Update in Acute Lung Injury and Mechanical Ventilation 2011

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In this Update, we highlight studies published in 2011 in the *Journal* and selected manuscripts from other journals that advanced our understanding of experimental and clinical aspects of acute lung injury (ALI), acute respiratory distress syndrome (ARDS), and mechanical ventilation (MV).

ADVANCES IN UNDERSTANDING THE PATHOGENESIS OF ALI

Inflammation, Oxidant Stress, Mitochondrial Dysfunction, and Cell Fate in ALI

It is widely accepted that inflammation plays a key role in the pathogenesis of ALI. Inflammation associated to inappropriate activation of neutrophils as well as novel mediators and regulators of inflammation were the focus of several studies. For example, prolyl hydroxylase 3, a regulator of hypoxia-inducible factor-1α, has been identified as a modulator of neutrophil lifespan, thereby linking hypoxia signaling to neutrophilic inflammation in ALI (1). Gefitinib, a selective inhibitor of epidermal growth factor receptor–tyrosine kinase that was shown to be effective in patients with non-small cell lung cancer with epidermal growth factor receptor mutations but was also associated with severe acute interstitial pneumonia in some cases, has now been shown to cause neutrophil sequestration, thereby inhibiting airway repair after lung injury (2). An interesting manuscript focused on the contribution of low-density lipoprotein receptor–related protein-1 (LRP-1) to the pathogenesis of ARDS. This study demonstrated that the ectodomain of LRP-1, which can be shed from the cell surface, thereby antagonizing ligand endocytosis by cellular LRP-1, was significantly increased in bronchoalveolar lavage (BAL) fluids from patients with ARDS impairing clearance of the matrix metalloproteinase-2 and -9, thereby contributing to tissue destruction and worse outcomes (3). The structural determinants of soluble Fas ligand (FasL) bioactivity in ALI have now also been described, showing that neutrophil myeloperoxidase caused methionine oxidation of FasL and promoted aggregation of soluble FasL in BAL fluid from patients with ARDS, thereby regulating its biological activity (4).

Oxidant stress has long been recognized as an important factor in the pathogenesis of ALI. The mechanism of hyperoxia-induced ALI has now been demonstrated to be mediated by mitochondrial matrix-generated oxidants, which by activation of the intrinsic apoptotic pathway, requiring the proapoptotic Bcl-2 family members BAX and BAK, significantly contributed to hyperoxia-induced mortality in mice. Overexpression of superoxide dismutase 2, which catalyzes the conversion of superoxide to hydrogen peroxide, which is further metabolized to oxygen and water by catalase or glutathione peroxidase in the mitochondrial matrix, prevented BAX activation and cell death and prolonged survival of mice exposed to hyperoxia (5). Interestingly, respiratory syncytial virus, a major cause of lower respiratory tract infections in children, has also been shown to induce oxidative lung injury by down-regulating the expression and activity of superoxide dismutase, catalase, glutathione peroxidase, and glutathione S-transferase in infected murine lungs and in airways of children with severe bronchiolitis (6). Furthermore, E2-related factor 2, a transcription factor that is required for expression of detoxifying and antioxidant genes, was also significantly down-regulated. Of note, mitochondrial dysfunction also played a central role in impaired cellular function and proliferation secondary to elevated CO_2 levels (hypercapnia) that may occur in severe respiratory diseases and particularly in patients with ALI who are ventilated with low tidal volume (7).

Fibroproliferation in the Pathogenesis of ALI

Fibroproliferation plays a pivotal role in the persistence of ALI leading to a prolonged impairment of gas exchange and poor clinical outcomes. Leptin, a hormone that regulates the balance between food intake and energy expenditure, has now been identified as a pathogenic factor of fibroproliferative ARDS, as in patients with ARDS leptin promoted transforming growth factor (TGF)-β_1–dependent fibroproliferation via a mechanism that required peroxisome proliferator-activated receptor-γ. These findings may explain the better outcomes of patients with diabetes in ARDS, as this patient population demonstrates a resistance to leptin signaling (8). A central role for TGF-β receptor II in fibroproliferative ALI and pulmonary fibrosis has also been established by generating mice in which the receptor was specifically deleted in the lung epithelium that exhibited increased survival and resistance to bleomycin-induced lung injury (9). Another study investigated the role of adenosine signaling via the adenosine 2B receptor ($A_{2B}R$) in ALI and pulmonary fibrosis secondary to bleomycin exposure and highlighted the distinct roles of $A_{2B}R$ in acute and chronic stages of lung injury (10).

