Clinical Year in Review II

Mechanical Ventilation, Acute Respiratory Distress Syndrome, Critical Care, and Lung Cancer

M. Elizabeth Wilcox¹, M. Patricia Rivera², Catherine Sassoon³, Lorraine B. Ware⁴, Hannah Wunsch⁵, and Margaret S. Herridge¹

¹Interdepartmental Division of Critical Care and Department of Medicine, University Health Network, University of Toronto, Toronto, Ontario, Canada; ²Department of Medicine, University of North Carolina in Chapel Hill, Chapel Hill, North Carolina; ³Department of Medicine, University of California, Irvine, and VA Long Beach Healthcare System, Long Beach, California; ⁴Departments of Medicine and Pathology, Microbiology and Immunology, Vanderbilt University School of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee; and ⁵Departments of Anesthesiology and Epidemiology, Columbia University, New York, New York

MECHANICAL VENTILATION

Catherine Sassoon
*University of California Irvine
Irvine, California*

Complication of Mechanical Ventilation

Animal data show that diaphragm muscle proteolysis occurs early during controlled mode mechanical ventilation (MV). There is limited information about the timing or mechanism for this in human subjects. A recent study demonstrated that muscle atrophy in human diaphragm muscle occurs within hours of the onset of MV (1), and this has important implications for successful liberation from mechanical ventilation.

Jaber and colleagues demonstrated that prolonged mechanical ventilation has harmful effects on the diaphragm, including preferential fiber atrophy and up-regulation of proteolytic proteins (2). Diaphragmatic strength was measured as the maximal twitch airway occlusion pressure generated during phrenic nerve stimulation in short-term (0.5 h; $n = 6$) and long-term (> 5 d; $n = 6$) mechanically ventilated groups. Diaphragmatic biopsies obtained during thoracic surgery (MV for 2–3 h; $n = 10$) and from brain-dead organ donors (MV for 24–249 h; $n = 15$) underwent histochemical evaluation, including ultrastructural evaluation for sarcomeric disruption, cross-sectional area of diaphragm fiber size for atrophy, and biochemical indices for the expression of proteolytic-related proteins (2). Airway occlusion pressure generated by the diaphragm decreased progressively during mechanical ventilation, with a mean reduction of 32 ± 6 ($\pm$ SD)% after 5 to 6 days (2). In the thoracic surgery subgroup, as compared with the brain-dead organ groups, prolonged periods of MV were associated with greater ultrasound fiber injury ($26 \pm 5\%$ as compared with $5 \pm 0.6\%$ area), increased loss of cross-sectional area ($1,904 \pm 220 \mu\text{m}^2$ as compared with $3,100 \pm 329 \mu\text{m}^2$), and increased expression of proteolysis-related proteins (ubiquitinated proteins, p65 nuclear factor- κ B, and calcium-activated proteases calpain-1, -2, and -3), respectively (2). The authors conclude that diaphragm weakness, injury, and atrophy occur rapidly and correlate with duration of ventilator support.

Limitations of this study include an atypical study sample, which is not representative of most ICU patients. Controlled

mode MV is not commonly applied unless patients receive deep sedation or paralytics. In addition, the time course on diaphragmatic function was not done in the same patient sample as the evaluation of proteolytic protein activation. The etiology for diaphragm muscle injury or diaphragmatic atrophy is likely multifactorial and may be an important determinant of long-term respiratory and functional impairment. It remains unclear whether a mode of MV that maintains partial diaphragmatic activation will diminish the effects of ventilator-induced diaphragmatic dysfunction.

Adjunct Therapy to Mechanical Ventilation

Extracorporeal membrane oxygenation (ECMO) may be indicated in the management of severe acute respiratory distress syndrome (ARDS), characterized by profound hypoxemia, uncompensated hypercapnia, and/or the presence of excessively high end-inspiratory plateau pressures on MV (3). Noah and colleagues (4) compared hospital mortality between patients with H1N1-related ARDS referred for ECMO and those who were not. Patients were matched using data from the Swine Flu Triage study (5). The primary study end-point was survival to hospital discharge, and intention-to-treat analyses were used (4). Twenty-two patients (27.5%) transferred to one of the four UK ECMO centers died. The hospital mortality rate was 23.7% for ECMO-referred patients compared with 52.5% for non-ECMO-referred patients (risk ratio [RR], 0.45; 95% confidence interval [CI], 0.26–0.79); when GenMatch matching was used, hospital mortality was 24.0% and 50.7%, respectively (RR, 0.47; 95% CI, 0.31–0.72) (4). The authors conclude that in patients with H1N1-related ARDS, referral to an ECMO center was associated with lower hospital mortality compared with non-ECMO-referred patients (4).

Although recent experience with ECMO for severe cases of ARDS from the 2009 influenza A (H1N1) pandemic generated widespread interest in this technique, similar cases in which ECMO was not used also had favorable outcomes (6). Therefore conclusions drawn from this observational study are limited to patients with severe H1N1-related ARDS and centers experienced in the provision of advanced support for respiratory failure (e.g., ECMO-referral centers).

Airway Management during Mechanical Ventilation

Tracheostomy is commonly used in patients requiring prolonged intubation, but optimal timing for this procedure is unclear (7). A prospective, single-center, randomized controlled trial by Trouillet and colleagues evaluated the clinical outcomes of early percutaneous tracheostomy (immediately after randomization on Postoperative Day 4) compared with late tracheostomy (15 days after randomization) in adults requiring mechanical ventilation

(Received in original form June 28, 2012; accepted in final form August 13, 2012)

Correspondence and requests for reprints should be addressed to M. Elizabeth Wilcox, M.D., M.P.H., University Health Network, 399 Bathurst St., 2nd Floor, MCL 411H, Toronto, ON, M5T 2S8 Canada. E-mail: elizabeth.wilcox@utoronto.ca

Proc Am Thorac Soc Vol 9, Iss. 4, pp 190–196, Oct 1, 2012

Copyright © 2012 by the American Thoracic Society

DOI: 10.1513/pats.201206-033TT

Internet address: www.atsjournals.org

for 4 or more days after cardiac surgery (8). Sedation and weaning policies were rigorously controlled in this study.

