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Critical Care [ALERT]

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ABSTRACT & COMMENTARY

Early Neuromuscular Blockade in Moderate-to-Severe Acute Respiratory Distress Syndrome

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

SYNOPSIS: When the early use of a continuous infusion of cisatracurium was compared to contemporary supportive care for moderate-to-severe ARDS, including a light sedation target, high positive-end expiratory pressure, and conservative fluid strategy, there was no difference in 90-day mortality. Patients in the early neuromuscular blockade group more frequently experienced a severe cardiovascular event and ICU-acquired weakness by day 28.

SOURCE: National Heart, Lung, and Blood Institute PETAL Clinical Trials Network, Moss M, Huang DT, et al. Early neuromuscular blockade in the acute respiratory distress syndrome. *N Engl J Med* 2019;380:1997-2008.

Acute respiratory distress syndrome (ARDS) has a spectrum of severity, with the severe form being least common but associated with the greatest mortality.[1,2] Prior to publication of the Re-evaluation of Systemic Early Neuromuscular Blockade (ROSE) trial,[3] the ARDS et Curarisation Systematique (ACURASYS) trial was the largest multicenter study to investigate the safety and efficacy of neuromuscular blockade in moderate-to-severe ARDS.[4] Authors of the ACURASYS trial found that early administration of neuromuscular blockade improved adjusted 90-day survival and increased ventilator-free days without increasing muscle weakness.[4] Over the past decade, however, the supportive care provided to patients with ARDS has become exceedingly advanced.[2] Researchers performed the ROSE trial to evaluate the effects of early neuromuscular blockade in the setting of

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contemporary supportive management strategies for severe ARDS.[3]

Investigators conducted a randomized, open-label trial in 49 medical centers in the United States.[3] Mechanically ventilated patients with a PaO_2:FiO_2 < 150 and positive end expiratory pressure (PEEP) ≥ 8 cm H_2O who met other criteria for moderate-to-severe ARDS were randomized within a median of 7.6 hours to a 48-hour infusion of cisatracurium 37.5 mg/hour with concomitant deep target sedation or usual care without routine neuromuscular blockade and light target sedation. A high PEEP strategy was employed unless patient clinical status dictated otherwise. Prone positioning and open-label cisatracurium 20 mg bolus injections were allowed per physician discretion in both groups.

Almost all (97.4%) patients in the intervention group received cisatracurium infusions during the 48-hour intervention period, and one-sixth (17.0%) of patients in the usual care group received cisatracurium boluses (median dose, 38 mg). Patients in the intervention group had lower PEEP requirements on day 1 and lower minute ventilation and FiO_2 requirements on days 1 and 2; however, the PaO_2:FiO_2 was similar between days 1 and 7. Patients maintained an approximately net even fluid balance throughout the first 72 hours of interventions. Only 18% of patients received any rescue therapy (i.e., prone positioning, inhaled epoprostenol or nitric oxide, recruitment maneuvers, or extracorporeal membrane oxygenation). The trial enrollment was stopped early because no difference in 90-day in-hospital mortality was observed between the intervention and usual care groups (42.5% vs. 42.8%, 95% confidence interval [CI], -6.4 to 5.9, $P = 0.93$). The finding of similar mortality remained after treatment-by-subgroup interactions were considered, including ARDS severity, ARDS duration, and previous neuromuscular blockade use. Days free from mechanical ventilation, ICU care, and hospital care were similar between groups. More than 98% of patients who received cisatracurium did not recall paralysis. The Medical Research Council scale for muscle strength scores were similar between the intervention and usual care groups at days 7 and 28, although more patients in the intervention group experienced ICU-acquired weakness on day 28 (46.8% vs. 27.5%, between-group difference 95% CI, -38.2 to -0.6). Serious cardiovascular events (including hypotension and bradycardia) occurred more frequently in the intervention group (14 events vs. 4 events, $P = 0.02$).

