rapid and efficient clinical data synthesis in real time; such techniques have been employed to enhance early detection of patient physiological deterioration and predict treatment responsiveness (70). Online decision support systems using such computational approaches could integrate a wide range of prognostic factors to guide shared decision-making between clinicians and families (71). However, it remains to be seen whether the unprecedented detail with which individual patients may now be characterized at the molecular, physiological, and epidemiological levels will lead to any major advances in patient-centered clinical outcomes or treatment success in the field of critical care medicine. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1. Perkins GD, Gates S, Park D, Gao F, Knox C, Holloway B, McAuley DF, Ryan J, Marzouk J, Cooke MW, *et al*.; BALTI-Prevention Collaborators. The β Agonist Lung Injury Trial prevention: a randomized controlled trial. *Am J Respir Crit Care Med* 2014;189: 674–683.
2. Czikora I, Alli A, Bao H-F, Kaftan D, Sridhar S, Apell H-J, Gorshkov B, White R, Zimmermann A, Wendel A, *et al*. A novel tumor necrosis factor–mediated mechanism of direct epithelial sodium channel activation. *Am J Respir Crit Care Med* 2014;190: 522–532.
3. Jacobson JR, Barnard JW, Grigoryev DN, Ma S-F, Tuder RM, Garcia JGN. Simvastatin attenuates vascular leak and inflammation in murine inflammatory lung injury. *Am J Physiol Lung Cell Mol Physiol* 2005; 288:L1026–L1032.
4. Tleyjeh IM, Kashour T, Hakim FA, Zimmerman VA, Erwin PJ, Sutton AJ, Ibrahim T. Statins for the prevention and treatment of infections: a systematic review and meta-analysis. *Arch Intern Med* 2009;169: 1658–1667.
5. McAuley DF, Laffey JG, O'Kane CM, Perkins GD, Mullan B, Trinder TJ, Johnston P, Hopkins PA, Johnston AJ, McDowell C, *et al*.; HARP-2 Investigators; Irish Critical Care Trials Group. Simvastatin in the acute respiratory distress syndrome. *N Engl J Med* 2014;371: 1695–1703.
6. Truwit JD, Bernard GR, Steingrub J, Matthay MA, Liu KD, Albertson TE, Brower RG, Shanholtz C, Rock P, Douglas IS, *et al*.; National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. *N Engl J Med* 2014;370:2191–2200.
7. Budinger GRS, Mutlu GM. β_2-Agonists and acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2014;189:624–625.
8. Rubenfeld GD. Who cares about preventing acute respiratory distress syndrome? *Am J Respir Crit Care Med* 2015;191: 255–260.
9. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012;307: 2526–2533.
10. Morty RE, Walley KR. A step forward toward the clinical application of palifermin for acute respiratory distress syndrome? *Am J Respir Crit Care Med* 2014;189:1455–1456.
11. Ware LB, Matthay MA. Keratinocyte and hepatocyte growth factors in the lung: roles in lung development, inflammation, and repair. *Am J Physiol Lung Cell Mol Physiol* 2002;282:L924–L940.
12. Faner R, Rojas M, Macnee W, Agustí A. Abnormal lung aging in chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2012;186:306–313.
13. Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, Stern EJ, Hudson LD. Incidence and outcomes of acute lung injury. *N Engl J Med* 2005;353:1685–1693.
14. Bustos ML, Huleihel L, Kapetanaki MG, Lino-Cardenas CL, Mroz L, Ellis BM, McVerry BJ, Richards TJ, Kaminski N, Cerdenes N, *et al*. Aging mesenchymal stem cells fail to protect because of impaired migration and antiinflammatory response. *Am J Respir Crit Care Med* 2014;189:787–798.
15. Kneyber MCJ, Zhang H, Slutsky AS. Ventilator-induced lung injury: similarity and differences between children and adults. *Am J Respir Crit Care Med* 2014;190:258–265.
16. Futier E, Constantin J-M, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, Marret E, Beaussier M, Gutton C, Lefrant J-Y, *et al*.; IMPROVE Study Group. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med* 2013;369:428–437.
17. Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJ; PROVE Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology. High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. *Lancet* 2014;384:495–503.
18. Goligher EC, Kavanagh BP, Rubenfeld GD, Adhikari NKJ, Pinto R, Fan E, Brochard LJ, Granton JT, Mercat A, Marie Richard J-C, *et al*. Oxygenation response to positive end-expiratory pressure predicts mortality in acute respiratory distress syndrome: a secondary analysis of the LOVS and ExPress trials. *Am J Respir Crit Care Med* 2014;190:70–76.