Immediate tracheostomy compared with late tracheostomy did not decrease 28- or 90-day mortality (16% vs. 21%; $P = 0.30$ and 30% vs. 30%; $P = 1.0$, respectively), length of ICU (mean, 23.9 ± 21.3 d vs. 25.5 ± 22.2 d; $P = 0.85$) or hospital stay (mean, 39 ± 27 d vs. 37.5 ± 26.9 d; $P = 0.56$), or increase the number of ventilator-free days (mean, 30.4 ± 22.4 d vs. 28.3 ± 23.7 d; $P = 0.5$) (8). Further, the incidence of ventilator-associated pneumonia was similar in both groups (46% vs. 44%; $P = 0.77$) (8). Early tracheostomy did reduce the use of sedatives measured by both duration of intravenous sedation as well as the mean cumulative doses of sedation (propofol, sufentanil, and midazolam) (8). However, early tracheostomy was found to ease nursing care and improve patient comfort.

Studies on early versus late tracheostomy are challenging because it is difficult to predict which patients will require prolonged MV. From these data, it appears that early tracheostomy does not shorten duration of mechanical ventilation, ICU, or hospital length of stay or decrease the incidence of ventilator-associated pneumonia. However, there may be beneficial effects of early tracheostomy on patient comfort, ability to wean sedation, and facilitation of early mobility and ICU-based rehabilitation. Each of these requires further study.

Weaning from Mechanical Ventilation

Difficult-to-wean patients are common. In a prospective cohort study of 257 medical and surgical patients for whom weaning was attempted, the incidence of difficult and prolonged weaning were 26% and 14%, respectively (9).

Girault and colleagues evaluated the effectiveness of noninvasive ventilation (NIV) as an early weaning/extubation technique in difficult-to-wean patients with chronic hypercapnic respiratory failure (10). In 13 French and Tunisian ICUs with significant NIV experience, 208 patients with chronic hypercapnic respiratory failure intubated for acute respiratory failure and failing their first spontaneous breathing trial were randomly assigned to either (1) conventional invasive weaning group, (2) extubation followed by standard oxygen therapy, or (3) NIV (10). NIV was permitted as rescue therapy for both non-NIV groups in the event of failed extubation. The primary endpoint of this study was reintubation within 7 days; secondary endpoints included occurrence of post-extubation acute respiratory failure, death within 7 days of extubation, use of rescue post-extubation NIV, and weaning time. Reintubation rates among the three groups were similar (30%, 37%, and 32%, respectively; $P = 0.66$) (10). Weaning failure rates, including post-extubation acute respiratory failure, reintubation, and death within 7 days, were 54%, 71%, and 33%, respectively ($P < 0.001$) (10). The use of NIV for rescue therapy was 45% in the conventional invasive weaning group and 57% in the extubation with standard oxygen therapy group ($P = 0.18$) (10). The duration of ventilator support for weaning was significantly longer in the NIV compared with the conventional invasive weaning group (2.5 d; 95% CI, 0.5–3.5 d vs. 1.5 d; 95% CI, 0.5–3.5; $P = 0.03$) (10).

While reintubation rates were similar across groups, these data suggest that NIV may have a role in select patients with chronic hypercapnic respiratory failure who are difficult to wean and have post-extubation acute respiratory failure.

Extubation Outcome

Extubation failure is associated with a poor prognosis (11). In a prospective longitudinal study by Thille and colleagues, the

impact of planned or unplanned failed extubation on patient outcome and associated predictors were evaluated (12). Consecutive mechanically ventilated patients from a 13-bed medical ICU were screened and followed until death or hospital discharge. Daily data on extubation episodes were collected prospectively (12).

In 340 patients, 26 (15%) of the 168 planned extubations failed compared with 20 (65%) of the 31 unplanned extubations. Of those failing planned extubation, seven (27%) patients were diagnosed with pneumonia within 72 hours after extubation, and ICU mortality was 50% (12). None of the patients who remained successfully extubated had pneumonia, and their ICU mortality was 5% (12). At the time of extubation, patients did not differ significantly with respect to severity of illness, duration of mechanical ventilation, or other physiologic measures (e.g., arterial blood gas values) (12). Age and pre-existing cardiac and respiratory comorbidities were the only factors associated with extubation failure ($P < 0.01$), pneumonia, and death (12). Older patients with chronic cardiac and respiratory disease are at high risk for poor outcome after failed extubation.

