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ABSTRACT & COMMENTARY

Early Initiation of Continuous Renal Replacement Therapy May Reduce Mortality in Patients Who Require Dialysis

By Samuel Nadler, MD, PhD

Critical Care, Pulmonary Medicine, The Polyclinic Madison Center, Seattle; Clinical Instructor, University of Washington, Seattle

Dr. Nadler reports no financial relationships relevant to this field of study.

SYNOPSIS: Initiation of continuous renal replacement therapy for patients with Kidney Disease: Improving Global Outcomes stage 2 renal failure reduced 90-day all-cause mortality.

SOURCE: Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs. delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: The ELAIN Randomized Clinical Trial. *JAMA* 2016;315:2190-2199.

The decision to start continuous renal replacement therapy (CRRT) in critically ill patients requires careful analysis of risks and benefits. The timing of initiating CRRT remains unclear. The ELAIN trial sought to inform this decision in a single center, randomized trial of early vs. late initiation of CRRT. Inclusion criteria were: Kidney Disease: Improving Global Outcomes (KDIGO) stage 2 acute kidney injury (AKI) (i.e., two-fold increase in serum creatinine or urine output < 0.5 mL/kg/hr for > 12 hours), neutrophil gelatinase-associated lipocalin (NGAL) > 150 ng/mL, 18-90 years of age, and one additional condition such as severe sepsis, vasopressor requirement, refractory fluid overload, PaO_2/FiO_2 < 300, or increase in Sequential Organ Failure Assessment (SOFA) score > 2. Patients who presented with chronic kidney disease, dialysis, previous AKI, pregnancy, or kidney transplantation were excluded.

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[INSIDE]

Comparing Laryngoscopy Techniques page 75

Chaplain-assisted Spiritual Care page 76

Categorizing ARDS page 78

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Patients were randomized to early vs. late initiation of CRRT. Early CRRT started within eight hours of diagnosis of KDIGO stage 2 AKI. Delayed CRRT started within 12 hours of patients progressing to KDIGO stage 3 AKI (urine output < 0.3 mL/kg/hr for 24 hours and/or three-fold increase in serum creatinine or serum creatinine > 4 mg/dL with an acute increase of at least 0.5 mg/dL within 48 hours), or if any of the criteria for renal replacement therapy (RRT) were met: blood urea level > 100 mg/dL, potassium > 6 mEq/L and/or with ECG changes, magnesium > 8mEq/L, urine output < 200 mL per 12 hours, or organ edema resistant to diuretics. Once started, all patients received identical prescriptions for CRRT that continued until urine output exceeded 400 mL/24 hours without diuretic treatment or 2,100 mL/24 hours with diuretics.

The primary endpoint was 90-day mortality with secondary outcomes, including 28- and 60-day mortality, SOFA scores, recovery of renal function, need for hemodialysis after day 28, duration of CRRT, hospital length of stay (LOS), and biologic markers of inflammation. Overall, 231 patients were included in the intention-to-treat analysis, although 11 patients in the delayed group did not receive dialysis. Many patients were recruited after surgical procedures, including coronary artery bypass grafting (CABG), valve replacements, trauma, bowel resection, and liver transplantation. Most were mechanically ventilated and required vasopressors. Early initiation of CRRT was associated with decreased 90-day mortality (39.3% vs. 54.7%; odds ratio, 0.66; $P = 0.03$). In contrast, 28-day and 60-day mortality were not statistically different between the early and late groups, although there was a trend toward benefit for the early group. There were reductions in hospital LOS and duration of mechanical ventilation for those who were randomized to early initiation of CRRT.

■ COMMENTARY

The ELAIN trial was published just before the AKIKI study group published a similar study[1] with contrasting results, and any analysis should consider both studies. The AKIKI study was a multicenter, randomized trial of 630 patients that examined when to start CRRT. In that trial, early initiation occurred within six hours of the diagnosis of stage 3 AKI while delayed initiation occurred if oliguria/anuria lasted for > 72 hours or severe electrolyte abnormalities occurred. In the AKIKI trial, no benefit was seen in 28- or 60-day mortality, although patients in the early initiation arm did exhibit higher rates of catheter-related infections.

