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SPECIAL FEATURE

Massive Hemorrhage and Transfusion Protocols in Trauma and Nontrauma Patients

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

Massive hemorrhage with hemodynamic instability or shock may arise from multiple causes and is a medical emergency requiring intensive care. Hemorrhagic shock typically develops with the loss of 30-40% of blood volume. Thankfully, its incidence is likely low, estimated to be 2.5-4.5 per 10,000 person-years.[1] Treatment is focused on resuscitative efforts to restore blood volume and stop bleeding. Time is required to locate and secure the sources of blood loss. It is in this setting that resuscitation to maintain oxygen concentration, cardiac output, and circulating blood volume is necessary for survival. Massive transfusion protocols (MTPs) have been developed to provide rapid access to and administration of blood products in these situations.

Massive transfusion is defined as receiving at least 10 units of packed red blood cells within 24 hours. Given the acuity and need for rapid identification, alternative definitions with a shorter time interval, such as three or even four units of packed red blood cells over one hour, may be more meaningful.[2] Patients requiring massive transfusions may have baseline coagulopathy due to comorbidities. In addition, these patients may develop secondary coagulopathy due to the activation and consumption of clotting factors from direct tissue trauma (acute traumatic coagulopathy). Further, patients may exhibit reduced factor activity resulting from hypoxia, acidosis, or hypothermia or as a result of the dilutional effects of resuscitative efforts.

In trauma patients, it is estimated that 25% of severely injured patients are coagulopathic from hyperfibrinolysis and endothelial activation resulting from direct tissue damage, hypoperfusion, and inflammation.[3]

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TRAUMA

Most available data regarding critical bleeding and massive transfusion are focused within the trauma literature. Up to 40% of trauma deaths occurring during hospital admission are from massive hemorrhage.[4] In the early 2000s, the term "damage control resuscitation" was established to encompass the principles of rapid hemorrhage control with early administration of balanced blood components, prevention of coagulopathy, immediate correction of coagulopathy, and the minimization of crystalloid fluids. It became the standard of care for battlefield resuscitation.

Over the past decade, several retrospective, observational studies in both military and civilian trauma populations have demonstrated increased survival when the amount of plasma and platelets transfused increased comparatively to packed red blood cells.[5-9] Changes in these ratios also have shown a reduction in multiorgan failure and postinjury complications, such as pneumonia and abdominal compartment syndrome.[10] During this same period, the rate of trauma patients requiring massive transfusion also decreased by 40%.[11]

In 2015, Holcomb et al published a large multicenter, randomized trial in which they reported that among a civilian trauma population with severe trauma and major bleeding, there was not a significant difference in primary end-points of mortality at 24 hours (12.7% vs. 17.0% $P = 0.12$) and 30 days (22.4% vs. 26.1%; $P = 0.26$) when patients were transfused by ratios of 1:1:1 or 1:1:2 (plasma:platelets:red blood cells).[4] Holcomb et al showed that more patients achieved hemostasis, and there were fewer deaths at 24 hours in the 1:1:1 group.

In response to this expanding knowledge regarding the physiology and management of massive hemorrhage in trauma patients, medical professionals developed a protocol-driven concept concerning a fixed-ratio of packed red blood cells to other blood component resuscitation. MTPs have been shown to expedite delivery of blood products, probably through improved communication and planning. When massive transfusion events driven by protocol are compared to those in hospitals without established protocols, there is a significant improvement in survival, as well as reductions in blood product use, waste, and incidence of transfusion-related complications.[12]

These protocols have been adopted widely across the United States and are now a requirement of several accrediting organizations, such as the American College of Surgeons Trauma Quality Improvement Program and the AABB (formerly the American Association of Blood Banks)/The Joint Commission Patient Blood Management standards. Societal recommendations for the initiation of massive transfusion protocols in trauma patients are variable, but generally include a clinical assessment of both tissue perfusion and the estimated blood loss combined with a validated prediction score.

There are two different prediction scores recommended by separate societies, both of which have been validated. The Assessment of Blood Consumption score is recommended by the American Society of Anesthesiologists and the American College of Surgeons. This simple scoring system considers four variables to predict massive transfusion risk: systolic blood pressure < 90 mmHg, heart rate > 120 beats per minute, positive focused assessment with sonography for trauma (FAST), and penetrating mechanism of injury. A score of 2 is the threshold. The Task Force for Advanced Bleeding Care in Trauma recommends the Trauma Associated Severe Hemorrhage Score, which is a seven-variable score requiring two lab results.

