

# Critical Care [ALERT]

Authoritative, evidence-based summaries for the critical care clinician

## SPECIAL FEATURE

### Timing of Initiation of Renal Replacement Therapy in the ICU

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.

**A**cute kidney injury (AKI) is common in patients admitted to the ICU and is associated with high mortality. The decision to initiate renal replacement therapy (RRT) for these patients is complicated. Not only is the optimal time for starting therapy unclear, decisions to transfer patients to higher levels of care often are driven by the perceived need to initiate hemodialysis or continuous RRT.

#### CRITERIA FOR ACUTE KIDNEY INJURY

Multiple systems to grade AKI have been developed. These include the RIFLE criteria (Risk, Injury, Failure, Loss, End-stage kidney disease), KDIGO criteria (Kidney Disease: Improving Global Outcomes), and AKIN criteria (Acute Kidney Injury Network).<sup>1-3</sup> (See Table 1.) Investigators have studied the ability of each of these criteria to predict mortality. The authors of a multicenter, prospective analysis of 3,107 patients admitted to the ICU demonstrated rates of AKI varying from 38.4% with AKIN to 46.9% with RIFLE to 51% with

KDIGO.<sup>4</sup> The areas under the curve for each receiver operator characteristic (ROC) for in-hospital mortality were 0.746 for AKIN, 0.738 for RIFLE, and 0.757 for KDIGO. Similarly, the authors of a retrospective, observational study of 49,518 patients admitted to the hospital reported ROC for hospital mortality of 0.69, 0.77, and 0.78 for AKIN, RIFLE, and KDIGO, respectively.<sup>5</sup> Specifically in patients admitted to the ICU with sepsis, the ROCs for in-hospital mortality with each criterion were similar for each system (RIFLE, 0.652; AKIN, 0.686; KDIGO, 0.658).<sup>6</sup>

These models of AKI predict mortality, not the need for RRT. This prompted the development of biomarkers that may be more predictive of the need for RRT. Beyond serum creatinine (sCr), these markers include serum cystatin C (sCysC) and urinary neutrophil gelatinase-associated lipocalin (uNGAL), as well as others. The utility of these remains an area of continuing study. The authors of a prospective study of

**Financial Disclosure:** *Critical Care Alert's* Physician Editor Betty Tran, MD, MSc, Nurse Planner Jane Guttendorf, DNP, RN, CRNP, ACNP-BC, CCRN, Peer Reviewer William Thompson, MD, Editor Jonathan Springston, Accreditations Manager Amy M. Johnson, MSN, RN, CPN, and Editorial Group Manager Leslie Coplin report no financial relationships relevant to this field of study.

[INSIDE]

Medication Errors When Patients  
Transition Out of ICU

page 29

Efficacy of Preoxygenation Methods Prior  
to Endotracheal Intubation

page 30

*Critical Care Alert* (ISSN 1067-9502) is published monthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *Critical Care Alert*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.

GST Registration Number: R128870672.

© 2019 Relias LLC. All rights reserved. No part of this newsletter may be reproduced in any form or incorporated into any information-retrieval system without the written permission of the copyright owner.

This is an educational publication designed to present scientific information and opinion to health professionals to stimulate thought and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual.

**SUBSCRIBER INFORMATION**  
(800) 688-2421  
customerservice@reliasmedia.com  
[ReliasMedia.com](http://ReliasMedia.com)

**Subscription Prices**  
United States  
Print: 1 year with free *AMA PRA Category 1 Credits™*, \$349  
Add \$19.99 for shipping & handling.  
**Online only: 1 year (Single user) with free *AMA PRA Category 1 Credits™*, \$299**

**Back issues: \$42.** Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and \$30 shipping.  
Elsewhere: Add \$30 shipping.

**ACCREDITATION**  
Relias LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCM) to provide continuing medical education for physicians.

Relias LLC designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credit(s)™*. Physicians should claim only credit commensurate with the extent of their participation in the activity.

Relias LLC is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Contact hours [2] will be awarded to participants who meet the criteria for successful completion. California Board of Registered Nursing, Provider CEP# 13791.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2 MOC Medical Knowledge points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

This CME activity is intended for critical care physicians and nurses. It is in effect for 36 months from the date of the publication.

310 patients receiving mechanical ventilation (MV) demonstrated ROCs for RRT for uNGAL of 0.727 and sCysC of 0.764, compared with sCr of 0.785 and Acute Physiology and Chronic Health Evaluation (APACHE) II severity of 0.728.<sup>7</sup> Combining these markers improved their predictive accuracy but they did not perform much better than the sCr and APACHE II scores alone. Thus, predicting which patients will require RRT remains difficult.