(*Received in original form March 30, 2012; accepted in final form May 2, 2012*)

Support by grants from the Deutsche Forschungsgemeinschaft (DFG/IRTG1062), the Excellence Cluster "Cardio Pulmonary System" (ECCPS), the German Center for Lung Research (DZL), the Landes-Offensive zur Entwicklung Wissenschaftlich-ökonomischer Exzellenz (LOEWE) of the Hessen State Ministry of Higher Education, Research and the Arts, and the University Medical Center Giessen and Marburg (grant 62589064; I.V.). I.V. was supported by the Else Kröner Memorial Award.

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Am J Respir Crit Care Med Vol 186, Iss. 1, pp 17–23, Jul 1, 2012

DOI: 10.1164/rccm.201203-0582UP
Internet address: www.atsjournals.org

Alveolo-capillary Barrier Dysfunction in ALI

A hallmark of ALI is the dysfunction of the alveolo-capillary barrier, restoration of which plays an important role in the resolution of ALI and patient outcomes. The molecular mechanisms regulating the function of Na,K-ATPase remain the focus of intense research, as the activity of the Na^+ pump is the primary driving force of alveolar edema clearance. It has now been demonstrated that hypoxia leads to Ca^{2+} release from the endoplasmic reticulum, which via Ca^{2+} release-activated Ca^{2+} channels resulted in calcium entry into alveolar epithelial cells and AMP-activated protein kinase-mediated down-regulation of the Na,K-ATPase (11). Other than inhibiting the Na,K-ATPase, hypoxia also impaired alveolar epithelial barrier integrity by rapidly down-regulating the tight junction protein occludin at the plasma membrane of alveolar epithelial cells in a superoxide-, protein kinase C-ζ– and protein phosphatase 2A-dependent manner (12), further elucidating the role of hypoxia in alveolar epithelial dysfunction during ALI. The down-regulation of Na,K-ATPase leading to impaired alveolar fluid reabsorption and accumulation of alveolar edema after induction of sepsis by cecal ligation and perforation in rats (13), a model that simulates ALI secondary to sepsis (14), has been demonstrated, highlighting the role of impaired Na,K-ATPase function in the pathogenesis of sepsis-induced ALI.

Novel Approaches Assessing ALI Susceptibility and Identifying Biomarkers of ALI

Haplotype association mapping, a method that is similar to genome-wide association studies in humans, is a novel approach that aims to identify associations between the phenotype and the haplotypes of mouse inbred strains (15). Using haplotype association mapping, a study identified several candidate genes associated with acrolein-induced lung injury in mice and implicated activin A receptor, type 1 with increased susceptibility to ALI (16).

Critical illness is associated with altered metabolic homeostasis; therefore, investigating the metabolome may be useful for biomarker and drug target identification (17, 18). An excellent review focused on metabolomics, the global assessment of metabolites, describing its potential future role in critical care (17).

Advances in Understanding the Pathogenesis of Ventilator-induced Lung Injury

Several experimental studies examined the pathogenesis of ventilator-induced lung injury (VILI) and other ventilator-induced organ dysfunctions. For example, lung-derived, lipid-soluble molecules have been suggested to act as pathogenic mediators of VILI as perfusate collected from isolated mouse lungs ventilated with high V_T caused alveolar epithelial dysfunction in mice ventilated with low V_T, confirming the biotrauma hypothesis in VILI (19). p120-Catenin, an adherens junction-associated protein that regulates cell–cell adhesion, has now also been implicated in the pathogenesis of VILI, as cyclic stretch by down-regulating p120-catenin in a calpain-1–dependent manner induced gap formation and thus alveolar epithelial barrier dysfunction (20), suggesting a potential role for this protein in the repair of the injured epithelial barrier on ALI.