■ COMMENTARY

When the early use of continuous infusion cisatracurium was compared to contemporary supportive care for moderate-to-severe ARDS, including a light target sedation, more specialized volume-control ventilator modes, higher PEEP, and conservative fluid strategy, there was no difference in 90-day mortality. Compared to patients enrolled in the ACURASYS trial, ROSE trial subjects were more critically ill, could receive intermittent doses of a neuromuscular blocking agent, less frequently developed a pneumothorax, and were randomized to a treatment group approximately 10 hours sooner. These differences may have decreased the likelihood of detecting a mortality benefit with continuous infusion neuromuscular blockade. Notably, only 33-55% of patients in the usual care group received light sedation, and at least 17% received open-label cisatracurium bolus doses, which suggests modifications from the light sedation and no neuromuscular blockade strategy may be warranted in many adult patients with moderate-to-severe ARDS.

For those patients in whom neuromuscular blockade is provided, the depth of sedation necessary to preclude recall of paralysis appears to increase the risk of severe cardiovascular events (e.g., hypotension, bradycardia), which occurred more frequently in the intervention group. Additionally, ICU-acquired weakness was more common at day 28 in those who received neuromuscular blockade, although the impact of this negative effect on long-term, functional status did not appear to be significant based on similar between-group findings in neuromuscular assessments and activities of daily living at three, six, and 12 months. Early use of continuous infusion neuromuscular

blockade is unlikely to provide meaningful benefits in most patients with moderate-to-severe ARDS who can be managed according to high-quality, evidence-based usual care. Its use as salvage therapy still may be considered. ■

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ABSTRACT & COMMENTARY

NOACs vs. Warfarin: What Are the Data in Patients With Traumatic Brain Injury and Intracranial Hemorrhage?

By Kathryn Radigan, MD

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

SYNOPSIS: A three-year analysis of a prospectively maintained database with traumatic brain injury patients revealed that novel oral anticoagulant use is associated with increased risk of intracranial hemorrhage progression, neurosurgical intervention, and mortality.

SOURCE: Zeeshan M, Jehan F, O'Keeffe T, et al. The novel oral anticoagulants (NOACs) have worse outcomes compared with warfarin in patients with intracranial hemorrhage after TBI. *J Trauma Acute Care Surg* 2018;85:915-920.

Despite the increasing use of novel oral anticoagulants (NOACs) within the healthcare system, emergent reversal of these agents remains a management challenge. There is little data comparing the use of NOACs to warfarin in patients with intracranial hemorrhage (ICH) after traumatic brain injury (TBI). Zeeshan and colleagues conducted a three-year analysis of their prospectively maintained database examining the outcomes after TBI in patients taking NOACs compared to those taking warfarin. Researchers analyzed all adult trauma patients admitted to a single Level I trauma center with a diagnosis of TBI. Inclusion criteria were all adult TBI patients with ICH on initial head CT scans who received anticoagulation prior to injury. Anticoagulants included warfarin or NOACs, including direct thrombin inhibitors (dabigatran) and oral direct factor Xa inhibitors (rivaroxaban and apixaban). Patients with documented bleeding diathesis, chronic liver disease, penetrating mechanisms of injury, or those who died within 24 hours of trauma were excluded. The primary outcomes were ICH progression and the need for surgical intervention. Progression was defined as an increase in the size of an existing hemorrhage or development of a new hemorrhage not previously seen on CT head. The need for surgical intervention was defined as intracranial pressure monitoring, craniotomy, or craniectomy that was performed as a result of ICH progression. Secondary outcomes included complications in the hospital, discharge to rehabilitation hospital or skilled nursing facility (SNF), hospital and ICU length of stay, and in-hospital mortality.

From the 1,459 eligible patients, 210 matched TBI patients were identified (70 patients on NOACs and 140 patients on warfarin). The matched groups were similar in age ($P = 0.21$), Glasgow Coma Scale (GCS) score ($P = 0.54$), mechanism of injury ($P = 0.61$), Injury Severity Score ($P = 0.62$), and type and size of ICH ($P = 0.09$). Compared to patients on warfarin, patients who had been treated with NOACs prior to injury had a higher rate of progression ($P = 0.03$), neurosurgical intervention ($P = 0.04$), mortality ($P = 0.04$), and longer ICU length of stay ($P = 0.04$). There was no difference in hospital length of stay ($P = 0.22$) or SNF disposition ($P = 0.14$). A sub-analysis for severe TBI patients (defined as GCS ≤ 8) revealed no difference in rate of progression

(P = 0.59), neurosurgical intervention (P = 0.62), or mortality (P = 0.81). NOAC use was associated with an increased risk of ICH progression, neurosurgical intervention, and mortality after mild and moderate TBI. It is important to carefully keep these risks in mind when deciding on the optimal form of anticoagulation for each individual patient.