## CLINICAL TRIALS EXAMINING TIMING OF RRT

With the uncertainty in predicting which patients will need RRT, the last few years have seen the authors of several randomized, controlled trials evaluate the best initiation approach. These include the ELAIN and AKIKI trials in 2016 and the IDEAL-ICU study in 2018.<sup>8-10</sup> Other studies dating back to 2002 were included in a systematic review and meta-analysis in 2017 that did not include the IDEAL-ICU trial.<sup>11</sup>

The ELAIN trial was a single-center, parallel group trial of 231 patients admitted to the ICU.<sup>8</sup> It included patients aged 18-90 years with KDIGO stage 2 and a marker of disease severity (sepsis, vasopressor requirement, refractory fluid overload, Sequential Organ

Failure Assessment score  $\geq 2$ ). The criteria also included plasma NGAL > 150 ng/mL as a predictor of the need for RRT. It is notable that most patients were admitted with surgical indications. Exclusion criteria included chronic kidney disease (glomerular filtration rate [GFR] less than 30 mL/min), previous RRT, occlusion of the renal artery, glomerulonephritis, interstitial nephritis, vasculitis, post-renal obstruction, or thrombotic thrombocytopenic purpura/hemolytic uremic syndrome. Patients were randomized to early or delayed start of RRT. Early initiation occurred within eight hours of KDIGO stage 2, while delayed initiation occurred within 12 hours of KDIGO stage 3 AKI. Patients in the delayed initiation group could start early if any of the absolute indications for RRT were met (blood urea nitrogen [BUN] > 100 mg/dL, potassium > 6 mmol/L, or ECG changes, magnesium > 8 mEq/L, or urine production < 200 mL per 12 hours). Protocolized delivery of RRT ensured all patients received similar continuous venovenous hemodiafiltration. In this study, early initiation was associated with reduced 90-day mortality (hazard ratio [HR], 0.66;  $P = 0.03$ ), the primary outcome. However, 28- and 60-day mortality rates in the early and delayed groups were not statistically different. Patients in the early

**Table 1. Comparison of Criteria for Acute Kidney Injury**

Category	Serum Creatinine	Urine Output
<b>RIFLE</b>		
Risk	1.5 times baseline or glomerular filtration rate (GFR) decrease > 25%	< 0.5 mL/kg/hour for 6 hours
Injury	2 times baseline or GFR decrease > 50%	< 0.5 mL/kg/hour for 12 hours
Failure	> 3 times baseline, or GFR decrease > 75%, or increase > 4 mg/dL	< 0.3 mL/kg/hour for 24 hours or anuria for 12 hours
<b>KDIGO</b>		
Stage 1	1.5-1.9 times baseline or $\geq 0.3$ mg/dL increase	< 0.5 mL/kg/hour for 6-12 hours
Stage 2	2.0-2.9 times baseline	< 0.5 mL/kg/hour for $\geq 12$ hours
Stage 3	3.0 times baseline or increase to $\geq 4.0$ mg/dL	< 0.3 mL/kg/hour for $\geq 24$ hours or anuria for $\geq 12$ hours
<b>AKIN</b>		
Stage 1	1.5-2 times baseline or increase $\geq 0.3$ mg/dL	< 0.5 mL/kg/hour for > 6 hours
Stage 2	2-3 times baseline	< 0.5 mL/kg/hour for > 12 hours
Stage 3	> 3 times baseline or > 4 mg/dL and increase of > 0.5 mg/dL	< 0.3 mg/kg/hour for 24 hours or anuria for 12 hours

initiation arm had shorter hospital length of stay (LOS) and shorter duration of MV.

The AKIKI trial was a multicenter, randomized trial of patients with KDIGO stage 3 disease who required MV, vasopressors, or both. Patients were excluded if they had severe metabolic abnormalities, including BUN greater than 112 mg/dL, potassium > 6 mmol/L, pH < 7.15, or acute pulmonary edema requiring > 5 L/min O<sub>2</sub>. In the early initiation group, researchers started RRT within six hours of KDIGO stage 3. Meanwhile, in the delayed group, RRT was started if patients progressed to the above-mentioned exclusion criteria or if they became anuric for more than 72 hours after randomization. The choice of RRT was left to each study site; thus, there was some variability in the mode of RRT. The primary outcome was 60-day mortality. Most patients presented with severe sepsis or septic shock (> 70%). Unlike the ELAIN trial, the AKIKI trial investigators demonstrated no significant difference in 60-day mortality between the early and delayed groups. Although there were more patients in the early initiation arm who received RRT, the only other secondary outcomes that showed a difference was a higher incidence of catheter-related bloodstream infections in the early initiation arm (10% vs. 5%; *P* = 0.03) and higher incidence of hypophosphatemia.