Despite the availability of these scoring systems, it can be challenging to determine which patients will require massive transfusion. Even with a well-established MTP, only 19% of a large trauma center's annual activations met the historical definition of massive transfusion (> 10 units in 24 hours).[13]

NONTRAUMA

There are many other causes besides trauma that may result in significant bleeding. In a large U.S. trauma center, MTPs

are, not surprisingly, most commonly activated for trauma (77%), but also may be activated for other reasons, such as gastrointestinal hemorrhage (9%), ruptured aortic aneurysm (5%), and unexpected surgical bleeding or medical bleeding in malignancies.[13] However, many hospitals provide lower level trauma care and/or routine obstetrical care.

As demonstrated in a separate single academic center study, the pattern in these hospitals may be quite different, with trauma accounting for only 49% of MTP activations, whereas vascular rupture (37%), gastrointestinal bleeding (25%), cardiothoracic surgery (17%), and obstetric bleeding (8%) comprised a much larger percentage of activations.[14] Thus, in many hospitals, massive transfusion protocols are activated more frequently in the treatment of nontrauma surgical and critically ill patients.

The use of massive transfusion protocols for the treatment of hemorrhagic shock in nontrauma patients has been supported predominantly by the trauma literature described in this article so far. However, there are distinctions that must be made when comparing these separate patient populations. Nontrauma patients requiring massive transfusion are a heterogeneous group characterized by several comorbid conditions and coagulopathy profiles. They tend to be older, more likely to be on medications that affect platelet function and clotting (such as aspirin or heparin) while in the hospital, and present with a history of liver failure, renal failure, or a malignancy.[14]

In liver disease, normal coagulation factors are reduced. Also, there is an increased production of abnormal vitamin K-dependent factors that can further inhibit the enzymes of the coagulation pathway. In renal failure, uremia leads to platelet dysfunction by impairing platelet aggregation and adhesiveness through its interaction with fibrinogen and von Willebrand factor. Uremia also can cause an abnormal platelet-endothelial reaction.

Obstetric hemorrhage also is associated with a unique pathophysiology. During pregnancy, there is significant plasma volume expansion and dilutional anemia. In addition, routine pregnancy is a prothrombotic state. The placenta expresses a tissue factor that becomes active when there is vascular endothelial disruption, placental trauma, or necrosis. This is a cofactor for the coagulation cascade and clot formation. Disseminated intravascular coagulation may occur when this cascade overwhelms offsetting effects of the anticoagulant proteins, leading to depletion of the coagulation factors and platelets. Thrombocytopenia may result from alternate causes such as gestational thrombocytopenia, HELLP syndrome, immune thrombocytopenia, antiphospholipid syndrome, dilutional thrombocytopenia, or myeloproliferative neoplasm. Major obstetric hemorrhage (> 2.5 L blood loss or > 5 units transfused) complicated 3.7 per 1,000 births in the United Kingdom in the late 2000s. Postpartum hemorrhage accounts for 25% of maternal deaths worldwide.[15]

[Currently, there is no validated prediction score for nontrauma patients to assess the need for massive transfusion.]

Data evaluating nontrauma patients treated with massive transfusion are limited. Within an obstetric population, blood taken predelivery for in vitro testing of effects of blood component ratios revealed that a ratio of 1:1:1 resulted in optimal clot strength with significant strengthening from the addition of platelets.[15]

A retrospective, observational, single-center study conducted to compare transfusion ratios in a nontrauma, massively bleeding population from 2011-2015 revealed that there was no difference in 30-day mortality when patients were transfused above a 1:2 ratio of plasma to red blood cells or platelets to red blood cells.[16] However, the secondary endpoint of 48-hour mortality showed a significant improvement in the > 1:2 platelet to red blood cell group. The mean red blood cell transfusion requirements administered during a massive transfusion episode are similar with gastrointestinal hemorrhage (6.1 units), ruptured abdominal aortic aneurysm (5.7 units), and trauma (7.1 units).[13]

Massive transfusion protocols have been shown to be overactivated 53% of the time in nontrauma patients. Despite this, no unique disadvantage of resource allocation was identified, as there was no difference in product waste when compared to trauma activations, with platelet waste decreasing from 14% to 2%.[17] Currently, there is no validated prediction score for nontrauma patients to assess the need for massive transfusion.