■ COMMENTARY

Patients on oral antithrombotics are at increased risk of ICH after trauma.[1] Although vitamin K antagonists have been the only class of oral anticoagulants available for decades, many clinicians have substituted NOACs for warfarin because of the ease of use. NOACs have a rapid onset of action, fewer drug interactions, no dietary limitations, no laboratory monitoring requirements, and predictable pharmacokinetics.[2] The difficulty in NOAC reversal in cases of serious, life-threatening hemorrhage, especially from ICH after TBI, remains an important clinical concern in the setting of growing use of these agents. The findings of Zeeshan and colleagues underscore this problem, finding that prior NOAC use was associated with an increased risk of ICH progression, neurosurgical intervention, and mortality after a mild and moderate TBI when compared to similar patients receiving warfarin.

Previous data regarding the outcomes of TBI patients on NOACs were published by Kobayashi and colleagues and conducted by the American Association for the Surgery of Trauma.[3] Although in this study researchers found that TBI patients on NOACs were not at higher risk of ICH, ICH progression, or death, the study population was substantially different. These investigators included all trauma patients admitted to the hospital on prior dabigatran, rivaroxaban, apixaban, warfarin, aspirin, or clopidogrel. In the study by Kobayashi and colleagues, only 30% of the patients had ICH on presentation, while ICH was an inclusion criterion in the Zeeshan et al study. The Kobayashi study also included lower rates of subdural hematoma (SDH) (19% vs. 30%) and older patients with a lower Injury Severity Score. An additional limitation to the study was that only 10% of the study population was taking a NOAC.

Although NOACs often are favored for their attractive pharmacokinetic qualities previously discussed, the reversal strategies for these novel agents are still evolving.[4] Ideally, most forms of anticoagulation have a specific reversal agent or antidote for episodes of serious or life-threatening bleeding. Dabigatran's reversal agent is idarucizumab, but this anti-dabigatran monoclonal antibody fragment often is unavailable to many because of its cost.[5] Andexanet alfa recently was approved as a reversal agent for the oral direct factor Xa inhibitors (apixaban, betrixaban, edoxaban, and rivaroxaban), but again, it is costly with limited availability. There are other promising antidotes under development, including a small molecule antidote, PER977, and a mutant form of factor Xa, FXa(I16L), but they are not currently available. As a result, clinicians often are left with less targeted interventions, such as four-factor prothrombin complex concentrate (4-factor PCC) and fresh frozen plasma in this setting.

The use of NOACs will continue to rise, and critical care providers should ensure that their hospitals have a systematic protocol available to treat patients receiving these agents who present with life-threatening or uncontrolled bleeding. Although the Zeeshan study appears to have been more deliberate in addressing the question of NOAC vs. warfarin in TBI, it also had limitations that warrant further consideration. The study was a single-center, observational study without a true control group. Because it was an observational study, there is an association between NOAC use and increased risk of progression of ICH, neurosurgical intervention, and mortality after mild and moderate TBI, but causation cannot be assigned. There also is concern for sampling bias, since the institution was a Level I trauma center serving as a quaternary referral hospital. Although the manuscript relays the details of the reversal agents (fresh frozen plasma, prothrombin complex concentrate, vitamin K) were recorded, the results of these data points were not mentioned again throughout the manuscript. Not knowing the frequency, timing, or type of reversal agent for each case is a major limitation. Despite these substantial limitations, this study challenges a provider to balance risks and benefits of a particular anticoagulant carefully and to be ready to intervene with rapid recognition and reversal in patients with ICH. These findings also highlight the need for future larger, multicenter studies to further explore the outcomes of patients on NOACs after traumatic brain injury. ■

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ABSTRACT & COMMENTARY

Acute Kidney Injury With Combination Antibiotics in the Critically Ill

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

SYNOPSIS: In this retrospective study, a short course (24 to < 72 hours) of combination antibiotic therapy with piperacillin-tazobactam and vancomycin was not associated with an increased risk of acute kidney injury among critically ill patients when compared with other β-lactam and vancomycin combinations.