More recently, the IDEAL-ICU trial was a multicenter, randomized, controlled trial comparing early vs. late initiation of RRT for patients with AKI and sepsis.<sup>10</sup> Inclusion criteria included patients ≥ 18 years of age, admission to the ICU with sepsis within 48 hours of the start of vasopressor therapy, and AKI defined by “failure” under the RIFLE criteria. The early intervention group started RRT within 12 hours of meeting inclusion criteria, while the delayed group were monitored for the development of criteria for emergency RRT, including potassium 6.5 mmol/L, pH < 7.15, or fluid overload refractory to diuretics. If any of these criteria were met, RRT was started as soon as possible. If none of these criteria were met, RRT was initiated 48 hours after the diagnosis of AKI (unless spontaneous renal recovery occurred, defined by spontaneous urine output > 1,000 mL per 24 hours or > 2,000 mL per 24 hours with diuretics). The choice of RRT was at the discretion of each site. The primary outcome was 90-day mortality. After the second planned interim analysis, the authors ended the trial for futility. There was no difference in 90-day mortality between groups.

Prior to the IDEAL-ICU trial, a systematic review and meta-analysis of both the ELAIN and AKIKI trials (as well as seven other randomized, controlled trials for a total of 1,636 patients) was published.<sup>11</sup> The definitions for AKI and early and delayed initiation varied. For overall mortality, there was no difference in early vs. late initiation of RRT (HR, 0.98; 95% confidence interval, 0.78-1.23). Similarly, ICU LOS and hospital LOS were

similar in each group. There was no difference in renal recovery, dependence on RRT, duration of RRT, or time to renal recovery. However, there was a high degree of heterogeneity, and the authors warned these conclusions must be interpreted cautiously.

## DISCUSSION

What guidance can we take from these mostly negative trials of early vs. late initiation of RRT? A few lessons can be learned from the similarities and differences in each trial. The most recent trials contained absolute criteria for the initiation of RRT. (See Table 2.) In general, patients with serum potassium > 6-6.5 mmol/L or with ECG changes, BUN > 100-112 mg/dL, or pH < 7.15 should be dialyzed emergently regardless of RIFLE or KDIGO stage. However, each trial had different RRT modalities, and it remains unclear whether continuous RRT or intermittent RRT is most appropriate.

The ELAIN trial was the largest positive trial. Several features of this trial deserve special attention. First, most patients were admitted for surgical indications. Of the 231 patients randomized, 108 were admitted for cardiac surgery, 78 for abdominal surgery, and 28 for trauma. In contrast, AKIKI primarily included medical patients, with only 20% of patients admitted for surgical indications. IDEAL-ICU focused on patients who met

**Table 2. Absolute Indications to Start Renal Replacement Therapy in Each Trial**

	ELAIN	AKIKI	IDEAL-ICU
Potassium	> 6 mmol/L	> 6 mmol/L	> 6.5 mmol/L
Urine Output	< 200 mL/12 hours	Anuria	Anuria
pH	None	< 7.15	< 7.15
Fluid Overload	Yes	Yes	Yes
Blood Urea Nitrogen	> 100 mg/dL	> 112 mg/dL	None
Other	ECG changes, magnesium > 4 mmol/L		

## Help Us Help You

We'd love to hear from you how we can do better! Please take five minutes to complete our annual user survey (<https://bit.ly/2HK6BM7>), and we'll enter you to win a year-long subscription to Relias Media.

criteria for sepsis. Second, the inclusion criteria for ELAIN included elevated NGAL. This was intended to enrich the population for patients who would require RRT. Indeed, if one examines the proportion of patients in each study who underwent RRT, ELAIN was the highest, with 100% of the early arm and 91% of the late arm. (See Table 3.) In the AKIKI and IDEAL-ICU trials, only 51% and 62%, respectively, of the delayed arms ever underwent RRT, implying one-half to one-third of patients had spontaneous renal recovery. Third, the timing of initiation of RRT was much earlier in ELAIN than in the other trials. (See Table 4.)

The authors of these trials all started RRT in the early arm within four to eight hours of meeting criteria. However, the delayed arm in ELAIN started at a median of 25 hours, while AKIKI and IDEAL-ICU started at a median of 57 and 51.5 hours, respectively. The final key difference was the modality of RRT. ELAIN specified continuous venovenous hemodiafiltration, while the authors of the other studies allowed each participating site to make that decision.