ACUTE RESPIRATORY DISTRESS SYNDROME

Lorraine B. Ware

*Vanderbilt University School of Medicine
Nashville, Tennessee*

β -Adrenergic Agonists for Treatment of ARDS

Several studies have shown that β -agonists improve physiological outcomes in patients with ARDS (13, 14). In a single-center, double-blind, randomized controlled trial, patients randomized to treatment with intravenous β -adrenergic agonist (salbutamol; 15 $\mu\text{g/kg/h}$) had significantly lower extravascular lung water and plateau airway pressure at 7 days compared with placebo (14). Based on these findings, Smith and colleagues undertook a multicenter trial in 46 ICUs, enrolling a total of 326 patients of a planned 1,134 within 72 hours of ARDS onset (15). The primary outcome was death within 28 days of randomization. The analysis was intention-to-treat, but the study was stopped early due to safety concerns. Mortality at 28 days was 34% in the salbutamol group (15 $\mu\text{g/kg/h}$ for up to 7 d) compared with 23% in the placebo group (RR, 1.47; 95% CI, 1.03–2.08), although there was no significant difference in hospital mortality (15). Patients treated with salbutamol had fewer ventilator-free and organ failure-free days (risk difference -2.7 d; 95% CI, -4.7 to -0.7 d; -2.3 d; 95% CI, -2.3 to -0.1 , respectively) (15). Serious adverse events including tachycardia (RR, 11.71; 95% CI, 2.81–48.88), acute lactic acidosis (RR, 10.73; 95% CI, 1.36–84.82) and new arrhythmia (RR, 4.75; 95% CI, 1.39–16.23), sufficiently severe to stop the study drug, were more common in the salbutamol group (15).

In another large randomized trial of a β -adrenergic agonist in lung-injured patients, aerosolized albuterol at a dose of 5 mg every 4 hours for up to 10 days was compared with placebo (16). The primary outcome was ventilator-free days from the time of randomization. Secondary endpoints included 60- and 90-day mortality with unassisted breathing. Of a planned 1,000 patients, 282 patients were enrolled before this study was stopped early due to futility, as there were no significant differences observed in primary or secondary outcome measures comparing albuterol to placebo (ventilator-free days: 14.4 ± 0.9 d as compared with 16.6 ± 0.9 d, $P = 0.09$; and adjusted 60-d mortality, $22.2 \pm 7.6\%$ as compared with $18.7 \pm 7.3\%$, $P = 0.40$) (16).

Despite strong preclinical data and good biological rationale for β -agonist therapy, these two trials (15, 16) showed no benefit

from aerosolized or intravenously delivered β -adrenergic agonists in acute lung injury. Furthermore, intravenous delivery was poorly tolerated, as it had numerous associated adverse side effects.

Omega-3 Fatty Acids for Treatment of ARDS

There is growing interest in the use of omega-3 fatty acid supplementation because of its anti-inflammatory effects, improvement in oxygenation, lung mechanics, and decreased duration of mechanical ventilation in patients with ARDS (17). Patients with ARDS have very low levels of omega-3 fatty acids, and preclinical studies and small clinical trials suggest a potential benefit from supplementation (17). Stapleton and colleagues administered eicosapentaenoic acid (EPA; 9.75 g daily) and docosahexanoic acid (DHA; 6.75 g daily), omega-3 fatty acids in fish oil, for up to 14 days to 41 patients with acute lung injury (18). Forty-nine patients received saline placebo (18). The primary endpoint was interleukin-8 levels in bronchoalveolar lavage fluid. At both Days 4 and 8 there was no significant change in interleukin-8 levels from baseline compared with placebo (43 pg/ml: range, -656 to 604 pg/ml as compared with -241 pg/ml: range, -807 to 349 pg/ml; $P = 0.37$ and -531 pg/ml: range, -1,308 to 94 pg/ml as compared with -298 pg/ml: range, -870 to 397 pg/ml; $P = 0.55$) (18). In addition, there were no significant changes in interleukin-8 levels from baseline in plasma biomarker measurements. No significant differences were observed in physiologic outcomes (e.g., ratio of partial pressure of arterial oxygen to fraction of inspired oxygen) or clinical outcomes (e.g., ventilator-free days, ICU-free days, hospital length of stay, or hospital mortality) (18).

Preclinical data (19, 20) indicated that the n-6 γ -linolenic acid (GLA), in conjunction with the omega-3 fatty acid EPA, reduced neutrophil leukotriene synthesis and stimulated production of the vasodilator prostaglandin E_1 , effects that could modulate the systemic inflammatory response and improve outcomes in patients with ARDS. Based on this rationale, the OMEGA study, a randomized, double-blind, placebo-controlled, multicenter trial, investigated the use of GLA, DHA, and antioxidants (twice daily; enteral supplementation) compared with an isocaloric control in 272 adults within 48 hours of developing acute lung injury requiring ventilator support (21). The primary endpoint in this supplementation study was ventilator-free days. Secondary endpoints included 60-day mortality, organ-failure free days, plasma interleukin levels, and new infections. The analysis was intention-to-treat (21).

Planned enrollment was 1,000 patients. However, the study was stopped at the first interim analysis after 143 patients had been randomized to receive the supplement and 129 to the isocaloric control group (21). Fewer ventilator-free days from Day 1 to Day 28 were seen in the supplement compared with control group (14 d $\pm$ 11.1 d vs. 17.2 d $\pm$ 10.2 d; $P = 0.02$) (21). In addition, there was a trend toward greater adjusted 90-day mortality (25.1%: 95% CI, 9.2–41 versus 17.6%: 95% CI, 3.3–31.9) in the supplementation compared with the control group (21). There was no difference in the development of new infections between experimental groups. Patients receiving the supplement had more gastrointestinal complaints, which the authors attributed to the mechanism of administration (bolus as opposed to continuous enteral infusion) (21).

Together, these studies (18, 21) indicate that enteral supplementation of omega-3 fatty acids (with or without γ -linolenic acid and antioxidants) is not beneficial in patients with ARDS and may be harmful. Overall mortality was low in these two studies, consistent with more recent clinical trials in ARDS, suggesting that improvements in the management of MV, fluid

management, and other supportive care may have also influenced clinical outcomes.