The pivotal role of ubiquitination in the development of ALI and VILI has become increasingly evident in the past years (21). For example, inactivity-induced diaphragm dysfunction due to mechanical ventilation has been shown to be mediated by ubiquitination and subsequent directed degradation of muscle fibers. A novel study showed enhanced ubiquitin-proteasome pathway-mediated proteolysis of the myosin heavy chain and α-actin in diaphragm biopsies of patients receiving mechanical ventilation for a prolonged time. These changes were associated with activation of the atrophic Akt (also known as protein kinase B)/forkhead box "Other" (FoxO) protein signaling pathway, as decreased phospho-Akt prevented phosphorylation of FoxO1, which resulted in increased binding of FoxO1 to the consensus sequence for the E3 ubiquitin ligases atrogin-1 and (muscle RING-finger protein-1) MuRF1, resulting in enhanced transcription of the E3 ligases (22). Oxidative stress can promote protein degradation; however, the mechanisms were unidentified. It has now been identified that a novel signaling pathway initiated by oxidative stress including Fos, FoxO1, signal transducer and activator of transcription 3 (STAT-3), and Bcl-2–interacting mediator of cell death (BIM) activates proteasomal degradation, intrinsic apoptosis, and autophagy, thus contributing to ventilator-induced diaphragm dysfunction (23). Ubiquitination of proteins may also promote trafficking of targets, thereby regulating their activity. The role of site-specific ubiquitination of Akt leading to its activation or degradation and the regulation of these events by growth arrest and DNA damage-inducible α (GADD45a), a stress-induced protein that may contribute to VILI susceptibility, have now been described, further elucidating the molecular mechanisms by which mechanical stretch induce lung injury (24).

Clinical Aspects of VILI, Recruitment, and Derecruitment

The physical principles behind the occurrence of VILI could have direct implications for clinical practice, for instance by adjusting the ventilator pressures and volumes based on direct measurements of lung volumes and transpulmonary pressures. Lung strain (ratio of the increase in volume due to positive end-expiratory pressure [PEEP] and V_T to the baseline functional residual capacity) and stress (the transpulmonary pressure) have been described by Caironi and colleagues, who also recently showed that the time to develop VILI was highly dependent on lung strain among mammals with healthy lungs (25). Protti and colleagues used a pig model with V_T producing strains between 0.45 and 3.30 (26). Some animals increased their lung weight, with deterioration in respiratory mechanics, gas exchange, hemodynamics, and systemic inflammation, and others did not. V_T induced a strain of 2.16 in the former and 1.29 in the latter group, and a stress of 13 and 8 cm H_2O. VILI developed only when a strain greater than 1.5 to 2 was reached or overcome. Differences in intrinsic lung properties prevent from directly translating these findings to humans.

During ALI, MV can aggravate inflammation by promoting alveolar distension and cyclic recruitment–derecruitment. Positron emission tomography can be used to estimate the regional intensity of inflammation, through a quantification of metabolic activity (27). In 13 mechanically ventilated patients with ALI and relatively high PEEP, metabolic activity of normally aerated lung was positively correlated with plateau pressure, with a pronounced increase above 26 to 27 cm H_2O, and with regional V_T. Regions undergoing cyclic recruitment–derecruitment did not have high metabolic activity, which could suggest that distension is more of concern than cyclic recruitment–derecruitment. Whether the metabolic signal comes from activated neutrophils and whether it reflects stretch or preexisting inflammation are, however, unknown. The regional resolution of CT scan may not be sufficient to depict cyclic derecruitment within regions with aerated alveoli. Last, the level of PEEP was high.