With these features in mind, certain populations might benefit from early initiation of RRT. First, surgical patients without other medical complexities might perform better with earlier RRT. Ninety-day mortality in the early arm of the ELAIN trial was 39.3%, significantly lower than the early arms of the other trials (58% in IDEAL-ICU; 48.5% 60-day mortality in AKIKI). These patients simply may tolerate RRT better. Second, early initiation likely works best for patients who will need RRT so that the benefits outweigh the risks. In ELAIN, 100% and 91% of the early and late arms, respectively, received RRT. In contrast, in the late arm of AKIKI and IDEAL-ICU, only 51% and 62% required RRT, respectively. Thus, many patients in the early arms of these two trials may never have required RRT and, thus, no benefit was achieved. Third, early interventions for AKI may prevent organ dysfunction. ELAIN initiated

RRT much earlier than AKIKI and IDEAL-ICU. (See Table 4.) These latter trials may have missed the window. Initiating RRT 57 hours (AKIKI) and 52.5 hours (IDEAL-ICU) after meeting criteria for renal failure may have been too late to achieve benefit. Finally, it is notable that the largest positive trial clearly specified continuous venovenous hemodiafiltration at very specific flows and pump rates, while the negative trials were more heterogeneous.

## CONCLUSION

The optimal time for initiating RRT in patients admitted to the ICU remains uncertain. For most patients, there is no clear difference in mortality between early and delayed initiation. However, patients admitted for strictly surgical indications did demonstrate a benefit for earlier RRT. As we become better at predicting which patients will need RRT, early initiation may be beneficial for those patients specifically. Otherwise, there does not seem to be harm in delaying RRT until absolute indications for RRT are met. ■

## REFERENCES

- Bellomo R, et al. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004;8:R204-R212.
- KDIGO Workgroup. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012;2:124-138.
- Mehta RL, et al. Acute kidney injury network: Report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007;11:R31.
- Luo X, et al. A comparison of different diagnostic criteria of acute kidney injury in critically ill patients. *Crit Care* 2014;18:R144.
- Fujii T, et al. Validation of the Kidney Disease Improving Global Outcomes criteria for AKI and comparison of three criteria in hospitalized patients. *Clin J Am Soc Nephrol* 2014;9:848-854.
- Pereira M, et al. Acute kidney injury in patients with severe sepsis or septic shock: A comparison between the 'Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease' (RIFLE), Acute Kidney Injury Network (AKIN) and Kidney Disease: Improving Global Outcomes (KDIGO) classifications. *Clin Kidney J* 2017;10:332-340.
- Pipili C, et al. Prediction of the renal replacement therapy requirement in mechanically ventilated critically ill patients by combining biomarkers for glomerular filtration and tubular damage. *J Crit Care* 2014;29:692.e7-13.
- Zarbock A, 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.
- Gaudry S, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med* 2016;375:122-133.
- Barbar SD, et al. Timing of renal-replacement therapy in patients with acute kidney injury and sepsis. *N Engl J Med* 2018;379:1431-1442.
- Yang X, et al. A comparison of early versus late initiation of renal replacement therapy for acute kidney injury in critically ill patients: An updated systematic review and meta-analysis of randomized controlled trials. *BMC Nephrol* 2017;18:264.

**Table 3. Number of Patients Receiving Renal Replacement Therapy in Each Arm of Each Trial**

	ELAIN	AKIKI	IDEAL-ICU
Early	112 of 112	305 of 311	239 of 246
Late	108 of 119	157 of 308	149 of 242

**Table 4. Median Time in Hours to Initiation of Renal Replacement Therapy (Interquartile Range)**

	ELAIN	AKIKI	IDEAL-ICU
Early	6 (4-7)	4.3 (2.7-5.9)	7.6 (4.4-11.5)
Late	25 (18.8-40.3)	57 (25-83)	51.5 (34.6-59.5)

# Medication Errors When Patients Transition Out of ICU

By *Drayton Hammond, PharmD, MBA, BCPS, BCCCP*

*Clinical Pharmacy Specialist, Adult Critical Care, Rush University Medical Center, Chicago*

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

**SYNOPSIS:** Three factors associated with decreased odds of an error occurring were daily patient care rounds in the ICU, discontinuing and rewriting medication orders during the transition of care from the ICU to a non-ICU setting, and 16-20 ICU beds in the transferring ICU.

**SOURCE:** Tully AP, et al. Evaluation of medication errors at the transition of care from an ICU to non-ICU location. *Crit Care Med* 2019;47:543-549.