SOURCE: Schreier DJ, Kashani KB, Sakhuja A, et al. Incidence of acute kidney injury among critically ill patients with brief empiric use of antipseudomonal β-lactams with vancomycin. *Clin Infect Dis* 2019;68:1456-1462.

In this retrospective study, the authors attempted to define the incidence of acute kidney injury (AKI) with a short course (at least 24 but less than 72 hours of therapy) of β-lactam and vancomycin combination therapy in the critically ill. AKI was defined by the Acute Kidney Injury Network (AKIN) criteria based on both urine output and serum creatinine (SCr). The three antibiotic combinations assessed for outcomes were piperacillin-tazobactam/vancomycin (PTZ/VAN), cefepime/vancomycin (CEF/VAN), and meropenem/vancomycin (MER/VAN).

The authors created an electronic alert that continuously "sniffed" the medical record for changes in either urine output or baseline serum creatinine. Baseline SCr was defined as the median of all creatinine values in the preceding six months prior to the index admission during which exposure to the β-lactam/vancomycin combination occurred. The authors manually confirmed AKI when a "sniff" (i.e., electronic alert) popped up. The primary endpoint for the purpose of analysis was the incidence of AKI (stage 2 or 3). Secondary endpoints included maximal stage AKI and a composite of major kidney events 60 days after the start of therapy ($MAKE_{60}$), consisting of a new need for renal replacement therapy (RRT), persistent doubling of serum creatinine at 60 days, or death. Researchers reviewed 5,791 patient records (regardless of ICU type) and they used 3,299 patient data sets for analysis. Exclusion criteria included use of more than one antipseudomonal drug, recent use of combination antibiotic therapy, presence of stage 2 or 3 AKI at baseline, or death within 48 hours of the start of therapy. Patients with end-stage renal disease also were excluded.

AKI incidence was assessed beginning 24 hours after the start of continuous concurrent therapy with one of the three antibiotic combination groups (PTZ/VAN, CEF/VAN, or MER/VAN). Logistic regression models were fit using AKI as the outcome variable and the three combination therapies as independent variables. One model was fit using a validated AKI risk score as a predictor variable that assigns points for chronic conditions, acute conditions, and nephrotoxin exposure in the intensive care unit. The second model used all patient and treatment variables as predictors thought to affect AKI risk.

All three combination antibiotic groups had similar characteristics at baseline, although the MER/VAN group had a slightly greater frequency of acidosis, anemia, sepsis, and need for mechanical ventilation. The overall incidence of any stage AKI was 34%, with most developing stage 1 AKI (26%). With unadjusted analysis, no increased risk of AKI stage 2 or 3 was found with short courses of PTZ/VAN when compared to short courses of CEF/VAN or MER/VAN. Similarly, the antibiotic group was not associated with an increased risk of stage 2 or 3 AKI in the multivariable models adjusting for baseline AKI risk. The authors performed stratified analyses according to the presence or absence of stage 1 AKI at initiation of antibiotic therapy and similarly found no increased risk of stage 2 or 3 AKI development with any of the three combination antibiotic regimens. A numerically higher incidence of AKI stage 1 was noted in patients treated with PTZ/VAN relative to other groups, but was attributed to competitive inhibition of secretion of creatinine by piperacillin. With respect to the $MAKE_{60}$ composite endpoint, there were no differences between groups. When stratified by $MAKE_{60}$ subsets, there was an

increased risk of death in the MER/VAN group, reflecting higher baseline disease severity.

■ COMMENTARY

Previous studies have raised concerns about combination antibiotic therapy and AKI risk, but they did not exclusively study critically ill patients and/or were meta-analyses of small, heterogeneous studies.[1,2] A single-center, retrospective study that compared rates of AKI among critically ill patients receiving combination therapy (PTZ/VAN, CEF/VAN, or MER/VAN) showed increased odds of AKI using PTZ/VAN compared to the other groups.[3] The groups were well-matched except most patients were in surgical intensive care units and more patients in the surgical/burn/trauma ICUs received PTZ/VAN. However, this study assessed AKI with three to five days of combination antibiotic therapy. The incidence of AKI in this study also increased as the vancomycin trough increased.