Measuring alveolar recruitment at the bedside is still complex in clinical practice. In the critically ill patients, lung ultrasound (LUS) is proposed for assessing alveolar-interstitial syndrome, lung consolidation, pneumonia, pneumothorax, and pleural effusion. In a study performed in 40 patients with ALI, LUS was performed at two PEEP levels (28). An LUS score was calculated and

compared with the pressure–volume curve method with a good correlation between PEEP-induced lung recruitment measured by pressure–volume curves and ultrasound reaeration score. LUS cannot assess hyperinflation but could be used at the bedside to detect and quantify to what extent PEEP (or a recruitment procedure) reaerates the lung (i.e., induces alveolar recruitment).

RESOLUTION OF ALI AND NOVEL EXPERIMENTAL THERAPIES

Macrophages in the Resolution and Repair of ALI

Macrophages have been shown to be involved in both initiation and resolution of ALI (29); thus, the fate of macrophages during ALI is of high relevance. By tracking the kinetics of resident and recruited alveolar macrophages, an interesting study demonstrated massive accumulation of recruited macrophages shortly after the onset of LPS- or H1N1 influenza virus–induced ALI, which was followed by a rapid decline in the number of these macrophages as inflammation resolved, whereas resident macrophages showed a prolonged lifespan. Interestingly, recruited macrophages expressed high levels of the death receptor Fas, activation of which led to their apoptosis and subsequent phagocytic clearance, thereby contributing to the accelerated turnover (30).

A protective role for CC-chemokine receptor 2–expressing exudate macrophages in experimental ALI has now been established. Using bone marrow chimeric and adoptive cell transfer mouse models, it was demonstrated that CC-chemokine receptor 2^+ macrophages, by the release of IL-1 receptor antagonist, which by binding to IL-1R1 counteracts IL-1β, exhibited antiinflammatory and barrier-protective properties in *Klebsiella pneumonia*– and LPS-induced ALI (31). A protective role of a unique type of macrophages has also been described, as the antiinflammatory and immunoregulatory galectin-9 attenuated LPS-induced ALI by expanding $CD11b^+Gr\text{-}1^+$ plasmacytoid dendritic cell-like macrophages in the lung. Interestingly, galectin-9 also promoted a phenotype change of LPS-induced macrophages from $CD14^+CD11b^+Gr\text{-}1^+$ to $CD14^-CD11b^+Gr\text{-}1^+$, resulting in a suppression of the cells and thereby inhibiting inflammation (32).

Cell-based Therapies for ALI

Several studies assessed the effects of cell-based therapies in ALI. For example, the cellular processes underlying the repair and remodeling of the lung after chronic epithelial injury have now been investigated, and Clara cells were identified as critical airway progenitor cells, depletion of which resulted in squamous metaplasia and inhibited epithelial repair (33). The role and regulation of proliferation and transdifferentiation of the progenitor alveolar epithelial type II cells into type I cells in ALI was also investigated. In lung injury secondary to *Pseudomonas aeruginosa* pneumonia, an important role for the transcription factor forkhead box protein M1 (FoxM1) has been established in regulating the restoration of the alveolar epithelial barrier (34).

There has been a significant advance in stem cell research in repair and regeneration processes after ALI. For example, an interesting study investigated the effects of mesenchymal stem cells stably transfected with 7ND, a truncated, dominant-negative variant of chemokine CC-ligand 2, on bleomycin-induced ALI and found significant attenuation of lung injury as a consequence of reduced macrophage recruitment and activation (35), suggesting that inhibiting the effects of macrophages may greatly enhance the ability of stem cells to effect lung repair. An official American Thoracic Society research statement reviewed data on hematopoietic stem cell transplantation-associated idiopathic pneumonia syndrome, a noninfectious acute lung dysfunction, and discussed potential future strategies to prevent this disorder (36).