Medication errors may occur at any point during a patient's hospitalization, although transition points from different levels of care (e.g., ED to ICU, ICU to floor, and floor to outpatient setting) add an additional element of potentiating the error until the patient's next formal interaction with a healthcare provider.<sup>1,2</sup> The financial costs and mortality attributable to these errors in the United States represent at least \$19.5 billion and 98,000 deaths, respectively.<sup>3</sup> Guidelines and best practice statements for transition of care (TOC) focus predominantly on hospital discharge, which has many similarities but also differences compared to an inpatient TOC.<sup>4,5</sup> The extent to which medication errors occur during the TOC from the ICU to a lower acuity inpatient setting and risk factors associated with development or prevention of those errors has not been described.

Tully et al completed a multicenter, observational, seven-day, study of patients' first transfer from an ICU to a non-ICU setting within the same institution to describe the point prevalence and types of medication errors and patient-, medication-, and system-specific factors associated with their development.<sup>6</sup> A pharmacist evaluated medication orders that were active within one hour pre- and post-ICU transfer for potential medication errors. These pharmacists were provided training and reference documents to facilitate valid and reliable identification of potential medication errors. Prevalence and characteristics of errors were determined using descriptive statistics. Characteristics between those TOCs with and without a medication error were compared. Characteristics with a *P* value < 0.05 were considered for inclusion in a multivariate logistic regression analysis to determine independent risk factors for medication errors at TOC.

Of the 985 TOCs evaluated, 450 had at least one medication error. Most patients experienced a single error (55.1%), although the mean number of errors was 1.88 (standard deviation, 1.30; range, 1-9). The most common error types were continuation of a medication with an ICU-specific indication (28.4%), untreated condition

(19.4%), and medication without a clear indication (11.9%). The most common untreated conditions were cardiac (27.6%) or neurologic (12.9%) in nature. Three-quarters of errors reached patients, although 94.2% did not cause patient harm. For those errors that did cause patient harm, the most common types of errors were incorrect dose (22.6%) and untreated condition (18.9%), and medication classes were anti-infective (28.6%), cardiovascular (18.4%), and neurologic (12.2%). Patient-specific factors associated with increased odds of medication errors were renal replacement therapy during ICU stay (odds ratio [OR], 2.93; 95% confidence interval [CI], 1.42-6.05) and number of medications ordered following TOC (OR, 1.08; 95% CI, 1.02-1.14). Medication-specific factors associated with increased odds of medication errors were receipt in the ICU of an anti-infective agent (OR, 1.66; 95% CI, 1.19-2.32), hematologic agent (OR, 1.75; 95% CI, 1.17-2.62), and intravenous fluid, electrolyte, or diuretic agent (OR, 1.73; 95% CI, 1.21-2.48). System-specific factors associated with increased odds of medication errors were community teaching hospital (OR, 3.96; 95% CI, 1.79-8.79) and 500-999 total inpatient hospital beds (OR, 4.26; 95% CI, 1.05-17.32). System-specific factors associated with lower odds of medication errors were daily patient care rounds in the ICU (OR, 0.15; 95% CI, 0.007-0.34), discontinuing and rewriting medication orders during the TOC from the ICU to a non-ICU setting (OR, 0.36; 95% CI, 0.17-0.73), and 16-20 ICU beds in the transferring ICU (OR, 0.40; 95% CI, 0.21-0.74).

## ■ COMMENTARY

Medication errors occur in almost 50% of patients transitioning from the ICU to a non-ICU setting. While all errors placed patients at an increased risk for harm, approximately 5% resulted in patient harm during the hospitalization. The quantity and extent of harm from these errors likely are underestimated for at least three reasons. First, errors that were recognized and resolved during order verification likely were underreported because the data collection process was more complex

for capturing and recording these types of errors. Additionally, the duration errors persisted, including presence of the error at hospital discharge, was not evaluated. Because of the retrospective nature of this research, interventions to resolve these errors were unable to be provided after they were identified. Finally, there was at least one dedicated pharmacist for each ICU from which patients were transferred. Pharmacists frequently recognize and resolve minor and major medication errors.<sup>7,8</sup> However, approximately one-third of ICUs in the United States do not employ a partially or fully dedicated pharmacist.<sup>9</sup> The quantity and harm from medication errors at institutions without dedicated ICU pharmacist services likely is greater than reported in this research.<sup>7</sup>