The study by Schreier et al reviewed here included a large cohort of critically ill patients from mixed ICU settings, used validated risk scores, and applied a rigorous multivariable model to determine risk. More than one-third of patients exposed to β-lactam/vancomycin developed AKI with a short course of therapy, with most of those developing stage 1 AKI. Additionally, when therapy was de-escalated rapidly, the risk of AKI was identical regardless of type of β-lactam/vancomycin combination chosen. It appears that if therapy lasts for less than three days, the risk of AKI is not different for the most commonly used β-lactam/vancomycin combinations regardless of duration used inside the 72-hour "safe window." This finding points to the importance of obtaining relevant cultures early to facilitate early antibiotic de-escalation, within 72 hours or sooner. However, practitioners still need to be aware of the higher risk of AKI with PTZ/VAN combinations in the critically ill when used for more than three days, especially in surgical ICU patients. Scenarios necessitating prolonged empiric therapy for MDR organisms, combination therapy other than PTZ/VAN may be appropriate. ■

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ABSTRACT & COMMENTARY

Decision-Making Capacity in the ICU

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

SYNOPSIS: A multicenter, one-day prevalence, prospective, observational, double-blind study in 19 ICUs revealed that the decision-making capacity of ICU patients was widely overestimated by all clinicians as compared with a capacity score measured by the Mini-Mental Status Examination and the Aid to Capacity Evaluation.

SOURCE: Bertrand PM, Pereira B, Adda M, et al. Disagreement between clinicians and score in decision-making capacity of critically ill patients. *Crit Care Med* 2019;47:337-344.

Decision-making capacity is a complex cognitive function defined as the ability to comprehend all pertinent information, to appreciate the scenario and its consequences, to weigh treatment options, and to communicate the final decision. Recognizing the limited data addressing decision-making capacity in the critically ill, Bertrand and colleagues performed a multicenter, one-day prevalence, prospective, observational, double-blind study in 19 ICUs in France comparing the assessment of decision-making capacity of ICU patients by clinicians (physicians, residents, and nurses) with a capacity score measured by the Mini-Mental Status Examination (MMSE) and Aid to Capacity Evaluation (ACE) if further information was needed. From May 2012 to August 2013, all clinicians who were working from 8:00 a.m. to 6:00 p.m. in the ICU on the day of the study were enrolled. The specific day chosen was different

for each ICU and was determined at least two weeks in advance to ensure participation from the usual members of the ICU team. All adult ICU patients participated as long as they were hospitalized in the ICU before 10:00 a.m. on the day of the study. Patients under judicial protection were excluded. Before inclusion, written informed consent from the clinicians and from either the patient or surrogate was obtained. On the day of the study, the clinicians attended a presentation on the study that included an outline of the objectives and methods along with a 10-minute talk about the definition and usefulness of assessment of decision-making capacity according to ethical principles. After their patient visit, all attending clinicians were asked to complete an anonymous survey on the assessment of decision-making capacity. Specifically, they were asked, "What is the current status of the patient's decision-making capacity?" They had to choose from the following responses: "patient with decision-making capacity," "patient with probable decision-making capacity," "probably incapacitated patient," and "incapacitated patient." Within an hour following the clinicians' assessment, a single-blinded, independent ICU physician observer trained in administering capacity interviews assessed the same patients. An MMSE was administered, and those with a score of less than 20 were deemed incapacitated; those with a score greater than 24 were considered to have decision-making capacity. For patients with a score from 20 to 24, an ACE questionnaire was completed to further determine capacity status. The primary outcome was agreement between physicians' assessments and the score. The secondary outcomes were agreement between nurses' or residents' assessments and the score and identification of factors associated with disagreement.

A total of 213 clinicians (57 physicians, 97 nurses, and 59 residents) assessed 206 critically ill patients. Compared to the independent observer's score, physicians determined more patients to have decision-making capacity (45% vs. 17%; absolute difference 28%; 95% confidence interval [CI], 20-37%; P = 0.001). There was a substantial difference among all clinician assessments compared to an observer score (kappa coefficient, 0.39, 95% CI, 0.29-0.50 for physicians; 0.39, 95% CI, 0.27-0.52 for nurses; 0.46, 95% CI, 0.35-0.58 for residents). The main factor associated with disagreement was a Glasgow Coma Scale (GCS) score between 10 and 15 (odds ratio 2.92, 95% CI, 1.18-7.19, P = 0.02 for physicians; 4.97, 95% CI, 1.5-16.45, P = 0.01 for nurses; 3.39, 95% CI, 1.12-10.29, P = 0.03 for residents). For GCS scores between 10 and 15, the proportion of disagreements between score and clinician assessment did not differ. Results revealed that the decision-making capacity of ICU patients was widely overestimated by all clinicians as compared with a capacity score measured by the MMSE (and ACE, if necessary). Overestimation of capacity occurred most commonly in patients with a GCS score between 10 and 15. These results suggest that clinicians may have misinterpreted a higher level of consciousness as possession of decision-making capacity.