19. Cressoni M, Cadringher P, Chiurazzi C, Amini M, Gallazzi E, Marino A, Brioni M, Carlesso E, Chiumello D, Quintel M, *et al*. Lung inhomogeneity in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2014;189:149–158.
20. Loring SH, Talmor D. Inhomogeneous computed tomographic densities in lungs in acute respiratory distress syndrome: stress multipliers leading to ventilator-induced injury? *Am J Respir Crit Care Med* 2014;189:123–124.
21. Combes A, Brodie D, Bartlett R, Brochard L, Brower R, Conrad S, De Backer D, Fan E, Ferguson N, Fortenberry J, *et al*.; International ECMO Network (ECMONet). Position paper for the organization of extracorporeal membrane oxygenation programs for acute respiratory failure in adult patients. *Am J Respir Crit Care Med* 2014; 190:488–496.
22. Schmidt M, Bailey M, Sheldrake J, Hodgson C, Aubron C, Rycus PT, Scheinkestel C, Cooper DJ, Brodie D, Pellegrino V, *et al*. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure: the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. *Am J Respir Crit Care Med* 2014;189:1374–1382.
23. Fan E, Pham T. Extracorporeal membrane oxygenation for severe acute respiratory failure: yes we can! (But should we?). *Am J Respir Crit Care Med* 2014;189:1293–1295.
24. Jaswal DS, Leung JM, Sun J, Cui X, Li Y, Kern S, Welsh J, Natanson C, Eichacker PQ. Tidal volume and plateau pressure use for acute lung injury from 2000 to present: a systematic literature review. *Crit Care Med* 2014;42:2278–2289.
25. Esteban A, Frutos-Vivar F, Muriel A, Ferguson ND, Peñuelas O, Abraira V, Raymondos K, Ríos F, Nin N, Apezteguía C, *et al*. Evolution of mortality over time in patients receiving mechanical ventilation. *Am J Respir Crit Care Med* 2013;188:220–230.
26. Chacko B, Peter JV, Tharyan P, John G, Jeyaseelan L. Pressure-controlled versus volume-controlled ventilation for acute respiratory failure due to acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). *Cochrane Database Syst Rev* 2015;1:CD008807.
27. Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, Zhou Q, Matté A, Walter SD, Lamontagne F, *et al*.; OSCILLATE Trial Investigators; Canadian Critical Care Trials Group. High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med* 2013;368:795–805.
28. Sud S, Sud M, Friedrich JO, Wunsch H, Meade MO, Ferguson ND, Adhikari NK. High-frequency ventilation versus conventional ventilation for treatment of acute lung injury and acute respiratory distress syndrome. *Cochrane Database Syst Rev* 2013;2:CD004085.

29. Young D, Lamb SE, Shah S, MacKenzie I, Tunnicliffe W, Lall R, Rowan K, Cuthbertson BH; OSCAR Study Group. High-frequency oscillation for acute respiratory distress syndrome. *N Engl J Med* 2013;368: 806–813.
30. Beck J, Campoccia F, Allo J-C, Brander L, Brunet F, Slutsky AS, Sinderby C. Improved synchrony and respiratory unloading by neurally adjusted ventilatory assist (NAVA) in lung-injured rabbits. *Pediatr Res* 2007;61:289–294.
31. de Wit M, Miller KB, Green DA, Ostman HE, Gennings C, Epstein SK. Ineffective triggering predicts increased duration of mechanical ventilation. *Crit Care Med* 2009;37:2740–2745.
32. Piastra M, De Luca D, Costa R, Pizza A, De Sanctis R, Marzano L, Biasucci D, Visconti F, Conti G. Neurally adjusted ventilatory assist vs pressure support ventilation in infants recovering from severe acute respiratory distress syndrome: nested study. *J Crit Care* 2014; 29:312.e1–e5.
33. Kallio M, Peltoniemi O, Anttila E, Pokka T, Kontiokari T. Neurally adjusted ventilatory assist (NAVA) in pediatric intensive care—a randomized controlled trial. *Pediatr Pulmonol* 2015;50:55–62.
34. Doorduin J, Sinderby CA, Beck J, van der Hoeven JG, Heunks LM. Automated patient–ventilator interaction analysis during neurally adjusted non-invasive ventilation and pressure support ventilation in chronic obstructive pulmonary disease. *Crit Care* 2014;18:550.