The three factors associated with lower odds of an error were system- and process-focused in nature and represent opportunities for improving patient safety while also likely improving other financial and patient care metrics.<sup>10</sup> While implementing or improving the structure and formality of direct patient care rounds is a significant undertaking, the benefits can be substantial.<sup>10</sup> Similarly, reducing the size of the critical care service to accommodate 16-20 patients at most may require additional resources but likely will increase the ability of all members of the healthcare team to adequately provide care for these patients. The final factor (discontinuing and rewriting medication orders during TOC) is straightforward to implement in most electronic health records and TOC workflow processes.<sup>11</sup> The research by Tully et al may serve as both a call to action for institutions that are at an increased risk for medication errors and a trove of hypothesis-generating data for

investigators interested in improving patient safety through process changes. ■

## REFERENCES

1. Bell CM, et al. Association of ICU or hospital admission with unintentional discontinuation of medications for chronic diseases. *JAMA* 2011;306:840-847.
2. Schnipper JL, et al. Role of pharmacist counseling in preventing adverse drug events after hospitalization. *Arch Intern Med* 2006;166:565-571.
3. Andel C, et al. The economics of health care quality and medical errors. *J Health Care Finance* 2012;39:39-50.
4. Agency for Healthcare Research and Quality. Strategy 4: Care Transitions From Hospital to Home: IDEAL Discharge Planning. Available at: <http://bit.ly/2K7w9W3>. Accessed June 10, 2019.
5. World Health Organization. Transitions of Care: Technical Series on Safer Primary Care, 2016. Available at: <http://bit.ly/2Xy3IDA>. Accessed June 10, 2019.
6. Tully AP, et al. Evaluation of medication errors at the transition of care from an ICU to non-ICU location. *Crit Care Med* 2019;47:543-549.
7. Leape LL, et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. *JAMA* 1999;282:267-270.
8. Hammond DA, et al. Cost avoidance associated with clinical pharmacist presence in a medical intensive care unit. *J Am Coll Clin Pharm* 2019;1-6.
9. Maclaren R, et al. Critical care pharmacy services in United States hospitals. *Ann Pharmacother* 2006;40:612-618.
10. Bhamidipati VS, et al. Structure and outcomes of interdisciplinary rounds in hospitalized medicine patients: A systematic review and suggested taxonomy. *J Hosp Med* 2016;11:513-523.
11. Barnsteiner JH. Medication Reconciliation. In: Hughes RG, editor. *Patient Safety and Quality: An Evidence-Based Handbook for Nurses*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008. Chapter 38. Available at: <http://bit.ly/2ZiUH1H>. Accessed June 10, 2019.

## ABSTRACT & COMMENTARY

# Efficacy of Preoxygenation Methods Prior to Endotracheal Intubation

By *Vibhu Sharma, MD*

*Attending Physician, Division of Pulmonary and Critical Care Medicine, John H. Stroger Hospital of Cook County; Assistant Professor of Medicine, Rush University Medical Center, Chicago*

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

**SYNOPSIS:** A post-hoc analysis of data from the MACMAN trial revealed noninvasive ventilation may be the preferred preoxygenation approach for intubation, especially in the setting of severe hypoxemia.

**SOURCE:** Bailly A, et al. Compared efficacy of four preoxygenation methods for intubation in the ICU: Retrospective analysis of McGrath Mac Videolaryngoscope versus Macintosh Laryngoscope (MACMAN) trial. *Crit Care Med* 2019;47:e340-e348.

**T**he authors of the McGrath Mac Videolaryngoscope Versus Macintosh Laryngoscope (MACMAN) trial randomized critically ill patients undergoing endotracheal intubation to video laryngoscopy (VL) and direct laryngoscopy (DL) using a Macintosh (curved) blade.

Bailly et al analyzed the four groups retrospectively for outcomes with respect to preoxygenation technique: bag valve mask (BVM) ventilation using oxygen at 15 L/minute flow (no positive-end expiratory pressure [PEEP] valve was used) for three minutes, nonbreather (NRB)

mask with oxygen at 15 L/minutes for three minutes, noninvasive ventilation (NIV) with 100% oxygen for at least three minutes, and high-flow nasal cannula (HFNC) oxygen (Optiflow) at 60 L/minute flow at 100% FiO<sub>2</sub> for three minutes. Intubators were free to choose any one of the four methods. The association of nadir pulse oximetry (SpO<sub>2</sub>) during endotracheal intubation and two hours after intubation with the preoxygenation technique was the primary objective of the study. The secondary objectives included assessment of risk factors for SpO<sub>2</sub> below 80%, 90%, and a composite endpoint of cardiac arrest; systolic blood pressure (SBP) < 90 mmHg; or SpO<sub>2</sub> below 80%. During the study, standardized forms collected data, including primary diagnosis, duration of preoxygenation, duration of endotracheal intubation, baseline SpO<sub>2</sub>, and baseline PaO<sub>2</sub>/FiO<sub>2</sub> ratio.