Potential Novel Therapeutic Approaches in ALI and VILI

Because inflammation, cell death, barrier dysfunction, and impaired fibroproliferation play pivotal roles in the pathogenesis of ALI and VILI, it is logical that novel experimental therapies aim to target these dysfunctions. Modulating inflammation was the goal of a study that investigated the role of Toll-like receptor 4 signaling in ALI and its resolution by assessing lung injury and repair in Toll-like receptor 4–defective mice and identified decreased biosynthesis of cysteinyl leukotriene, an agent that impairs vascular permeability, and induction of suppressor of cytokine signaling 3 expression, thereby decreasing oxidative stress and barrier dysfunction and modulating disease severity (37). The potential role of the cholinergic antiinflammatory reflex as a therapeutic mean in VILI has also been investigated. Although vagotomy exacerbated VILI in mice ventilated with high V_T, electrical and pharmacological stimulation of the vagus nerve attenuated VILI by limiting inflammation and apoptosis in an α7 acetylcholine nicotinic receptor–dependent manner (38).

Several studies targeted the impaired alveolar epithelial barrier. One study showed that mitochondrial antigens released from damaged cells that act as danger signals may act as formyl peptide receptor ligands and promote epithelial wound closure and thus may play a role in repairing barrier dysfunction (39). Another report established a protective role for poloxamer 188, a macromolecule that has been shown to have plasma membrane-sealing properties, in the alveolar epithelium of isolated rat lungs and live animals as well as injured alveolar epithelial monolayers (40). Also, the protective effects of the serine elastase inhibitor elafin on hyperoxia-induced signaling and lung growth arrest were investigated. Of note, intratracheal elafin treatment of newborn mice prevented elastin degradation, TGF-β activation, and apoptosis, thereby attenuating the fibroproliferation and structural abnormalities secondary to hyperoxia and mechanical ventilation (41).

Clinical Trials Addressing Novel Therapies for ALI

There is no effective pharmacological treatment for ALI. Search for drug therapy for this heterogeneous syndrome is often based on pathophysiological observations of the consequences of this syndrome. Several trials have shown that treatment with exogenous surfactant can result in improvement in oxygenation and synthetic surfactant containing recombinant surfactant protein C has excellent activity in animal models. A prospective randomized blinded study was performed at 161 centers (42) using this surfactant. Surprisingly, surfactant administration had no clinical benefit to patients with severe direct ALI. The unexpected lack of improvement in oxygenation, coupled with the results of *in vitro* tests, suggested that the administered suspension may have had insufficient surface activity. This trial is the most recent of a relatively long list of studies failing to show benefits of surfactant administration in adult ARDS.

Despite their controversial role, corticosteroids are often administered to patients with ARDS secondary to viral pneumonia. The impact of corticosteroid therapy on outcomes of patients having ARDS associated with influenza A/H1N1 pneumonia was assessed in two large cohort studies (43, 44). Patients from the French registry of critically ill patients with influenza A/H1N1 2009 infection and adult patients admitted to the intensive care units (ICUs) of 28 hospitals in South Korea were selected. No evidence of a beneficial effect of corticosteroids could be observed in either of the two cohorts, both using propensity-based matched pair analysis. In addition, both studies strongly suggested that corticosteroid therapy may be harmful, especially when given early. The steroid groups were more likely to have superinfection and had more prolonged ICU stays.

Because β_2-adrenergic receptor agonists accelerate resolution of pulmonary edema in experimental and clinical studies (45), the hypothesis that aerosolized albuterol may accelerate the resolution of ALI was tested a multicenter, randomized, placebo-controlled clinical trial (46). Unfortunately, it did not improve clinical outcomes. Recently another large randomized controlled trial using intravenous salbutamol for the same indication was stopped for safety concerns (47). Routine use of β_2-agonist therapy for the treatment of ALI cannot be recommended.

Statins are a potential new therapy for ALI because they modify many of the underlying processes important in ALI. A randomized, double-blinded, placebo-controlled trial in patients with ALI (48) compared 80 mg simvastatin or placebo: ICU mortality was 30% in both groups. Simvastatin significantly decreased BAL IL-8, and plasma C-reactive protein decreased in both groups but failed to achieve significance in the placebo group.