35. Emeriaud G, Larouche A, Ducharme-Crevier L, Massicotte E, Fléchelles O, Pellerin-Leblanc A-A, Morneau S, Beck J, Jouvet P. Evolution of inspiratory diaphragm activity in children over the course of the PICU stay. *Intensive Care Med* 2014;40:1718–1726.
36. Carteaux G, Mancebo J, Mercat A, Dellamonica J, Richard J-CM, Aguirre-Bermeo H, Kouatchet A, Beduneau G, Thille AW, Brochard L. Bedside adjustment of proportional assist ventilation to target a predefined range of respiratory effort. *Crit Care Med* 2013;41: 2125–2132.
37. Cecchini J, Schmidt M, Demoule A, Similowski T. Increased diaphragmatic contribution to inspiratory effort during neurally adjusted ventilatory assistance versus pressure support: an electromyographic study. *Anesthesiology* 2014;121:1028–1036.
38. Güldner A, Braune A, Carvalho N, Beda A, Zeidler S, Wiedemann B, Wunderlich G, Andreeff M, Uhlig C, Spieth PM, *et al*. Higher levels of spontaneous breathing induce lung recruitment and reduce global stress/strain in experimental lung injury. *Anesthesiology* 2014;120: 673–682.
39. Yoshida T, Torsani V, Gomes S, De Santis RR, Beraldo MA, Costa ELV, Tucci MR, Zin WA, Kavanagh BP, Amato MBP. Spontaneous effort causes occult pendelluft during mechanical ventilation. *Am J Respir Crit Care Med* 2013;188:1420–1427.
40. Güldner A, Pelosi P, Gama de Abreu M. Spontaneous breathing in mild and moderate versus severe acute respiratory distress syndrome. *Curr Opin Crit Care* 2014;20:69–76.
41. Needham DM, Wozniak AW, Hough CL, Morris PE, Dinglas VD, Jackson JC, Mendez-Tellez PA, Shanholtz C, Ely EW, Colantuoni E, *et al*.; National Institutes of Health NHLBI ARDS Network. Risk factors for physical impairment after acute lung injury in a national, multicenter study. *Am J Respir Crit Care Med* 2014;189: 1214–1224.
42. Fan E, Dowdy DW, Colantuoni E, Mendez-Tellez PA, Sevransky JE, Shanholtz C, Himmelfarb CRD, Desai SV, Ciesla N, Herridge MS, *et al*. Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. *Crit Care Med* 2014;42: 849–859.
43. Wunsch H, Christiansen CF, Johansen MB, Olsen M, Ali N, Angus DC, Sørensen HT. Psychiatric diagnoses and psychoactive medication use among nonsurgical critically ill patients receiving mechanical ventilation. *JAMA* 2014;311:1133–1142.
44. Hermans G, Van Mechelen H, Clerckx B, Vanhullebusch T, Mesotten D, Wilmer A, Casaer MP, Meersseman P, Debaveye Y, Van Cromphaut S, *et al*. Acute outcomes and 1-year mortality of intensive care unit–acquired weakness: a cohort study and propensity-matched analysis. *Am J Respir Crit Care Med* 2014;190:410–420.
45. Chevret S. Propensity-matching analysis is not straightforward. *Am J Respir Crit Care Med* 2014;190:362–363.
46. Herridge MS, Batt J, Santos CD. ICU-acquired weakness, morbidity, and death. *Am J Respir Crit Care Med* 2014;190:360–362.
47. Fan E, Cheek F, Chlan L, Gosselink R, Hart N, Herridge MS, Hopkins RO, Hough CL, Kress JP, Latronico N, *et al*.; ATS Committee on ICU-acquired Weakness in Adults; American Thoracic Society. An official American Thoracic Society Clinical Practice guideline: the diagnosis of intensive care unit–acquired weakness in adults. *Am J Respir Crit Care Med* 2014;190:1437–1446.
48. Hooijman PE, Beishuizen A, de Waard MC, de Man FS, Vermeijden JW, Steenvoorde P, Bouwman RA, Lommen W, van Hees HWH, Heunks LMA, *et al*. Diaphragm fiber strength is reduced in critically ill patients and restored by a troponin activator. *Am J Respir Crit Care Med* 2014;189:863–865.
49. Kim WY, Suh HJ, Hong S-B, Koh Y, Lim C-M. Diaphragm dysfunction assessed by ultrasonography: influence on weaning from mechanical ventilation. *Crit Care Med* 2011;39:2627–2630.
50. Demoule A, Jung B, Prodanovic H, Molinari N, Chanques G, Coirault C, Matecki S, Duguet A, Similowski T, Jaber S. Diaphragm dysfunction on admission to the intensive care unit: prevalence, risk factors, and prognostic impact—a prospective study. *Am J Respir Crit Care Med* 2013;188:213–219.