Three factors may explain the differences between the ELAIN and AKIKI results. First, the patient populations in each study were different. As noted, much of the recruitment for the ELAIN trial involved post-surgical patients, while the AKIKI trial involved primarily medical patients. Although many co-morbidities were similar, surgical and medical ICU patients often follow different hospital courses. Many of the AKIKI patients in the delayed initiation group never received dialysis, and it is likely many of the patients in the early initiation group would not have required CRRT. In contrast, the inclusion of NGAL criteria in the ELAIN trial was intended to improve discernment for those who would ultimately require CRRT. Second, the ELAIN trial started CRRT sooner than AKIKI. The "delayed" group in ELAIN started at a similar time to the "early" group in AKIKI. A subgroup analysis of the ELAIN trial comparing patients in the delayed arm that started CRRT due to stage 3 disease (similar to AKIKI "early" group) and patients that required CRRT for electrolyte disturbances (similar to the AKIKI "delayed" group) found no difference in duration of CRRT, ICU, or hospital stay. Thus, earlier initiation of CRRT may have an effect on outcomes. Third, while ELAIN reported a 90-day mortality benefit for early initiation of CRRT, both studies failed to show 28- and 60-day mortality benefits. It is unclear why there was only a 90-day mortality benefit as neither trial seemed to show less dependence on long-term dialysis, although the ELAIN trial indicated less dependence when excluding patients who died during the trial.

Comparing the ELAIN and AKIKI trials informs the decision when to start CRRT in the ICU. In patients who will require CRRT, early initiation may have benefits. However, identifying these patients is challenging as commonly used endpoints such as KDIGO stage are not reliable predictors. Clinical judgment and patient-specific factors remain important in the risk-benefit analysis of patients presenting with AKI in the ICU. ■

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ABSTRACT & COMMENTARY

A Prospective, Randomized Comparison of Video and Direct Laryngoscopy

By Alexander Niven, MD

Senior Associate Consultant, Division of Pulmonary/Critical Care Medicine, Mayo Clinic, Rochester, MN

Dr. Niven reports no financial relationships relevant to this field of study.

SYNOPSIS: In the largest prospective, randomized trial to date, use of video laryngoscopy improved glottic visualization but did not increase procedural success or decrease complications compared to direct laryngoscopy in medical ICU patients.

SOURCE: Janz DR, Semler MW, Lentz RJ, et al. Randomized trial of video laryngoscopy for endotracheal intubation of critically ill adults. *Crit Care Med* 2016;44:1980-1987.

Intubation in the critically ill is a high-risk procedure, with complication rates that remain unacceptably high despite significant advances over the past decade. The incidence of a difficult airway in ICU patients is approximately 10%, and prospective identification of these patients remains challenging. Increasing availability and experience with video laryngoscopy (VL) has led many to suggest that these tools should be preferentially used for endotracheal intubation in the ICU. Uncontrolled series and small prospective, randomized trials have suggested that VL provides a higher rate of first pass success than direct laryngoscopy (DL) in the critically ill, but this topic remains the subject of considerable debate.

The FELLOW investigators conducted a single center, prospective, randomized trial to compare the rate of first attempt success using VL and DL in critically ill patients intubated by pulmonary/critical care fellows in the medical ICU. Of the first 196 patients who met inclusion criteria, 23 (12%) were excluded because clinical urgency precluded randomization and 18 (9%) because the treating clinicians felt video or fiberoptic intubation was warranted. The remaining 150 patients were randomized to VL or DL for their first laryngoscopy attempt in an intention-to-treat analysis. Operators could select their preferred airway tools and medications within these arms, and all procedures were supervised by a staff intensivist or anesthesiologist.

