Update in Critical Care 2015

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Abstract

This review documents important progress made in 2015 in the field of critical care. Significant advances in 2015 included further evidence for early implementation of low tidal volume ventilation as well as new insights into the role of open lung biopsy, diaphragmatic dysfunction, and a potential mechanism for ventilator-induced fibroproliferation. New therapies, including a novel low-flow extracorporeal CO_2 removal technique and mesenchymal stem cell–derived microparticles, have also been studied. Several studies examining the role of improved diagnosis and prevention of ventilator-associated pneumonia also showed relevant results. This review examines articles published in the *American Journal of Respiratory and Critical Care Medicine* and other major journals that have made significant advances in the field of critical care in 2015.

Keywords: critical care; acute respiratory failure; mechanical ventilation; sepsis

Critical illness is among the leading medical, social, and economic burdens in the developed world. This article focuses on critical care research published in the *American Journal of Respiratory and Critical Care Medicine* and other journals in 2015 and will update the reader on acute respiratory failure (including use of high-flow nasal cannula, noninvasive ventilation [NIV], acute respiratory distress syndrome [ARDS], diaphragm dysfunction, weaning, and extracorporeal approaches), infections in the critically ill (including ventilator associated pneumonia [VAP], community-acquired pneumonia [CAP], and sepsis) and intensive care unit (ICU) organizational challenges.

Acute Respiratory Failure

High-Flow Nasal Cannula

Over the past 2 decades, systems to deliver heated and humidified oxygen at high flows through nasal cannula have been developed as an alternative to standard oxygen delivery systems (i.e., Venturi masks or nasal prongs) and NIV. In 310 patients with acute hypoxemic respiratory failure without hypercapnia, the use of high-flow humidified oxygen via nasal cannula (HFNC), standard oxygen, or NIV were compared in a randomized clinical trial (1). The use of HFNC resulted in a similar rate of endotracheal intubation but significantly increased ventilator-free days and reduced mortality in the ICU and at 90 days when compared with either NIV or standard oxygen (1). In a *post hoc* adjusted analysis that included the 238 patients with severe initial hypoxemia (Pa_{O_2}:$FI_{O_2} \leq 200$ mm Hg), the intubation rate was significantly lower among patients who received HFNC than among patients in the other two groups (1). The reduction in intubation rate in the severely hypoxemic patient subgroup probably explains the lower mortality rate encountered at 90 days postrandomization in the HFNC group as compared with standard oxygen and NIV groups.

Among a growing list of indications, there is increasing interest in the use of HFNC to provide apneic oxygenation during laryngoscopy. This preventive approach aims to increase the lowest arterial oxygen saturation experienced by patients

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undergoing endotracheal intubation. Until now, only anecdotal case reports, case series, and some "before and after" studies have provided an evidence base to guide the use of HFNC in adults requiring endotracheal intubation for respiratory failure. In an open-label randomized trial reported in the journal, apneic oxygenation did not increase lowest arterial oxygen saturation during endotracheal intubation of critically ill patients compared with usual care (2). A separate multicenter, randomized, open-label, controlled trial in 2015 found similar results (3).

NIV

NIV may improve the outcome of patients who succeed in NIV by avoiding intubation but may worsen outcome by delaying intubation in those who fail an NIV attempt (4). Data on current NIV use indicates better patient selection and a reduced NIV failure rate (5). In immunocompromised patients with acute nonhypercapnic respiratory failure, Lemiale and colleagues reported that early NIV compared with oxygen therapy alone did not reduce 28-day mortality (6). Nevertheless, because the observed mortality rate was lower than expected, the study power was limited.

ARDS

New insights into disease pathogenesis. Despite the widespread adoption of low tidal volume (V_T) ventilator strategies, investigators continue to report early fibroproliferative activity in lungs of patients with ARDS (7, 8), a finding that has historically been associated with a poor prognosis with high mortality and/or prolonged ventilator dependence (9). Recent evidence demonstrates that mechanical ventilation, particularly where significant overstretch occurs, may drive the pathogenesis of fibrosis in patients with ARDS (10). Zhang and colleagues (11) demonstrated the role of midkine, a heparin-binding cytokine and growth factor associated with inflammation and tissue repair, on lung fibrosis. Midkine plasma levels in 17 mechanically ventilated patients with ARDS were threefold higher than in healthy volunteers, whereas cyclic mechanical stretch applied to cultured human lung epithelial cells induced epithelial-to-mesenchymal transition mediated by the midkine–Notch2–angiotensin-converting enzyme signaling pathway (11). Midkine knockout mice injured with acid aspiration and mechanical ventilation exhibited less pulmonary fibrosis.