Enteral Feeding Strategy in ARDS

The optimal timing, composition, and administration of nutrition in critically ill patients remains unclear. In a recent study by the National Heart, Lung, and Blood Institute, Acute Respiratory Distress Syndrome Clinical Trials Network, there was no difference in ventilator-free days, 60-day mortality, or infectious complications when low-dose enteral feeding was compared with full-dose feeding (22). In this trial, a full feeding group, in whom enteral nutrition ($n = 492$) was initiated immediately at 25 ml/hour and increased quickly to goal rates (25–30 kcal/kg/d) was compared with a low-dose or trophic nutrition group ($n = 508$), in whom enteral nutrition was initiated and maintained at 10 ml/hour (the first 272 patients also received omega-3 supplementation or placebo as part of the OMEGA study) (22). Feeding regimens were continued for the first 6 days of MV, at which time the trophic feeding group was advanced to full caloric supplementation. Despite receiving more prokinetic agents, the full-feeding group experienced more vomiting (2.2% vs. 1.7% of patient feeding days; $P = 0.05$), and constipation (3.1% vs. 2.1%; $P = 0.003$) (22). It would have been of additional interest to explore other outcomes including the differential effect of these feeding regimens on muscle mass and long-term function, though the study design did not incorporate these endpoints.

Cell-based Therapy for ARDS

Two recent studies, one by Gupta and colleagues (23) and the other by Curley and coworkers (24), have provided new insight into the protective mechanisms of mesenchymal stem cells (MSCs) in animal models of acute lung injury. Gupta and colleagues demonstrated in a murine model of *Escherichia coli* pneumonia that MSCs administered endotracheally 4 hours after infection improved 48-hour survival and enhanced bacterial clearance, resulting in less severe lung injury (23). The antibacterial effect of MSCs was found to be secondary to the up-regulation of the antibacterial protein lipocalin-2 (23).

Curley and coworkers administered MSCs intravenously immediately after the induction of severe ventilator-induced lung injury in rats, and again at 24 hours (24). MSC therapy was found to enhance the recovery and repair of the injured lung as systemic oxygenation and lung compliance was restored, total lung water reduced, and lung inflammation decreased. Histologic restoration of lung structure was also observed (24). The mechanism of enhancement of lung repair was thought to be related, in part, to keratinocyte growth factor paracrine signaling (24). Early phase clinical trials with MSCs in patients with ARDS will likely occur in the near future.

CRITICAL CARE

Hannah Wunsch
Columbia University
New York, New York

Sepsis and Atrial Fibrillation

Arrhythmias are common in critically ill patients. Walkey and colleagues used a database of patients, identified via California State Inpatient Database claims (2007), to determine the clinical significance of new-onset atrial fibrillation (AF) in severe sepsis (25). The study identified 49,082 patients with severe sepsis defined using ICD-9-CM codes from 3,144,787 hospitalized

adult claims (1.6% of admissions). New-onset AF occurred in 20,608 hospitalizations (0.65%; 95% CI, 0.65–0.66%); specifically, in patients with sepsis, new-onset AF occurred during 2,896 hospitalizations (5.9%; 95% CI, 5.7–6.1%) (25). Severe sepsis was present in 14% of hospitalized adults with new-onset AF (25). Patients with severe sepsis had an adjusted odds ratio (OR) of 2.7 (95% CI, 2.1–3.6) for in-hospital ischemic stroke; in patients with severe sepsis and new-onset AF, adjusted OR for in-hospital ischemic stroke was 2.8 (95% CI, 1.8–4.3) (25). Risk factors associated with increased risk of AF included demographics (e.g., increasing age, male sex), comorbidities (e.g., history of heart failure, obesity, malignancy), and acute factors such as increasing number of organ failures, use of right heart catheter, and new infection (25). There was a 13% increase in risk of in-hospital death in patients with new-onset AF and sepsis, compared with those with sepsis in the absence of AF (25). The generalizability of these results remains unclear, as do possible variations in outcomes dependent upon arrhythmia management (e.g., anticoagulation, cardioversion). Further research is warranted to determine what the best clinical care is for patients with new-onset AF in cases of severe sepsis.

Thromboprophylaxis

Patients admitted to the ICU are at high risk for deep venous thromboembolism (DVT) even after routine prophylactic anticoagulation. In a retrospective cohort study of 175,665 critically ill patients admitted to 134 ICUs in Australia and New Zealand (2006–2010), the crude ICU and hospital mortality rates in those who received thromboprophylaxis were 6.3% and 10.6%, respectively (26). In a randomized controlled trial in 67 ICUs by Cook and colleagues, the superiority of dalteparin (low-molecular-weight heparin) compared with unfractionated heparin was tested for prophylaxis against venous thromboembolism (27). The study enrolled 13,764 patients expected to remain in the ICU for at least 3 days. Patients were randomized to receive either dalteparin (5,000 IU once daily) or unfractionated heparin (5,000 IU twice daily) (27). The primary outcome was proximal leg DVT. Compression ultrasonography was performed within 2 days of admission, twice weekly thereafter, and when clinically indicated (27).

No difference in the rate of proximal leg DVT was found between the two groups (5.1% receiving dalteparin versus 5.8% receiving unfractionated heparin; $P = 0.57$) (27). The frequency of pulmonary embolism, however, was significantly lower in the dalteparin group (1.3% vs. 2.3%; $P = 0.01$) (27). However, there were no differences in the rates of major bleeding (hazard ratio [HR], 1.0; 95% CI, 0.75–1.3) or death (HR, 0.92; 95% CI, 0.80–1.1). Finally, fewer patients in the dalteparin group had heparin-induced thrombocytopenia (HR, 0.47; 95% CI, 0.16–1.4) (27).

This study suggests that in patients without contraindications, dalteparin may be preferable to unfractionated heparin as prophylaxis against DVT. Although it did not decrease the rate of proximal DVT, it did significantly reduce the rate of pulmonary emboli (27). It remains unclear why the rate of pulmonary emboli was different without any difference in the rates of DVT. Possibly the current mode of detection for DVT is not sufficiently sensitive to detect the most proximal thrombosis (e.g., pelvic burden).