CONCLUSIONS

Hemorrhagic shock requires a concerted effort to reach stability and prevent death. It is a common endpoint of many etiologies, with trauma by far the most widely studied. Through numerous

investigations on massive hemorrhage in both military and civilian trauma, we have gained crucial knowledge regarding the pathophysiology of acute traumatic coagulopathy, which results from direct tissue damage, hypoperfusion, and inflammation leading to fibrinolysis and endothelial activation.

The concept of damage control resuscitation focuses on rapid hemorrhage control with balanced blood component transfusions to correct acute traumatic coagulopathy, preserve oxygen-carrying capacity, and avoid dilutional coagulopathy. Massive transfusion protocols are employed widely and activated for trauma as well as massive hemorrhage from nontrauma causes.

Causes of massive hemorrhage other than trauma are a heterogeneous group associated with different comorbidities and abnormalities in coagulation. Special considerations must be made in certain cases, such as with hepatic and renal failure and obstetric hemorrhages. In these situations, it is difficult to predict who will require activation of the MTP because of the variability within the population. This decision currently requires a clinical assessment of tissue perfusion and blood loss.

In contrast to a trauma population, where prediction scores have been validated, it will be more challenging to develop a prediction tool that could be universal across the nontrauma population. Using the shock index as a variable has been considered. MTPs allow for the rapid delivery of blood components and are beneficial to patient survival. Further research in these areas will help define how treatment may be more effective. ■

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ABSTRACT & COMMENTARY

Can We Prevent Delirium in the ICU?

By Elaine Chen, MD

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

SYNOPSIS: Low-dose nocturnal dexmedetomidine infusion was shown to prevent delirium in critically ill patients.

SOURCE: Skrobik Y, Duprey MS, Hill NS, Devlin JW. Low-dose nocturnal dexmedetomidine prevents ICU delirium: A randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2018;197:1147-1156.

Delirium in the ICU is common and associated with numerous adverse outcomes. The goal is to minimize delirium, but no agents have shown efficacy in preventing or treating delirium in critically ill adults. Dexmedetomidine has been associated with less delirium than midazolam and propofol. Very low-dose nocturnal dexmedetomidine has been shown to improve sleep quality and efficacy. Skrobik et al hypothesized that nocturnal dexmedetomidine would prevent delirium and improve sleep during ICU admission.

The authors conducted a randomized, double blind, placebo-controlled trial in ICUs in two institutions. Both institutions already had well-established pain, sedation, and delirium assessment practices. One hundred patients were enrolled between 2013 and 2016, with 50 in each arm. Eligible patients could consent, received intermittent or continuous sedatives, and were expected to require at least 48 hours of ICU care without meeting exclusion criteria. Patients were randomized to receive nocturnal dexmedetomidine or placebo in a 1:1 ratio. The study drug was administered from 9:30 p.m. to 6:15 a.m. each night, all sedatives were decreased to half, and infusions were titrated by protocol to a target Richmond Agitation Sedation Scale of -1.

The main study outcome was the number of patients who remained delirium-free during critical illness. Taking dexmedetomidine at night was associated with a higher proportion of patients who stayed delirium-free during the stay in the ICU vs. placebo ($P = 0.006$). In the dexmedetomidine group, 80% of patients remained free of delirium compared with 54% in the placebo group, with an absolute risk reduction (RR) of 26% (RR, 0.44; 95% confidence interval, 0.23-0.82) during their ICU stay. Additionally, patients in the dexmedetomidine group logged fewer total days of coma ($P = 0.009$), received a lower average dose of propofol ($P < 0.001$), and took fentanyl at a lower rate (76% vs. 94%; $P = 0.02$). The Leicester sleep evaluation questionnaire did not reveal significant differences in sleep quality. There were no differences in antipsychotic or oral analgesic use, duration of mechanical ventilation, length of stay, ICU or hospital mortality, or frequency of bradycardia or hypotension.