Levels of the soluble form of the receptor for advanced glycation end-products (sRAGE) are elevated during ARDS and correlate with severity and prognosis (12). In a mouse model of acid-induced lung injury, and in 30 patients with ARDS, the rate of alveolar fluid clearance was inversely correlated with sRAGE levels in plasma and bronchoalveolar fluid (13). Therefore, sRAGE appears to be a valid marker of alveolar fluid clearance during ARDS.

Mortality in ARDS is strongly linked to nonpulmonary organ failure, yet the specific contribution of organ failure to ARDS mortality has not been evaluated (14). Recent findings support the idea that ARDS is an independent risk factor for delirium in mechanically ventilated patients, whereas at least some of the short-term mortality from ARDS may be attributable to this acute brain dysfunction (15).

Ventilation strategies. Currently, mechanical ventilation strategies in patients with ARDS consist of low V_Ts and high positive end-expiratory pressure (PEEP). However, the effects of increasing PEEP on outcomes are critically dependent on its effects on oxygenation (16). The beneficial effects of higher PEEP levels appear to be circumscribed to those patients with the most severe hypoxemia or to those having a significant oxygenation response to high PEEP (16, 17). It is now evident that the sooner this protective strategy is applied, the better the survival (18, 19). The principle is to minimize ventilator-induced lung injury by titrating V_T according to predicted body weight. On the basis of the hypothesis that in patients with ARDS, the proportion of lung available for ventilation is markedly decreased, Amato and colleagues proposed normalization of V_T to the respiratory system compliance rather than predicted lung volume (20). Using the combined individual data of nine randomized trials, they found that the ratio of V_T to respiratory system compliance (also called driving pressure, and easily measured on the ventilator) was the ventilation variable that best stratified mortality risk (20). However, the use of driving pressure is yet to be subjected to a high-quality randomized controlled trial confirming its clinical utility and safety.

Potential new therapies. There is a growing interest in the use of mesenchymal stem cells (MSCs) as a treatment for ARDS. In the multicentre, open-label, dose-escalation, START (STem cells for ARDS Treatment) trial, nine patients with moderate-to-severe ARDS tolerated treatment with either low-, intermediate-, or high-dose MSCs (21). Interestingly, in a mouse model of bacterial pneumonia, human MSC-derived microvesicles reduced lung inflammation and enhanced bacterial clearance in a similar manner to MSCs themselves, by enhancing monocyte phagocytosis and improving epithelial cell bioenergetics (22). MSCs are capable of transferring mitochondria to epithelial cells and macrophages (23). In addition, MSCs secrete RNA containing exosomes, growth factors, cytokines, and lipid mediators that diminish inflammation and enhance bacterial clearance and tissue repair (23).

Progress in the understanding of ARDS pathophysiology and management requires new trials. New findings suggest that outcomes of patients enrolled in trials focusing on mechanical ventilation could differ significantly from nonenrolled but eligible patients (24). Nonenrollment in the OSCILLATE trial (Oscillation for ARDS Treated Early Trial) was associated with increased risk of mortality. In addition, eligible but nonenrolled patients ventilated with conventional mechanical ventilation had less severe ARDS than study patients, whereas patients treated with high-frequency oscillation outside the trial had more severe ARDS than study patients (24). This study points to the need for prospective tracking and transparent reporting of this eligible but not enrolled cohort as part of trial management (25).

Ventilator-induced Diaphragm Dysfunction

The relationship between mechanical ventilation and diaphragm atrophy has been established in several human studies. Using daily diaphragm ultrasound, in a large-scale observational study, Goligher and colleagues demonstrated diaphragm atrophy by reporting decreases in diaphragmatic thickness over time in ventilated patients (26). Moreover, they correlated these changes with the levels of inspiratory effort. This important finding could be helpful to better titrate

the amount of ventilator assistance (27). From a more fundamental aspect, the activation of the ubiquitin-proteasome pathway has been involved in the development of contractile weakness during mechanical ventilation (28). This may indicate protein balance as an important therapeutic target to ameliorate diaphragm muscle weakness in critically ill patients (29).