There were no significant differences between study groups. Most patients were intubated for hypoxic or hypercarbic respiratory failure in the setting of sepsis or septic shock, and approximately one-third were obese (body mass index [BMI] > 30 kg/m^2). Fellows performing the procedure were experienced (≥ 47 prior intubations), although operators performing VL had performed less of these procedures (median of 10 cases, IQR 5-22). Almost all VL procedures were performed using the McGrath MAC (98.6%), and most patients received etomidate and either rocuronium or succinylcholine.

There was no difference in the first attempt success rate between VL and DL groups (68.9% vs. 65.8%, odds ratio, 1.15; 95% confidence interval, 0.58-2.28; P = 0.68), even when adjusted for operator experience, APACHE II score, and BMI. Most patients with an unsuccessful first intubation attempt were intubated using either an endotracheal tube introducer (SunMed Introducer Adult Bougie with Coude Tip) or VL. Use of VL significantly improved glottic visualization (P = 0.001) compared to DL, but time to intubation, lowest oxygen saturation and percent change, procedure-related complications, duration of mechanical ventilation, length of stay, and mortality were no different.

■ COMMENTARY

VL has provided consistently better glottic visualization in prior studies, with variable reports of better

first pass success and some concern about possible longer times to intubation. In the most comparable prospective, randomized study by Silverberg et al, first attempt success by fellows was achieved in 74% of patients using VL (GlideScope) and only 40% using DL ($P < 0.001$). High-risk patients were excluded in this trial, and procedures were performed both in the ICU and the less-controlled environment of ward cardiac arrests and rapid response team evaluations. Most patients received propofol 1 mg/kg or etomidate without neuromuscular blockade, and the level of fellow experience, although not directly reported, was likely less, based on the substantially lower rate of DL intubation than comparative trials.

The FELLOW trial is the largest prospective, randomized trial to compare VL with DL to date, and provides clinicians with important conclusions. VL offers better glottic visualization than DL but little more in an optimized ICU setting with experienced operators using both induction agents and neuromuscular blockade, even in obese patients without urgent need for intubation or other high-risk features. The investigators' post-hoc, qualitative observation that better glottic visualization may matter more in less experienced operators is concordant with the findings of Silverberg et al and a meta-analysis by Griesdale et al and perhaps also may be true in less controlled intubation settings. The small but significant population of patients excluded from randomization in the FELLOW trial due to urgency or clinician judgment unfortunately limits the generalization of these findings to other high-risk populations. Less rigorous studies in this setting also support the clear trend toward use of the bougie or VL when first intubation attempts fail.

The more traditional pharmacologic approach used in the FELLOW trial contrasts sharply with recent publications reporting a high rate of first attempt success using VL with propofol alone, frequently with vasopressor premedication. The best pharmacologic approach in ICU airway management, and the best use of VL (and which tool to use) in high-risk or failed airways in the critically ill, are all issues that warrant further study in well-designed, prospective, randomized trials such as this one. ■

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ABSTRACT & COMMENTARY

Reducing Stress and Anxiety in Mechanically Ventilated, Critically Ill Patients: Does Chaplain-assisted Spiritual Care Play a Role?

By Kathryn Radigan, MD

Attending Physician, Division of Pulmonary and Critical Care, Stroger Hospital of Cook County, Chicago

Dr. Radigan reports no financial relationships relevant to this field of study.

SYNOPSIS: In mechanically ventilated, critically ill patients without delirium or dementia, chaplain-led, picture-guided spiritual care is feasible and shows the potential for reducing anxiety and stress during and after an ICU admission.

SOURCE: Berning JN, Poor AD, Buckley SM, et al. A novel picture guide to improve spiritual care and reduce anxiety in mechanically ventilated adults in the intensive care unit. *Ann Am Thorac Soc* 2016;13:1333-1342.