Models to assess factors associated with the median minimal SpO<sub>2</sub> during intubation and two hours postintubation were identified. Logistic regression analysis models were created to identify factors associated with SpO<sub>2</sub> < 80% and < 90% across the four preoxygenation groups (BVM, NRB mask, NIV, and HFNC), with BVM serving as the index. Multiple logistic regression analyses were performed to identify factors associated with major complications (esophageal intubation, cardiac arrhythmias, dental injuries) and serious complications (death, cardiac arrest, SpO<sub>2</sub> < 80%, and SBP decline to < 90 mmHg).

Overall, 319 patients were included in the analysis (44 patients of the original MACMAN cohort were excluded due to multiple preoxygenation techniques used). All patients underwent rapid sequence intubation (RSI). The number of intubation attempts, duration of attempts to intubate, and proportion of intubation first attempts by a nonexpert were no different across groups. Clinical characteristics of patients in each group were similar, except for a higher proportion of patients with severe hypoxemia at baseline and those intubated for a primary respiratory diagnosis in the NIV group. While the duration of preoxygenation was longer in the NRB, NIV, and HFNC groups vs. the BVM group, it did not seem to affect the extent of drop in SpO<sub>2</sub> around intubation. Severity of illness scores (based on Simplified Acute Physiology Score [SAPS] II) and baseline SpO<sub>2</sub> were significant predictors of minimal SpO<sub>2</sub> value during endotracheal intubation plus two hours after intubation.

More attempts at intubation were associated with greater declines in SpO<sub>2</sub> levels during intubation and in the hours following intubation. Regardless of preoxygenation technique used, baseline SpO<sub>2</sub> was predictive of how far the SpO<sub>2</sub> would drop during and subsequent to intubation. Provision of NIV was associated with an adjusted odds ratio (aOR) of 0.10 with respect to BVM when predicting an SpO<sub>2</sub> drop below 90% (implying a “protective” effect). HFNC was worse than BVM (aOR

for hypoxemia, 5.75). Provision of a NRB mask had an aOR similar to BVM.

#### ■ COMMENTARY

The authors of this retrospective analysis concluded that NIV was the most efficacious preoxygenation technique, especially for those patients with significant hypoxemia to begin with. This study comes with all the drawbacks of a post-hoc analysis, which have been well-described — namely, discovering a finding that occurs purely by chance. The authors did not detail assessment of heterogeneity of treatment differences (however, they acknowledged the groups were heterogeneous). The authors further acknowledged that the study is underpowered for some treatment effects, needing 526 patients to provide > 90% power. Most importantly, preoxygenation devices were not allocated in randomized fashion. Keeping these limitations in perspective, this study demonstrated the (likely) superiority of NIV as a preoxygenation technique and confirms my practice in preoxygenating patients in the ICU.

Bailey et al did not suggest NIV settings, and these were not standardized in the MACMAN trial and were left to the discretion of the intubating physician. The duration of preoxygenation did not seem to affect the extent of the drop in SpO<sub>2</sub> across groups, which if confirmed in a clinical trial, would help inform the preintubation check list. Multiple attempts at intubation were associated with greater drops in SpO<sub>2</sub>, not just during intubation but also in the hours following intubation. This speaks to the importance of avoiding critical desaturation during intubation and choosing the most efficacious preoxygenation technique, especially in those with lower baseline SpO<sub>2</sub>. As noted above, NIV settings were not standardized, but typically aimed for exhaled tidal volume of 7-10 mL/kg and PEEP of 5 cm H<sub>2</sub>O. Higher levels of PEEP may be prudent for clinically greater ventilation/perfusion mismatch or intrinsic PEEP.

Baseline hypoxemia and severity of illness affected the severity of hypoxemia during endotracheal intubation, regardless of preoxygenation technique used. However, in this analysis, baseline hypoxemia was more severe in the NIV group, suggesting that NIV may be the preferred preoxygenation technique for sicker patients with worse baseline SpO<sub>2</sub>. This analysis also underlines the importance of ensuring that intubation is achieved with the fewest attempts possible and the need for a clear plan for those with significant hypoxemia despite adequate preoxygenation.