Feeding of Critically Ill Patients

Guidelines in Europe differ from those in Canada and the United States with respect to the use of early parenteral nutrition to reach caloric goals in patients with critical illness (28, 29). In

a study by Casaer and colleagues, 4,640 patients were randomized across 7 sites to compare early initiation of parenteral nutrition (within 48 h of admission to the ICU) to late initiation, supplementing enteral nutrition (to achieve daily caloric intake goal) after 8 days of critical illness (30). Patients in the late-initiation group had a small but significant reduction (6.3%) in ICU length of stay (30). As well, this group had fewer ICU-related infections (22.8% vs. 26.2%; $P = 0.008$), more patients requiring less than 48 hours of mechanical ventilation, fewer patients requiring renal replacement therapy, and slight reductions in associated cost (30). There were no statistically significant differences between the groups in terms of hospital or 90-day mortality (30). In summary, these investigators found no benefit in the early initiation of parenteral therapy to supplement enteral nutrition to reach target caloric goals. A large proportion of patients (60%) were admitted to the ICU after cardiac surgery (30), and outcomes in this patient population may not be generalizable to other critically ill patient populations.

It remains to be seen whether different supplementation regimens have an impact on ICU-acquired weakness, disability, or protracted rehabilitation in the post-ICU period.

Continuity of Patient Care

Adverse medical events can occur when information is transferred across patient care settings (31). Bell and colleagues conducted a population-based cohort study using administrative records from 1997 to 2009 of all hospitalizations and outpatient prescriptions in Ontario (32). The study examined rates of discontinuation after hospitalization of five categories of commonly prescribed medications for chronic disease (statins, antiplatelets/anticoagulant agents, levothyroxine, respiratory inhalers, and gastric acid-suppressing agents) (32). Patients admitted to the ICU were compared with other hospitalized patients as well as with nonhospitalized control subjects. Admission to the ICU was associated with an increased likelihood of prior discontinuation of statins, antiplatelets/anticoagulants, levothyroxine, respiratory inhalers, and gastric acid suppressors compared with both other hospitalized patients and control subjects (32). An increased risk of death, emergency department visits, or emergent hospitalization was associated with patients previously taking statins or antiplatelets/anticoagulants, including patients admitted to the ICU and other hospitalized patients (32).

The authors conclude that patients taking medications for chronic diseases were at risk of potential discontinuation after hospital admission. Admission to the ICU was associated with higher risk of medication discontinuance (32). Improved continuity of care, including rigorous medication reconciliation during different in-hospital transition periods and improved communication with general practitioners, is needed to ensure proper follow-up after ICU care.

Discharge after Intensive Care

Endorsed by the National Quality Forum as hospital quality measures, hospital mortality and length of stay are important outcome measures in patients with critical illness (<http://www.qualityforum.org>). In a study by Hall and colleagues, data from the University Health System Consortium in 2008–2009 was used to assess the association between discharge practices and reported hospital mortality and length of stay (33). The authors determined that variations seen between hospitals were significantly dependent upon the transfer of ventilated patients to long-term acute care hospitals (33). Focusing on patients requiring mechanical ventilation for greater than 96 hours, multivariable

modeling showed that long-term acute care transfer rates explain 14% variation in hospital mortality indices, and 37% of the variation in hospital length of stay indices among 137 hospitals (33). The study suggests that such factors, unrelated to quality of medical care or severity of illness, should be considered when interpreting mortality and length of stay as quality indicators.

Fluid Resuscitation

Fluid resuscitation is considered a fundamental component of the treatment of critically ill patients with severe sepsis (34). In a randomized controlled trial of fluid boluses for children with severe febrile illnesses and evidence of impaired perfusion, 3,141 children were randomized to receive either albumin (20–40 ml; 5% albumin) or saline (20 ml/kg) or neither for resuscitation; all children received 2.5 to 4.0 ml/kg/h of intravenous maintenance fluids, antibiotics, antimalarials, antipyretics, and antiepileptics as clinically indicated (35). These children were identified in six hospitals in Africa (Uganda, Kenya, or Tanzania) where there is limited access to intensive care services and were treated primarily on general pediatric wards. The primary endpoint was 48-hour mortality, and secondary outcomes were incidence of pulmonary edema, increased intracranial pressure, and mortality or significant neurologic sequelae at 4 weeks (35).

Recruitment was stopped after enrollment of 3,141 children because of safety concerns in the albumin- and saline-bolus groups. Overall malaria status (57%) and severity of illness were similar across all three groups (35). There was an increased risk of death at 48 hours in children having received bolus therapy (10.6% in the albumin-bolus group, 10.5% in the saline-bolus group, and 7.3% in the control group; RR for albumin-bolus versus control, 1.0; 95% CI, 0.8–1.3 and RR for saline-bolus versus control, 1.4; 95% CI, 1.1–1.9) (35). Further, 4-week mortality was again greater in the groups receiving fluid boluses (12.2%, 12.0%, and 8.7%, respectively; $P = 0.004$ for the comparison of bolus with control) (35). There were no differences in mortality between the albumin- and saline-bolus groups (RR, 1.0; 95% CI, 0.78–1.29; $P = 0.96$) (35). Of note, the increased risk of death occurred in all subgroups of children, including those with and without malaria (35). Caution must be exercised with regard to the implementation of guidelines in resource-limited settings. The underlying mechanism for increased mortality rates seen in these children has yet to be determined.