CHALLENGES IN ALI MANAGEMENT, MV, AND CRITICAL CARE MEDICINE

Pneumonia

Treatment with inhaled corticosteroids for patients with chronic obstructive pulmonary disease (COPD) has been shown to be associated with an increased incidence of pneumonia. The effects of prior use of inhaled corticosteroids for patients with COPD hospitalized with pneumonia were retrospectively evaluated (49). The study looked at 8,271 with, and 7,497 with no use of inhaled steroids, all admitted for COPD and pneumonia. A benefit of prior steroid treatment was observed, with a significant difference for 90-day mortality, also confirmed by regression analyses at 30 days.

Early-onset pneumonia seems frequent after out-of-hospital cardiac arrest and resuscitation in the ICU. Therapeutic hypothermia could play a role in this high incidence (50). A retrospective analysis of a large cohort study of patients successfully resuscitated after out-of-hospital cardiac arrest and admitted in two ICUs disclosed therapeutic hypothermia as the single independent risk factor of early-onset pneumonia (odds ratio, 1.90; 95% confidence interval, 1.28–2.80). It was associated with prolonged respiratory support and ICU stay but did not seem to significantly influence ICU mortality.

The attributable mortality of ventilator-associated pneumonia (VAP) is debated. Data from randomized prevention studies suggest that it may be around 10% (51). The attributable mortality of VAP was reexamined in a large multicenter cohort (4,479 patients) using statistical methods from the field of causal inference (52): 15% of patients acquired at least one episode of VAP. The authors estimated that 4.4% (95% confidence interval, 1.6–7.0%) of the deaths in the ICU on Day 30 are attributable to VAP. ICU mortality attributable to VAP was calculated to reach about 1% on Day 30.

Underinflation of the tracheal cuff frequently occurs in critically ill patients and may constitute a risk factor for microaspiration of contaminated oropharyngeal secretions and gastric contents, and could play a role in the pathogenesis of VAP. The impact of continuous control of tracheal cuff pressure on microaspiration of gastric contents was evaluated in a randomized controlled trial of 122 patients evaluating the presence of pepsin in tracheal secretions (53). Patients with abundant microaspiration (18 vs. 46%), bacterial concentration in tracheal aspirates, and VAP rate (9.8 vs. 26.2%) were all lower in the intervention group. In an editorial (54), Bonten discussed the concept of the gastropulmonary route for infection, which has generated four types of intervention: modulation of gastric colonization with different approaches of stress ulcer prophylaxis, the semirecumbent patient position, subglottic aspiration, and maintaining tracheal cuff pressure.

Weaning

A new classification of weaning based on the duration of liberation of MV has been proposed, distinguishing simple, prolonged, and difficult weaning (55). A secondary analysis of the international MV study included 2,714 patients (56). Simple weaning was observed in 55% of the patients, difficult weaning in 39%, and prolonged weaning in 6%. After adjusting on major risk factors for prolonged duration of ventilation and death, it was shown that the daily probability of death during weaning was not modified until Day 7 (the limit for difficult weaning), at which point it increased to 12.1%.

Noninvasive ventilation (NIV) has been proposed an early weaning/extubation technique in difficult-to-wean patients with chronic hypercapnic respiratory failure. In 13 ICUs, 208 patients intubated for acute respiratory failure who failed a spontaneous breathing trial were assigned to conventional invasive weaning group, extubation followed by standard oxygen therapy, or NIV (57). NIV was permitted as rescue therapy. Reintubation rates were 30, 37, and 32% for invasive weaning, oxygen therapy, and NIV groups. No significant outcome difference was observed between groups.

Diaphragmatic Weakness

Controlled MV has been shown to promote diaphragm atrophy (58). In a new study (59), phrenic nerve stimulation showed a progressive decrease in force during MV, with a mean reduction of $32 \pm 6\%$ after 6 days. Diaphragmatic biopsies obtained during thoracic surgery and from brain-dead organ donors were also analyzed. Longer periods of MV were associated with significantly greater ultrastructural fiber injury, decreased cross-sectional area of muscle fibers, increased ubiquitinated protein, higher expression of p65 nuclear factor-κB, and greater levels of proteases in the diaphragm.