Chaplains have been instrumental in providing spiritual care for hospitalized patients that are facing serious illness. Unfortunately, mechanically ventilated patients, who are potentially at highest risk of stress due to their inability to communicate, typically are not offered spiritual support. To determine the feasibility and effectiveness of chaplain-led spiritual care for mechanically ventilated, critically ill patients, Berning et al conducted a quasi-experimental study at an urban, tertiary care medical center. From March 2014-July 2015, 50 mechanically ventilated adults without delirium or dementia in a medical or surgical ICU received spiritual care from a hospital chaplain. Spiritual care included using an illustrated communication card to assess the patients' spiritual affiliations, emotions, and needs. For the first 25 patients enrolled in the study, investigators performed semi-structured interviews with eight ICU survivors to identify how spiritual care affected their ICU experience. For the remaining 25 participants, researchers measured anxiety on 100-mm visual analog scales (VAS) immediately before and after the first chaplain visit. They also conducted semi-structured interviews with 18 ICU survivors with added measurements of pain and stress (±100-mm VAS).

Participant mean age was 59 (±16) years, median days of mechanical ventilation was 19.5 (IQR 7-29) days, and in-hospital mortality was 30% (n = 15 patients). With the use of a communication card, all 50 participants were able to communicate spiritual affiliation, 47 (94%) acknowledged one or more emotions, 45 (90%) were able to rate the severity of their spiritual pain, and 36 (72%) selected the form of chaplain intervention they preferred. Immediately after the first chaplain visit, patient anxiety decreased 31% (mean score change -20; 95% confidence interval [CI], -33 to -7). Of the 28 ICU survivors, 26 (93%) recalled their chaplain visit and underwent the semi-structured interview. Eighty-one percent felt more capable of dealing with their hospitalization, and 0% felt worse. Among the 18 survivors who underwent additional VAS testing during follow-up interviews, there was a 49-point reduction in stress (95% CI, -72 to -24) and no significant change in physical pain as a result of the picture-guided spiritual care. In summary, researchers concluded that chaplain-led, picture-guided spiritual care not only is feasible but also shows potential for reducing anxiety and stress after an ICU admission.

■ COMMENTARY

Critically ill patients often deal with the intense emotions of pain, isolation, depression, fear, anxiety, and/or confusion.[1] Historically, hospital chaplains and palliative care teams have been instrumental in providing patients with spiritual care that helps them cope with their symptoms and prognosis.[2] One can imagine that experiencing these emotions in isolation without the ability to communicate due to the need for mechanical ventilation may be even more challenging. Within the past decade, it has become widely recognized that mechanically ventilated, critically ill patients experience substantial psychoemotional stress, and survivors often are plagued with anxiety, depression, and PTSD.[3,4] With this new understanding, improving outcomes in our critically ill patients has taken on a new meaning. Researchers are interested in improving the quality of life of ICU patients and are actively investigating the mental and physical sequelae of ICU survivorship. However, despite this interest, the area of spiritual care in our mechanically ventilated patients as a topic of research is almost non-existent.

[Future studies are needed to address the health of ICU survivorship, including how spirituality in the ICU may benefit quality of life. For now, asking our mechanically ventilated patients and their families if they need spiritual care is a great place to start.]

To investigate the benefits of spiritual care in mechanically ventilated patients, Berning et al conducted a trial to determine feasibility and measure the effects of chaplain-led, picture-guided spiritual care for mechanically ventilated adults in the ICU. The ICU chaplain developed an illustrated spiritual care communication card that included four different sections addressing the main domains of spiritual assessment typically assessed by a chaplain: identification of spiritual or religious affiliations, identification of a range of feelings, rating of spiritual pain, and selection of a desired religious, spiritual, or non-spiritual intervention that a chaplain may offer. The chaplain then provided all the picture-guided spiritual care. Through these interventions, researchers demonstrated that chaplain-led, picture-guided spiritual care was feasible and that it reduced both anxiety and stress after an ICU admission.