51. Takala J. Of delirium and sedation. *Am J Respir Crit Care Med* 2014; 189:622–624.
52. Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, Davidson JE, Devlin JW, Kress JP, Joffe AM, *et al*.; American College of Critical Care Medicine. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013;41:263–306.
53. Carson SS, Kress JP, Rodgers JE, Vinayak A, Campbell-Bright S, Levitt J, Bourdet S, Ivanova A, Henderson AG, Pohlman A, *et al*. A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. *Crit Care Med* 2006; 34:1326–1332.
54. Lonardo NW, Mone MC, Nirula R, Kimball EJ, Ludwig K, Zhou X, Sauer BC, Nechodom K, Teng C, Barton RG. Propofol is associated with favorable outcomes compared with benzodiazepines in ventilated intensive care unit patients. *Am J Respir Crit Care Med* 2014;189: 1383–1394.
55. Ferrell BA, Girard TD. Sedative choice: a critical decision. *Am J Respir Crit Care Med* 2014;189:1295–1297.
56. Patel SB, Poston JT, Pohlman A, Hall JB, Kress JP. Rapidly reversible, sedation-related delirium versus persistent delirium in the intensive care unit. *Am J Respir Crit Care Med* 2014;189:658–665.
57. Page VJ, Davis D, Zhao XB, Norton S, Casarin A, Brown T, Ely EW, McAuley DF. Statin use and risk of delirium in the critically ill. *Am J Respir Crit Care Med* 2014;189:666–673.
58. Bender BG. Pain control in the intensive care unit: new insight into an old problem. *Am J Respir Crit Care Med* 2014;189:9–10.
59. Puntillo KA, Max A, Timsit J-F, Vignoud L, Chanques G, Robleda G, Roche-Campo F, Mancebo J, Divatia JV, Soares M, *et al*. Determinants of procedural pain intensity in the intensive care unit: the Europain® study. *Am J Respir Crit Care Med* 2014;189: 39–47.
60. Kajdacsy-Balla Amaral AC, Barros BS, Barros CCPP, Innes C, Pinto R, Rubenfeld GD. Nighttime cross-coverage is associated with decreased intensive care unit mortality: a single-center study. *Am J Respir Crit Care Med* 2014;189:1395–1401.
61. Halpern SD. Cross-coverage in the intensive care unit: more than meets the "I"? *Am J Respir Crit Care Med* 2014;189:1297–1298.
62. Churpek MM, Yuen TC, Winslow C, Robicsek AA, Meltzer DO, Gibbons RD, Edelson DP. Multicenter development and validation of a risk stratification tool for ward patients. *Am J Respir Crit Care Med* 2014; 190:649–655.
63. Amaral ACKB. The art of making predictions: statistics versus bedside evaluation. *Am J Respir Crit Care Med* 2014;190:598–599.
64. Cook D, Rocker G. Dying with dignity in the intensive care unit. *N Engl J Med* 2014;370:2506–2514.
65. Hua MS, Li G, Blinderman CD, Wunsch H. Estimates of the need for palliative care consultation across United States intensive care units using a trigger-based model. *Am J Respir Crit Care Med* 2014;189: 428–436.
66. Ford DW. Palliative care consultation needs in United States intensive care units: another workforce shortage? *Am J Respir Crit Care Med* 2014;189:383–384.

67. Harhay MO, Wagner J, Ratcliffe SJ, Bronheim RS, Gopal A, Green S, Cooney E, Mikkelsen ME, Kerlin MP, Small DS, *et al*. Outcomes and statistical power in adult critical care randomized trials. *Am J Respir Crit Care Med* 2014;189:1469–1478.
68. Blackwood B, Clarke M, McAuley DF, McGuigan PJ, Marshall JC, Rose L. How outcomes are defined in clinical trials of mechanically ventilated adults and children. *Am J Respir Crit Care Med* 2014;189: 886–893.
69. Marini JJ, Vincent J-L, Annane D. Critical care evidence—new directions. *JAMA* 2015;313:893–894.
70. Pinsky MR, Dubrawski A. Gleaning knowledge from data in the intensive care unit. *Am J Respir Crit Care Med* 2014;190:606–610.
71. Cox CE, White DB, Abernethy AP. A universal decision support system: addressing the decision-making needs of patients, families, and clinicians in the setting of critical illness. *Am J Respir Crit Care Med* 2014;190:366–373.