Venous Thromboembolism

Deep venous thromboembolism is difficult to diagnose in critically ill patients, although it may increase morbidity and mortality. The cost-effectiveness of two strategies to reduce morbidity from venous thromboembolism was compared: weekly compression ultrasound screening plus investigation for clinically suspected deep venous thromboembolism (case finding) was compared with case finding alone (60). Programs achieving increased adherence to best-practice venous thromboembolism prevention were cost-effective. Resources should therefore be targeted at optimizing thromboprophylaxis.

OUTCOME AND QUALITY IMPROVEMENT

Outcome Studies

In terms of MV, there is a growing interest in the long-term outcome of patients submitted to MV. Elderly survivors of MV are interesting for follow-up, because their outcome is often poor after hospitalization. A retrospective population-based longitudinal cohort study of Medicare beneficiaries aged 65 years and older (61) found that the level of disability was substantially higher for a patient who survived after hospitalization with MV compared with an otherwise identical patient who survived hospitalization without MV or who was not hospitalized.

Outcome studies are often used to benchmark the results of different groups of ICUs or countries. Two large cohorts of critically ill patients hospitalized in 137 ICUs in the United States and in 160 in the United Kingdom were compared (62). The United States has seven times as many ICU beds per capita as the United Kingdom. United Kingdom (vs. United States) admissions are less likely to come from the emergency room, they had longer

hospital stays before admission, fewer were very old, and they had a higher severity of illness. Discharge practices were also different, making difficult direct comparisons of hospital death rates. This study based on two countries with extremely different ICU systems shows that interpretation of between-country hospital outcomes is confounded by differences in case mix, processes of care, and discharge practices.

The question of the influence of insurance coverage on the outcome of critically ill patients was raised by Lyon and colleagues (63). Uninsured patients were compared with those with private insurance in a retrospective cohort study using Pennsylvania hospital discharge data with clinical risk adjustment (138,720 critically ill adult patients). They found that the uninsured have a higher mortality and receive fewer procedures when compared with privately insured patients. Differences were not attributable to hospital-level effects.

Quality Improvement

Providing relatives of patients dying in the ICU with a brochure on bereavement and using a proactive communication strategy may lessen the burden of bereavement. A cluster-randomized trial evaluated the effectiveness of a quality-improvement intervention to improve ICU end-of-life care (64). The intervention targeted clinicians' education, local champions, academic detailing, clinician feedback of quality data, and system supports. There was no change in family or nurse satisfaction, no improvement in quality of dying, and no change in ICU length of stay. Improving end-of-life care may require interventions with more direct contact with patients and families.

Checklists may reduce errors of omission for critically ill patients, but their real efficacy is debated. The usefulness of adding prompting to a checklist was tested in a medical ICU (65). Intervention team physicians were prompted to address six parameters from a daily rounding checklist, whereas a second team used the identical checklist without prompting. The stand-alone checklist had no effect compared with historical control subjects. Checklist-based prompting, however, improved several processes of care, with a possible effect on mortality and length of stay. The manner in which checklists are implemented seems of great consequence.

HISTORICAL PERSPECTIVES

Marini reviewed the concept of auto-PEEP (66) and dynamic hyperinflation, which has changed the practice of MV in patients with obstructive lung disease. This concept is still relevant today, and can affect hemodynamics, work of breathing and dyspnea, patient–ventilator synchrony, or monitoring (67). An influential pioneer of critical care medicine, Dr. Weil,[†] described the historical evolution of Critical Care Medicine in relationship to its predecessor, Intensive Therapy (68). The review starts in the 1850s, with Florence Nightingale. The review insists on the technology that increasingly distinguished the specialty and the fact that the techniques of critical care medicine have been extended to emergency departments and even out-of-hospital emergency medical providers.

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

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