The results of a small randomized trial (n = 52) suggests that NIV is superior to BVM with oxygen, but larger trials are needed to confirm this finding (one is ongoing).<sup>1,2</sup> In the interim, provision of NIV as a preoxygenation technique for the sickest patients with the worst hypoxemia at baseline seems prudent. ■

#### PHYSICIAN EDITOR

**Betty Tran, MD, MSc**  
Assistant Professor of Medicine  
Pulmonary and Critical Care Medicine  
Rush University Medical Center  
Chicago

#### PEER REVIEWER

**William Thompson, MD**  
Associate Professor of Medicine  
University of Washington, Seattle

#### NURSE PLANNER

**Jane Guttendorf, DNP, RN, CRNP, ACNPBC, CCRN**  
Assistant Professor, Acute & Tertiary Care,  
University of Pittsburgh, School of Nursing

#### EDITORIAL ADVISORY BOARD

**Kay Ball, PhD, RN, CNOR, FAAN**  
Professor of Nursing, Otterbein University,  
Westerville, OH

#### Cody J. Benthin, MD

Staff Physician  
Pulmonary and Critical Care Medicine  
Northwest Permanente  
Portland, OR

#### Elaine Chen, MD

Assistant Professor, Department of Internal  
Medicine, Division of Pulmonary and Critical  
Care Medicine, Section of Palliative Medicine,  
Rush University Medical Center,  
Chicago

#### Drayton A. Hammond, PharmD, MBA, BCPS, BCCCP

Clinical Pharmacy Specialist  
Adult Critical Care  
Rush University Medical Center  
Chicago

#### James E. McFeely, MD

Medical Director, Critical Care Units, Alta Bates  
Summit Medical Center, Berkeley, CA

#### Samuel Nadler, MD, PhD

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

#### Alexander Niven, MD

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

#### Kathryn Radigan, MD, MSc

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

#### Trushil Shah, MD, MS

Assistant Professor of Medicine  
University of Texas Southwestern

#### Vibhu Sharma, MD, MS

Attending Physician, Division of Pulmonary  
and Critical Care Medicine  
John H. Stroger Hospital of Cook County  
Assistant Professor of Medicine  
Rush University Medical Center  
Chicago

#### EDITOR EMERITUS

**David J. Pierson, MD**  
Professor Emeritus  
Pulmonary and Critical Care Medicine University  
of Washington, Seattle

#### EDITOR

Jonathan Springston

#### EDITORIAL GROUP MANAGER

Leslie Coplin

#### ACCREDITATIONS MANAGER

Amy M. Johnson

## REFERENCES

1. Baillard C, et al. Noninvasive ventilation improves preoxygenation before intubation of hypoxic patients. *Am J Respir Crit Care Med* 2006; 174: 171-177.
2. Frat JP, et al. Preoxygenation with non-invasive

ventilation versus high-flow nasal cannula oxygen therapy for intubation of patients with acute hypoxic respiratory failure in ICU: The prospective randomised controlled FLORALI-2 study protocol. *BMJ Open* 2017;7:e018611.

## CME/CE INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to **ReliasMedia.com** and click on My Account. First-time users must register on the site. Tests are taken after each issue.
3. Pass the online test with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the test, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be emailed to you.

## CME/CE QUESTIONS

1. **Randomized, controlled trials of early vs. late initiation of renal replacement therapy (RRT) demonstrated:**
  - a. benefit in all patients.
  - b. benefit in patients with chronic kidney disease.
  - c. mixed results, although most trials did not demonstrate benefit.
  - d. no difference in mortality in any patient group.
2. **Which of the following is an absolute indication to start RRT in clinical trials of early vs. late initiation of RRT?**
  - a. pH > 7.15
  - b. Potassium < 6-6.5 mmol/L
  - c. Blood urea nitrogen < 100-112 mg/dL
  - d. Anuria
3. **In the study by Tully et al, what percentage of patients who transferred from an ICU to a non-ICU setting within the same institution had at least one medication error occur during the transition of care (TOC)?**
  - a. 15.7%
  - b. 25.7%
  - c. 35.7%
  - d. 45.7%
4. **In the study by Tully et al, which factor was associated with lower odds of a medication error occurring during TOC?**
  - a. A total of 500-999 inpatient hospital beds
  - b. Community teaching hospital
  - c. Discontinuing and rewriting medication orders during the TOC from the ICU to a non-ICU setting
  - d. Number of medications ordered following TOC
5. **Which preoxygenation technique is associated with the lowest risk for a drop in pulse oximetry (SpO<sub>2</sub>) around the time of intubation?**
  - a. Noninvasive ventilation
  - b. Bag valve mask ventilation
  - c. Nonbreather mask
  - d. High-flow nasal cannula oxygen

## 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.

Interested in reprints or posting an article to your company's site? There are numerous opportunities for you to leverage editorial recognition for the benefit of your brand. Call us at (800) 688-2421 or email us at reprints@reliamedia.com.

Discounts are available for group subscriptions, multiple copies, site licenses, or electronic distribution. For pricing information, please contact our Group Account Managers at groups@reliamedia.com or (866) 213-0844.

To reproduce any part of Relias Media newsletters for educational purposes, please contact The Copyright Clearance Center for permission at info@copyright.com or (978) 750-8400.