■ COMMENTARY

"No doubt I appeared perfectly competent. I was, after all, propped up in bed, reading the *Guardian Weekly* and the *London Review of Books*. I was appropriately responsive to questions. But I was a psychological mess and shouldn't have been taken to be fit to participate in decisions."[1] These quotes came from the perspective of a patient and academic philosopher who spent weeks in an intensive care unit. The purpose of her article was to address how certain assumptions were made by her caregivers and how she felt compelled to improve these assumptions, including medical-decision making. Medical decision-making by patients is a complex process. Inappropriate decisions made by an incapacitated patient who goes unrecognized is a major ethical issue. Bertrand and his colleagues confirmed that the decision-making capacity of ICU patients was widely overestimated by all clinicians as compared with a capacity score, underlining this significant problem.

Although not formally covered within our medical educational system, assessing capacity is an important skill in clinical practice. It is important to assess capacity through a face-to-face interview with the patient using a series of open-ended questions related to the medical decision. The assessment of capacity should specifically address the patient's understanding of the medical issues, whether the patient has an appreciation of how these issues apply to his or her life, whether the patient can reason appropriately (compare the different options and sequelae of each option), and whether the patient can express a decision that makes sense after weighing all these factors.[2] This deliberate approach can take considerable time, and many clinicians will proceed with their own subjective assessment that often is clouded by their own personal values. These values may raise ethical concerns, especially in the setting of life or death decisions, such as a decision to forgo life-sustaining treatment. When clinicians are faced with complicated cases or when there is disagreement, validated instruments, such as the MacArthur Competency Assessment Tool for Treatment, Assessment of Capacity for Everyday Decisions, or the Capacity to Consent to Treatment Interview, can be used to formally assess capacity.[3] Most often, the ideal methods to assess decision-making capacity in

research studies have been the MMSE using two cut-offs and the ACE.[4]

Interestingly, the authors of this study found that a GCS score between 10 and 15 was the main factor associated with disagreement between the clinician's assessment and an objective score. GCS is a consciousness score that quickly assesses motor, verbal, and eye responses. A score of 10 or less often is the cut-off for severe dysfunction, and moderately altered patients with a normal state of consciousness often have a GCS score between 10 and 15. Assuming that a patient in a coma does not have capacity, clinicians often will assume that recovery of consciousness after coma results in recovery of decision-making without using a rigorous and focused objective method to assess their patients.

These results should encourage all clinicians to take more time in assessing patient capacity with a face-to-face interview along with using a scoring system that objectively supports their initial subjective assessment. Within this study, 41 of the 71 patients who consented to enroll in the study because the attending physician had considered them to have decision-making capacity were identified later as incapacitated by the score. Further studies are necessary to refine how best to perform these assessments in a busy clinical environment, how they may be customized further for specific patient populations, and how best to develop these clinical skills within medical training to ensure that clinicians are proficient. ■

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CME/CE QUESTIONS

1. In the ROSE trial, which adverse effect occurred more frequently in the early neuromuscular blockade group?
a. Recall of paralysis
b. Lower Medical Research Group scale for muscular strength score
c. ICU-acquired weakness at day 28
d. Barotrauma

2. In the Schreier study, which of the following is hypothesized as a possible cause for the increased risk of acute kidney injury stage 1 seen with piperacillin/tazobactam/vancomycin treatment?
a. Acute tubular necrosis
b. Acute interstitial nephritis
c. Competitive inhibition of creatinine secretion by piperacillin
d. Crystallization of piperacillin/vancomycin adduct in the glomerulus

3. Clinicians confused which of the following with decision-making capacity?
a. Consciousness
b. Orientation
c. Alertness
d. Verbal responsiveness