In support of these findings, previous studies have demonstrated that patients and families in the non-ICU setting have found religion to be the single

most important factor enabling them to cope with a serious illness.[5] Critical illness is a catastrophic event for an individual's whole being and affects physical, mental, and spiritual health. During critical illness, patients and their loved ones frequently reflect on spiritual, religious, or existential questions. Surveys have shown that 70% of patients in a death-and-dying setting welcome a spiritual inquiry from their physician, and 50% of terminally ill patients would find active prayer by their physician acceptable.[6] Despite all this research, clinicians often are unable to address spiritual care as a priority in the overall care of their patients. Hurdles include the time associated with these discussions, burnout and fatigue, and the fear of not broaching the subject appropriately or appearing to "give up."

This study was helpful in highlighting that chaplain-led spiritual care is not only feasible among mechanically ventilated adults but also helpful in reducing anxiety and stress. Future studies are needed to address the health of ICU survivorship, including how spirituality in the ICU may benefit quality of life. For now, asking our mechanically ventilated patients and their families if they need spiritual care is a great place to start. ■

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ABSTRACT & COMMENTARY

Categorizing Acute Respiratory Distress Syndrome as Direct vs. Indirect Injury

By Richard Kallet, MS, RRT, FCCM

Director of Quality Assurance, Respiratory Care Services, San Francisco General Hospital

Mr. Kallet reports no financial relationships relevant to this field of study.

SYNOPSIS: This retrospective observational study compared patients with acute respiratory distress syndrome classified as presenting with direct vs. indirect lung injury and found distinct differences in traditional predictors of hospital mortality between these subgroups.

SOURCE: Luo L, Shaver CM, Zhao Z, et al. Clinical predictors of hospital mortality differ between direct and indirect acute respiratory distress syndrome. *Chest* 2016 Sept 20. [Epub ahead of print].

Luo et al conducted a post-hoc analysis of 417 patients with acute respiratory distress syndrome (ARDS) categorized as presenting with either direct lung injury (pneumonia, aspiration) or indirect injury (sepsis, pancreatitis). Those with direct ARDS exhibited significantly higher lung injury scores, lower SAPS II and APACHE II scores, as well as fewer non-pulmonary organ failures compared to indirect ARDS. However, mortality was not different between the direct and indirect groups (28% vs. 31%, respectively; $P = 0.49$). Both intensive care and hospital length of stay were lower in those with direct ARDS. Ventilator-free days also was higher in direct vs. indirect ARDS, but this did not reach statistical significance (21 [2-24] vs. 15 [2-23] days, respectively; $P = 0.054$).

When the entire cohort was analyzed, factors such as age, lung injury score, and the number of organ failures were predictive of mortality, whereas the presence of diabetes was not. Both increasing age and lung injury score were only predictive of mortality in direct ARDS, and the presence of diabetes was protective in those with direct injury (odds ratio [OR], 0.47; 95% confidence interval [CI], 0.22-0.99; $P = 0.04$). In contrast, the only predictor of hospital mortality for indirect ARDS was the number of organ failures; the presence of

diabetes was not protective (OR, 1.41; 95% CI, 0.64-3.09; *P* = 0.39).

■ COMMENTARY

Beginning in the late 1990s, studies suggesting that ARDS presents differently according to whether the primary site of injury was the alveolar epithelium ("direct," "pulmonary") vs. the vascular endothelium ("indirect," "extrapulmonary") focused on the effects of positive end-expiratory pressure (PEEP) and alveolar recruitment maneuvers to improve oxygenation and chest compliance. These studies suggested that direct pulmonary insults tend to result in more alveolar consolidation and less recruitable alveolar units. In contrast, indirect insults associated with trauma, sepsis, and pancreatitis primarily cause endothelial injury in the pulmonary and systemic vasculature, leading to global edema. The pulmonary significance of this is a pronounced reduction in chest wall compliance and increased congestive compressive atelectasis that is more amenable to PEEP and recruitment maneuvers.