LUNG CANCER

M. Patricia Rivera
*University of North Carolina
Chapel Hill, North Carolina*

Screening for Lung Cancer

The National Lung Screening Trial (NLST) was the first study to determine the impact of low-dose computed tomography (CT) on lung cancer associated mortality (36). This was a randomized study of 53,454 high-risk individuals from 33 sites in the United States in which participants received three annual screenings from August 2002 to September 2007 with either low-dose CT or single-view chest radiography (36). NLST participants tended to be younger (> 70% of participants were 55–64 yr of age), were more likely to be male (59%) and former smokers (48% were active smokers), and had a higher level of education (36). There was greater than 93% adherence to screening procedure in each group. The rate of positive screening tests was 24% with low-dose CT and 7% with radiography over all three rounds. In both the low-dose CT and radiology groups, 96.4% compared

with 94.5% of the positive screening results were false positives (36). The incidence of lung cancer was 10% greater in the low-dose CT group compared with the radiography group (rate ratio, 1.1; 95% CI, 1.0–1.2) (36). The rate of death from any cause was reduced by 6.7% in the low-dose CT group (95% CI, 1.2–13.6) (36). Despite the reduction in mortality, the significant number of false positive scans in this study was very worrisome. Investigations of these patients could possibly lead to unnecessary evaluations with potential complications and needless anxiety. Further, issues of implementation, follow-up of benign lesions, and cost effectiveness of such a screening intervention will fuel future debates on the usefulness of CT. Several organizations have published lung cancer screening recommendations on the basis of the findings of the NLST (37, 38).

Diagnosis of Lung Cancer

Peripheral pulmonary lesions (PPL) are focal radiologic opacities that may be classified as nodules (<3 cm) or masses (>3 cm) (39). In patients with low pre-test probability of malignancy, multiple minimally invasive diagnostic tools may be used to establish a tissue diagnosis (39). Recently, Memoli et al. found that the pooled diagnostic yield for novel bronchoscopic techniques for the evaluation of a pulmonary nodule was 70% higher than that of traditional transbronchial biopsy (40). In a meta-analysis by Steinfert and colleagues, bronchoscopic evaluation using radial probe endobronchial ultrasound (EBUS) had a point specificity of 1.00 (95% CI, 0.99–1.00) and point sensitivity of 0.73 (95% CI, 0.70–0.76) for the detection of lung cancer (41). Population-based estimates of risk for complications after transthoracic needle biopsy include hemorrhage (1.0%; 95% CI, 0.9–1.2%), and pneumothorax (15%; 95% CI, 14–16%) (41). Of the biopsies that resulted in pneumothorax, 6.6% required a chest tube (42). At this time, the diagnostic yield of guided bronchoscopic transbronchial biopsy seems to be lower than that of transthoracic needle aspiration, but its complication rate is lower. Further research may better compare strategies for pulmonary nodule management, including the “ideal” timing of biopsy and “best” technique to perform it.

Treatment of Lung Cancer

Advances in targeted therapy have resulted in a paradigm shift in the treatment of lung cancer. Chromosomal rearrangements involving the *ROS1* receptor tyrosine kinase gene have been recently described in a subset of non-small cell lung cancers (NSCLCs) (43). In a study by Bergethon and coworkers, 1,073 patients with NSCLC were screened and *ROS1* rearrangement status was correlated with clinical characteristics, overall survival, and, as possible, *ALK* rearrangement status (44). Patients with NSCLC who had a rearranged *ROS1* gene were found to have a clinical profile similar to those of patients with the *ALK*-rearranged NSCLC (44). These findings represent a group of patients who could benefit from newer chemotherapeutics, such as crizotinib (44).

In elderly patients with NSCLC, Quoix and colleagues found that despite increased toxic effects (neutropenia, asthenia), platinum-based doublet chemotherapy (carboplatin and paclitaxel) compared with monotherapy was associated with improved survival (median overall survival, 10.3 mo and 6.2 mo, respectively; HR, 0.64; 95% CI, 0.52–0.78) (45). In a single-center review by Port and coworkers of elderly patients who underwent lobectomy for NSCLC (1998–2009), no significant difference in survival was found between a video-assisted thoracic surgical (VATS) approach and open thoracotomy (46), but lower rates of complications (35% versus 63%; $P = 0.004$) were

seen in the VATS group. In addition, octagenarians undergoing VATS were less likely to require admission to an intensive care unit or to require rehabilitation after discharge. These findings would suggest that elderly patients can tolerate resection with mortality rates similar to those of the general lung cancer population (46). Several studies have shown that elderly patients with NSCLC have similar survival benefits and toxicity profiles after treatment with surgery, chemotherapy, and combined modalities. Elderly patients with NSCLC warrant a similar approach to treatment as younger patients with NSCLC.

A recent systematic review by Slatore and colleagues found that patients in the United States with either Medicaid or no insurance at all consistently had worse outcomes than other patients with lung cancer (47). Siegel and coworkers estimate that the elimination of racial and educational disparities could avoid approximately 37% of premature deaths among individuals aged 25 to 65 years in the year 2007 alone based on data from the National Cancer Institute, the Centers for Disease Control and Prevention, North American Association of Central Cancer Registries, and National Center for Health Statistics in the United States (48). Future research into barriers to access is needed to drive changes in health policy.