Weaning from Mechanical Ventilation

Thille and colleagues identified ineffective cough, prolonged duration of mechanical ventilation, and severe systolic left ventricular dysfunction as stronger determinants of extubation failure than delirium or ICU-acquired weakness (30). They also observed that only one-third of patients who failed extubation were considered at high risk for extubation failure (30). This is in line with another study designed to investigate the agreement between physicians, nurses, and patients in the subjective assessment of breathlessness with the Numerical Rating Scale score at the end of a spontaneous breathing trial (SBT) (31). Although there were no major differences in objective assessments of respiratory function in patients with moderate or severe breathlessness, no apparent relationship between breathlessness during the SBT and extubation outcome was observed either (31). This underlines the need for improved accuracy in the evaluation of patient dyspnea and discomfort (32). The use of another observation scale incorporating respiratory and behavioral signs, such as the Respiratory Distress Observation Scale, could be useful in this context (33).

In difficult-to-wean patients, cardiac preload independence (documented by the absence of increase in cardiac output during a passive leg raising maneuver) was significantly associated with the occurrence of weaning-induced pulmonary edema (34). Whether the effect of a preload dependence-directed fluid removal therapy can make the weaning process faster (35), as has been demonstrated for the B-type natriuretic peptide (36), should now be investigated.

Mehta and colleagues reported on the use, timing, and outcomes of tracheostomy in 1,352,432 patients (9% of the overall ventilated population) from 1993 to 2012 in the United States (37). They observed an increase in tracheostomies performed through 2008, rising from 6.9% of mechanically ventilated patients in 1993 to 9.8% in 2008, with a yearly decline thereafter. Over the 2 decades there were shifts toward earlier tracheostomy (median, 11 d in 1998 vs. 10 d in 2012), shorter hospital length of stay (median, 39 d in 1993 vs. 26 d in 2012), more frequent discharges to long-term care facilities (40.1 vs. 71.9%), and fewer discharges from hospital to home. Determining the optimal timing for tracheostomy is a challenging clinical decision, as is appropriate discharge to a post ICU facility (38). A metaanalysis pooling 13 trials (2,434 patients) showed that all-cause mortality in the ICU was not significantly lower in patients assigned to early versus late or no tracheostomy (39), although the incidence of VAP was lower in the early group.

Extracorporeal Approaches

The use of extracorporeal membrane oxygenation (ECMO) for both respiratory and cardiac failure is evolving rapidly. Despite major technologic advances, ECMO is still burdened with a high rate of complications (40). Akin to other areas of medicine (41, 42), there are now consistent data demonstrating a link between higher annual ECMO patient volume and lower case-mix–adjusted hospital mortality rate: patients receiving ECMO at hospitals with more than 30 adult ECMO cases per year had significantly lower odds of mortality (43). Whether 30 ECMO cases per year is an appropriate benchmark of a quality service is not a straightforward decision, because other predictors of good outcomes are not yet defined (44).

Extracorporeal carbon dioxide removal ($ECCO_2R$) has been proposed as a means to facilitate ultraprotective low V_T mechanical ventilation. An innovative and minimally invasive $ECCO_2R$ technique, namely respiratory electrodialysis, has been developed and tested successfully in swine (45). The respiratory electrodialysis gathers three devices in one: hemofilter, membrane lung, and an electrodialysis cell. It is designed to regionally convert bicarbonate to CO_2 before entering the membrane lung, enhancing membrane lung CO_2 extraction. If the results are confirmed in humans, it could offer the opportunity for a low blood flow $ECCO_2R$ device, with less invasive cannulation, to be applied as an adjunct to mechanical ventilation in patients with ARDS or as a potential alternative to invasive mechanical ventilation for the support of hypercapnic respiratory failure (46).

Infections in the Critically Ill

VAP Prevention and Diagnosis

In patients receiving invasive mechanical ventilation, colonization of the lower respiratory tract with oropharyngeal pathogens occurs rapidly after intubation. Modifications of the endotracheal tube cuff using polyurethane, a conical shape, or both, aimed at preventing the formation of porous longitudinal folds and achieving a more consistent seal with the trachea, have demonstrated promise in preclinical studies (47). A multicenter, open-label study (48) failed to show any advantage of the new cuff design or composition. The results indicated that colonization of the lower respiratory tract on Day 2 after intubation occurred in approximately two-thirds of all study patients, whereas only 14.4% of these patients developed subsequent VAP (47).