A skeptical view of direct vs. indirect ARDS centers on two issues. First, alveolar tissue features an approximate width of 1 micron. It's difficult to imagine that a substantial insult from caustic agents, such as gastric acid in aspiration or proteolytic enzymes in pancreatitis, would not seep across and injure other cell types in close proximity. Second, ARDS often presents as mixed etiologies (e.g., pneumonia leading to septic shock) rendering the distinction between direct and indirect injury essentially futile.

Some of the findings in the current study are important yet also unsurprising, such as the significant association of direct ARDS with age and mortality and indirect ARDS with organ failure and mortality. It's apparent that the risk for pneumonia and aspiration and its association with mortality increases with age, particularly among the elderly, just as multiple organ failure, particularly in sepsis, also leads to higher mortality. In contrast, the positive effect of diabetes on mortality in direct (but not indirect) ARDS is a novel and interesting finding. Previous studies that investigated the interactions between diabetes and ARDS (without reference to direct vs. indirect injury) have produced contradictory results.

In their discussion, the authors bolstered their findings by citing several pre-clinical studies that found diabetes and hyperglycemia produce opposite effects on the magnitude of damage in direct (less damage) vs. indirect (greater damage) lung injury.

Other intriguing findings on direct vs. indirect ARDS come from recent studies by the ARDS Network.[1] When considered together, these studies quell some of the skepticism regarding the importance of categorizing ARDS by injury vectors. Increased biomarker levels associated with alveolar epithelial injury (e.g., surfactant protein D, RAGE) were found in ARDS associated with pneumonia and aspiration. Likewise, indirect ARDS associated with sepsis demonstrated higher biomarker levels associated with alveolar endothelial injury (e.g., angiopoietin-2 and von Willebrand factor antigen). Direct ARDS compared to indirect ARDS was associated with lower proinflammatory mediator levels (IL-6 and IL-8), which corresponded with a strong trend toward lower mortality (29% vs. 35%, respectively; *P* = 0.06). These biomarkers previously have been associated with higher mortality in ARDS without reference to direct vs. indirect injury. However, investigators were unable to detect any interaction between ARDS subtypes and the prognostic value for any biomarker. Nonetheless, the two studies described above suggest the possibility that continued investigation of differences between direct and indirect ARDS, particularly in genetic propensities and biomarker expression, may lead to effective pharmacologic therapies targeting specific etiologies. ■

[The two studies suggest the possibility that continued investigation of differences between direct and indirect ARDS, particularly in genetic propensities and biomarker expression, may lead to effective pharmacologic therapies targeting specific etiologies.]

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CME/CE QUESTIONS

1. **The ELAIN trial demonstrated that early initiation of continuous renal replacement therapy led to:**
   a. improved 28-day mortality.
   b. improved 60- day mortality.
   c. improved 90-day mortality.
   d. no benefits.

2. **Video laryngoscopy has consistently been shown to improve which of the following when compared to direct laryngoscopy use in the critically ill?**
   a. Glottic visualization
   b. Time to intubation
   c. Intubation success
   d. Incidence of hypoxemia

3. **In mechanically ventilated, critically ill patients without delirium or dementia, chaplain-led, picture-guided spiritual care during their ICU stay is associated with a reduction in:**
   a. depression.
   b. anxiety.
   c. pain.
   d. All of the above

4. **Which of the following statements is true regarding indirect acute respiratory distress syndrome?**
   a. It represents injury primarily to the alveolar Type II cells.
   b. It is associated with increased chest wall compliance.
   c. It is associated primarily with pneumonia and aspiration.
   d. It represents injury primarily to the alveolar endothelium.

CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- identify relevant topics in the practice of critical care medicine;
- utilize recommendations from current clinical guidelines; and
- manage common critically ill patient and ICU administration scenarios.