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

References

- Levine S, Nguyen T, Taylor N, Friscia ME, Budak MT, Rothenberg P, Zhu J, Sachdeva R, Sonnad S, Kaiser LR, *et al.* Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med* 2008;358:1327–1335.
- Jaber S, Petrof BJ, Jung B, Chanques G, Berthet JP, Rabuel C, Bouyabrine H, Courouble P, Koechlin-Ramonatxo C, Sebbane M, *et al.* Rapidly progressive diaphragmatic weakness and injury during mechanical ventilation in humans. *Am J Respir Crit Care Med* 2010;183:364–371.
- Brodie D, Bacchetta M. Extracorporeal membrane oxygenation for ARDS in adults. *N Engl J Med* 2011;365:1905–1914.
- Noah MA, Peek GJ, Finney SJ, Griffiths MJ, Harrison DA, Grieve R, Sadique MZ, Sekhon JS, McAuley DF, Firmin RK, *et al.* Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *JAMA* 2011;306:1659–1668.
- Rowan KM, Harrison DA, Walsh TS, McAuley DF, Perkins GD, Taylor BL, Menon DK. The Swine Flu Triage (SwiFT) study: development and ongoing refinement of a triage tool to provide regular information to guide immediate policy and practice for the use of critical care services during the H1N1 swine influenza pandemic. *Health Technol Assess* 2010;55:335–492.
- Kumar A, Zarychanski R, Pinto R. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. *JAMA* 2009;302:1872–1879.
- Nathens AB, Rivara FP, Mack CD, Rubenfeld GD, Wang J, Jurkovich GJ, Maier RV. Variation in rates of tracheostomy in the critically ill trauma patient. *Crit Care Med* 2006;34:2919–2924.
- Trouillet JL, Luyt CE, Guiguet M, Ouattara A, Vaissier E, Makri R, Nieszkowska A, Leprince P, Pavie A, Chastre J, *et al.* Early percutaneous tracheotomy versus prolonged intubation of mechanically ventilated patients after cardiac surgery: a randomized trial. *Ann Intern Med* 2011;154:373–383.
- Funk GC, Anders S, Breyer MK, Burghuber OC, Edelmann G, Heindl W, Hinterholzer G, Kohansal R, Schuster R, Schwarzaier-D'Assie A, *et al.* Incidence and outcome of weaning from mechanical ventilation according to new categories. *Eur Respir J* 2010;35:88–94.
- Girault C, Bubenheim M, Abroug F, Diehl JL, Elatrous S, Beuret P, Richecoeur J, L'Her E, Hilbert G, Capellier G, *et al.*; VENISE Trial Group. Noninvasive ventilation and weaning in patients with chronic hypercapnic respiratory failure: a randomized multicenter trial. *Am J Respir Crit Care Med* 2011;184:672–679.
- Epstein SK, Ciubotaru RL, Wong JB. Effect of failed extubation on the outcome of mechanical ventilation. *Chest* 1997;112:186–192.
- Thille AW, Harrois A, Schortgen F, Brun-Buisson C, Brochard L. Outcomes of extubation failure in medical intensive care unit patients. *Crit Care Med* 2011;39:2612–2618.
- Maris NA, de Vos AF, Dessing MC, Spek CA, Lutter R, Jansen HM, van der Zee JS, Bresser P, van der Poll T. Antiinflammatory effects of salmeterol after inhalation of lipopolysaccharide by healthy volunteers. *Am J Respir Crit Care Med* 2005;172:878–884.
- Perkins GD, McAuley DF, Richter A, Thickett DR, Gao F. Bench-to-bedside review: beta2-agonists and the acute respiratory distress syndrome. *Crit Care* 2004;8:25–32.
- Gao Smith F, Perkins GD, Gates S, Young D, McAuley DF, Tunnicliffe W, Khan Z, Lamb SE; BALTI-2 Study Investigators. Effect of intravenous β -2 agonist treatment on clinical outcomes in acute respiratory distress syndrome (BALTI-2): a multicentre, randomised controlled trial. *Lancet* 2012;379:229–235.
- Matthay MA, Brower RG, Carson S, Douglas IS, Eisner M, Hite D, Holets S, Kallet RH, Liu KD, Macintyre N, *et al.*; The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Randomized placebo-controlled clinical trial of an aerosolized β 2-agonist for treatment of acute lung injury. *Am J Respir Crit Care Med* 2011;184:561–568.
- Gadek JE, DeMichele SJ, Karlstad MD, Pacht ER, Donahoe M, Albertson TE, Van Hoozen C, Wennberg AK, Nelson JL, Noursalehi M; Enteral Nutrition in ARDS Study Group. Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome. *Crit Care Med* 1999;27:1409–1420.
- Stapleton RD, Martin TR, Weiss NS, Crowley JJ, Gundel SJ, Nathens AB, Akhtar SR, Ruzinski JT, Caldwell E, Curtis JR, *et al.* A phase II randomized placebo-controlled trial of omega-3 fatty acids for the treatment of acute lung injury. *Crit Care Med* 2011;39:1655–1662.
- Palombo JD, Lydon EE, Chen PL, Bistrian RB, Armour Forse R. Fatty acid composition of lung, macrophage and surfactant phospholipids after short-term enteral feeding with n-3 lipids. *Lipids* 1994;29:643–649.
- Yaqoob P, Pala HS, Cortina-Borja M, Newsholme EA, Calder PC. Encapsulated fish oil enriched in alphatocopherol alters plasma phospholipid and mononuclear cell fatty acid compositions but not mononuclear cell functions. *Eur J Clin Invest* 2000;30:260–274.
- Rice TW, Wheeler AP, Thompson BT, deBoisblanc BP, Steingrub J, Rock P; NIH NHLBI Acute Respiratory Distress Syndrome Network of Investigators. Enteral omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation in acute lung injury. *JAMA* 2011;306:1574–1581.
- Rice TW, Wheeler AP, Thompson BT, Steingrub J, Hite RD, Moss M, Morris A, Dong N, Rock P; National Heart, Lung, Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA* 2012;307:795–803.
- Gupta N, Krasnodembskaya A, Kapetanaki M, Mouded M, Tan X, Serikov V, Matthay MA. Mesenchymal stem cells enhance survival and bacterial clearance in murine *Escherichia coli* pneumonia. *Thorax* 2012;67:533–539.
- Curley GF, Hayes M, Ansari B, Shaw G, Ryan A, Barry F, O'Brien T, O'Toole D, Laffey JG. Mesenchymal stem cells enhance recovery and repair following ventilator-induced lung injury in the rat. *Thorax* 2012;67:496–501.
- Walkey AJ, Wiener RS, Ghobrial JM, Curtis LH, Benjamin EJ. Incident stroke and mortality associated with new-onset atrial fibrillation in patients hospitalized with severe sepsis. *JAMA* 2011;306:2248–2254.
- Ho KM, Chavan S, Pilcher D. Omission of early thromboprophylaxis and mortality in critically ill patients: a multicenter registry study. *Chest* 2011;140:1436–1446.
- Cook D, Meade M, Guyatt G, Walter S, Heels-Ansdell D, Warkentin TE, Zytaruk N, Crowther M, Geerts W, Cooper DJ, *et al.*; The PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Dalteparin versus unfractionated heparin in critically ill patients. *N Engl J Med* 2011;364:1305–1314.
- Kreymann KG, Berger MM, Deutz NE, Nitenberg G, van den Bergh G, Wernermann J, Ebner C, Hiesmayr M, Jolliet P, Kazandjiev G, *et al.* ESPEN guidelines on enteral nutrition: intensive care. *Clin Nutr* 2006;25:210–223.

29. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN J Parenter Enteral Nutr* 2003;27:355–373.
30. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, Van Cromphaut S, Ingels C, Meersseman P, Muller J, *et al*. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med* 2011;365:506–517.
31. Bayley KB, Savitz LA, Rodriguez G, Gillanders W, Stoner S. Barriers associated with medication information handoffs. In: Henriksen K, Battles JB, Marks ES, Lewin DI, editors. *Advances in patient safety: from research to implementation*. Rockville, MD: Agency for Healthcare Research and Quality (US); 2005. pp.87–101.
32. Bell CM, Brener SS, Gunraj N, Huo C, Bierman AS, Scales DC, Bajcar J, Zwarenstein M, Urbach DR. Association of ICU or hospital admission with unintentional discontinuation of medications for chronic diseases. *JAMA* 2011;306:840–847.
33. Hall WB, Willis LE, Medvedev S, Carson SS. The implications of long-term acute care hospital transfer practices for measures of in-hospital mortality and length of stay. *Am J Respir Crit Care Med* 2012;185:53–57.
34. Dellinger RP, Levy MM, Marlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, *et al*. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2008;36:296–327.
35. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, Nyeko R, Mtove G, Reyburn H, Lang T, *et al*. Mortality after fluid bolus in African children with severe infection. *N Engl J Med* 2011;364:2483–2495.
36. Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM, Sicks JD; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395–409.
37. Bach PB, Mirkin JN, Oliver TK, Azzoli CG, Berry DA, Brawley OW, Byers T, Colditz GA, Gould MK, Jett JR, *et al*. Benefits and harms of CT screening for lung cancer: a systematic review. *JAMA* 2012;307:2418–2429.
38. National Comprehensive Cancer Network. National Comprehensive Cancer Network Guidelines Version 1.2012 Lung Cancer Screening. 2011 [accessed 23 July 2012]. Available from: <http://www.NCCN.org>.
39. MacMahon H, Austin JH, Gamsu G, Herold CJ, Jett JR, Naidich DP, Patz EFJ, Swensen SJ. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. *Radiology* 2005;237:395–400.
40. Memoli JSW, El-Bayoumi E, Pastis NJ, Tanner NT, Gomez M, Huggins JT, Onicescu G, Garrett-Mayer E, Armeson K, Taylor KK, Silvestri GA. Using endobronchial ultrasound features to predict lymph node metastasis in patients with lung cancer. *Chest* 2011;140:1550–1556.
41. Steinfurt DP, Khor YH, Manser RL, Irving LB. Radial probe endobronchial ultrasound for the diagnosis of peripheral lung cancer: systematic review and meta-analysis. *Eur Respir J* 2011;37:902–910.
42. Wiener RS, Schwartz LM, Woloshin S, Welch HG. Population-based risk for complications after transthoracic needle lung biopsy of a pulmonary nodule: an analysis of discharge records. *Ann Intern Med* 2011;155:137–144.
43. Rikova K, Guo A, Zeng Q, Possemato A, Jian Y, Herbert H, Nardone J, Lee K, Reeves C, Li Y, *et al*. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. *Cell* 2007;131:1190–1203.
44. Bergethson K, Shaw AT, Ou S-HI, Katayama R, Lovly CM, McDonald NT, Massion PP, Siwak-Tapp C, Gonzalez A, Fang R, *et al*. ROS1 rearrangements define a unique molecular class of lung cancers. *J Clin Oncol* 2012;30:863–870.
45. Quoix E, Zalcman G, Oster J-P, Westeel V, Pichon E, Lavole A, Dauba J, Debievre D, Souquet P-J, Bigay-Game L, *et al*. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. *Lancet* 2011;378:1079–1088.
46. Port JL, Mirza FM, Lee PC, Paul S, Stiles BM, Altorki NK. Lobectomy in octogenarians with non-small cell lung cancer: ramifications of increasing life expectancy and the benefits of minimally invasive surgery. *Ann Thorac Surg* 2011;92:1951–1957.
47. Slatore CG, Au DH, Gould MK; American Thoracic Society Disparities in Healthcare Group. An official American Thoracic Society systematic review: insurance status and disparities in lung cancer practices and outcomes. *Am J Respir Crit Care Med* 2010;182:1195–1205.
48. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin* 2011;61:212–236.