Several other measures aimed at preventing heavy colonization of the lower respiratory tract have been studied, including subglottic secretion drainage, head-of-bed elevation to 30 to 45°, selective digestive decontamination, chlorhexidine oral care, and probiotics (49). Branch-Elliman and colleagues (50) performed a cost–benefit analysis using model inputs from the medical literature and the U.S. Department of Labor to determine the preferred VAP prevention strategy. The preferred strategies included the use of subglottic suction endotracheal tubes, probiotics, and the Institute for Healthcare Improvement VAP Prevention Bundle. The accompanying commentary noted that increasing rates of VAP attributed to antibiotic-resistant bacteria may make more expensive preventative measures cost effective (51).

To improve the reliability of VAP surveillance data as an indication of quality improvement, the U.S. National Healthcare Safety Network has proposed an alternative definition, termed ventilator-associated events (VAEs) (52). A key entity within this new definition is the ventilator-associated condition, a respiratory deterioration identified on the basis of ventilator settings

that may in some cases subsequently be classified as infection-related ventilator-associated condition, or as possible or probable VAP. Heretofore, evidence has been limited as to whether, how, and to what extent VAEs are preventable, because the overlap between VAEs and VAP seems very limited (53, 54). Klompas and colleagues (55) performed a multicenter study on the preventability of VAE by using SBTs and spontaneous awakening trials. In ICUs adopting the intervention, they observed reduced duration of mechanical ventilation, shortened length of ICU and hospital stay, and lowered incidence of VAE per episode of mechanical ventilation, without a significant reduction of VAP incidence or an overall effect on in-hospital mortality (55, 56). However, the improved outcomes may have been related to an improving baseline outcome (i.e., "secular" trends) or the complex social and environmental effects of bringing collective attention to a recognized clinical challenge (i.e., a Hawthorne effect) (57).

Rapid identification of VAP and accurate selection of antimicrobial agents are important clinical goals (58). A significant proportion of patients may develop a bacterial infection before meeting the criteria for clinical diagnosis despite a substantial microbiological burden. Douglas and colleagues (59), in a prospective single-center cohort study, examined the role of surveillance with standard laboratory culturing versus a novel automated microscopy method with same-day phenotypic antibiotic susceptibility analysis to analyze lower respiratory tract specimens obtained before VAP clinical diagnosis. The results of clinical culture testing gave rise to changes in empiric antimicrobial prescribing for two of five patients (40%) found to be microbiologically positive for a VAP-associated pathogen but negative for VAP clinical diagnosis. In comparison with clinical culture results, pathogen identification by automated microscopy was both sensitive (100%) and specific (97%), and it was quick (4.5 h).

CAP

Empiric antibiotic therapy often is initiated when patients are critically ill and physicians are unable to distinguish systemic inflammatory response syndrome (SIRS) from infection. However, there is hope that systems biology approaches using high-throughput technologies will allow the development of better sepsis biomarkers (60). Expression profiling is one such rapid method for the unbiased screening of thousands of mRNAs in a single assay. In this respect, Scicluna and colleagues (61) defined a gene signature profile of 78 genes that distinguished patients with severe CAP from patients treated for pneumonia but subsequently found not to have had pneumonia (on the basis of a *post hoc* review of all available clinical, radiologic, and microbiologic evidence). Of the initial set of 78 selected gene transcripts, a ratio of two gene transcripts, FAIM3:PLAC8, proved to be the most robust discriminator between patients with and without severe CAP. The clinical utility of this gene array of the leukocyte host response to distinguish CAP from other causes of respiratory failure still has to be evaluated with sufficiently powered prospective trials (61).

Sepsis

A connection between patients' susceptibility to sepsis and alterations in the diverse microbial ecosystems on and in the human body (termed the microbiome) has been reinforced by a study of more than 10,000 hospital inpatients, stratified according to estimated degrees of intestinal dysbiosis (perturbation of the microbiome) (62). A strong and consistent dose–response relation was uncovered between disorder of the microbiome and subsequent development of severe sepsis. Further research is needed to define the natural history of microbiome recovery after hospitalization, to determine whether recovery can be accelerated (eg, via probiotics or fecal microbiota transplantation) and whether this can affect long-term outcomes.

Optimized antibiotic therapy is an intervention likely to improve treatment outcomes in severe sepsis (63). β-Lactam antibiotics display time-dependent activity where bacterial killing and treatment efficacy correlate with the duration of time that free plasma drug concentrations remain above the minimum inhibitory concentration of the offending pathogen. Dulhunty and colleagues (64) conducted a randomized controlled trial comparing the use of continuous infusion versus intermittent dosing of β-lactams in patients with severe sepsis. Disappointingly, the authors found no difference in a range of relevant clinical outcomes, including 28- and 90-day survival, ICU-free days, clinical cure defined as objectively as possible, Day 14 organ failure–free days, and bacteremia duration for the small patient subset with bloodstream infections (64). Of note, other clinical studies that have demonstrated benefit with continuous infusion dosing (65) recruited critically ill patients with conserved renal function (because patients with reduced drug clearances are less likely to manifest subtherapeutic antibiotic exposures) and isolated pathogens with high minimum inhibitory concentrations.

The fact that *Candida* infections are under-recognized and the lack of sensitivity of culture methods would suggest a possible role for empirical antifungals, particularly in patients with recent exposure to broad-spectrum antibiotics or immunosuppression. In an observational longitudinal study of 1,491 severely ill ICU patients, results showed that empiric antifungal therapy had no effect on 30-day mortality or occurrence of invasive candidiasis in nonneutropenic and nontransplanted ICU patients (66). This study (66) and others (67) highlight the challenge of demonstrating the benefit of antifungals in the absence of proven invasive candidiasis, even in ICU patient populations with multiple risk factors.

Catheter-related infections (CRIs) are associated with substantial morbidity and mortality in the critically ill, despite efforts to decrease infection rates with the use of central line intervention "bundles." Ethanol lock solutions, instilled as an antimicrobial solution into the lumen of the catheter, demonstrate efficacy on biofilms (a permanent source of bacteremia) *in vitro* and when used in a prophylactic fashion for the management of catheter-related bloodstream infection (68). Souweine and colleagues (69) evaluated the efficacy of a 2-minute ethanol lock (60% ethanol solution) to prevent CRI in 1,460 adult ICU patients who were undergoing insertion of a nontunneled dialysis catheter for dialysis, plasma exchange, or both. Overall, 1.6% of subjects in the control group and 2.3% of subjects in the ethanol lock group experienced CRI (a nonsignificant difference), whereas there was an increased incidence of catheter-related clinical sepsis in the ethanol group (0.5 and 1.8 events per

1,000 catheter-days; $P = 0.03$) (69). These results fail to suggest any benefit of ethanol lock in ICU patients and may challenge the use of other antimicrobial locks to prevent CRI in critically ill patients.

Many noninfectious conditions can result in the development of SIRS, but the SIRS criteria have been commonly used in sepsis bundles and as entry criteria for clinical trials. The need for two or more SIRS criteria to define severe sepsis could exclude a significant portion of patients with similar demographic characteristics and outcomes (70). On the other hand, Churpek and colleagues found that nearly half of all patients hospitalized on the wards met SIRS criteria at least once during their stay (71). The study strongly suggests that it is impractical to use the presence of two or more SIRS criteria in isolation as a screening tool for sepsis (72).

ICU Organization

Spending on hospital admissions involving intensive care accounts for nearly half of all hospital costs, making ICU admissions an important focus for reducing overall expenditures (73). Indeed, there is good evidence that intensive care is overused in the United States (74). Hospitals vary widely in their use of the ICU without apparent differences in mortality, and transient reductions in the availability of ICU beds lead to fewer ICU admissions without apparent harm to patients. Within the United States, there is substantial unexplained variation in the use of ICUs (75), the demand for which is growing rather than contracting (76).

One way of potentially reducing costs is the use of high-dependency units (HDUs, also termed step-down or intermediate care). HDUs provide a level of care between ICU and general ward care. Given the high costs of care in ICUs, understanding the current utilization of HDU beds is essential to ultimately improving patient flow and efficiency of care. Wunsch and colleagues (77) studied provision and use of HDU care in geographically separate units and determined that their use was associated with a decrease in delayed discharge from the ICU. This is important, as HDU beds have the potential to improve inpatient throughput by appropriately matching care to patients' needs. We know that inattention to patient flow leads to ICU bed rationing, and improving flow builds capacity without building beds (78).

Another contributor to high costs is physician staffing. Indeed, most studies suggest that intensivist staffing is associated with lower mortality in the ICU, and the major critical care professional societies have called for an increase in the intensivist supply (74). The view that exposure to trained intensivists is associated with improved outcomes for patients in the ICU has led to calls for intensivist staffing at night (79). However, multicenter observational studies (80) and one single-center randomized trial (81) found no benefit from maintaining such staffing through the night. Furthermore, in an examination of ICU discharges in 40 ICUs in Australia and New Zealand (82) (where nighttime coverage in the ICU is provided by ICU fellows and residents in training), after adjustment for patient characteristics including limitations on life support, there was no evidence of a heightened mortality risk among nighttime versus daytime discharges. ■

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