The authors concluded that nocturnal administration of low-dose dexmedetomidine in critically ill adults can help prevent ICU delirium and reduce days spent with coma and overall opiate requirements.

■ COMMENTARY

The Skrobik et al study provides useful information. Other investigators failed to identify a safe and effective pharmacologic strategy to either prevent or treat delirium in critically ill adults. In fact, the REDUCE trial showed that haloperidol, commonly used to treat ICU delirium, did not prevent delirium.[1] The complex interplay between critical illness, delirium, cerebral perfusion, medications, and sleep makes study of this topic difficult. Prevention and treatment are difficult to distinguish, as many investigators enroll both delirious and nondelirious patients. In this study, patients who were delirious at the time of screening were excluded, thus ensuring that prevention was studied, but limiting generalizability to patients with early-onset delirium.[2]

Additionally, sleep was evaluated by self-report rather than with polysomnography, the objective gold standard. It is unclear why the dexmedetomidine group received less fentanyl and whether this is related to prevention of delirium. As nocturnal dexmedetomidine was studied, it is unclear whether continuous infusion would affect delirium prevention. Limiting the drug to nocturnal-only administration potentially could limit side effects and cost, but also might limit benefit. Long-term outcomes such as cognitive impairment also should be studied.

The Skrobik et al study results offer exciting potential for the future of delirium management in the ICU. However, these results do not change practice yet. This article is hypothesis-generating and leads to more questions than answers. The use

of dexmedetomidine has increased over the past few years in our critically ill patients. I suspect its use will continue to increase.

Notably, this study was sponsored by Hospira Canada, the manufacturer of dexmedetomidine. Two authors were the first and second authors in the new clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in critically ill adult patients that were published in *Critical Care Medicine* in September 2018. Those guidelines do not yet recommend pharmacologic modalities for preventing delirium.[3] I look forward to future advances in delirium management and the potential varying uses of dexmedetomidine. ■

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ABSTRACT & COMMENTARY

Limited English Proficiency Associated With Significant Differences in End-of-life Care

By Betty Tran, MD, MSc, Editor

SYNOPSIS: In a retrospective cohort study, patients with limited English proficiency had lower rates of do not resuscitate orders, comfort measures orders, and advanced directives; higher rates of receiving certain types of life support; and longer hospital stays compared to their English-speaking counterparts.

SOURCE: Barwise A, Jaramillo C, Novotny P, et al. Differences in code status and end-of-life decision making in patients with limited English proficiency in the intensive care unit. *Mayo Clin Proc* 2018;93:1271-1281.

Limited English proficiency (LEP) has been associated with longer hospital stays, higher rates of readmission, less health education, worse interpersonal care, and lower patient satisfaction.[1-3] In addition, in the ambulatory setting, patients with LEP often engage in lower quality goals-of-care discussions and experience poor end-of-life symptom management, especially when professional interpreters are not used, which often is the case.[4] In the context of these prior findings, Barwise et al sought to close knowledge gaps regarding the effect of LEP on life support and end-of-life decisions in the ICU.

In this retrospective cohort study, 27,523 adults who were admitted to any of seven ICUs were analyzed. LEP was defined as primary language other than English as captured in the electronic medical record. The primary outcomes included code status on ICU admission, code status on ICU discharge, change in code status during ICU stay, use of life support (e.g., invasive and noninvasive mechanical ventilation, dialysis, vasopressors, cardiopulmonary resuscitation), presence of advance directives, and implementation of an institutional comfort measures only order set. Secondary outcomes included use of restraints, documentation of a family conference, presence of symptoms, ICU and hospital length of stay (LOS) and mortality, and hospital discharge location. Overall, patients with LEP were younger, more likely to be uninsured (14% vs. 2.1%; $P < 0.001$), scored lower on the APACHE III scale (54 vs. 58; $P < 0.001$), less likely to report Christian religion (38.3% vs. 77.3%; $P < 0.001$), or be high school graduates (18.9% vs. 30.7%; $P < 0.001$). After adjustment for APACHE III score, sex, educational level, and insurance status, patients with LEP were less likely to have advance directives on ICU admission (odds ratio [OR], 0.23; 95% confidence interval [CI], 0.18-0.28; $P < 0.001$), a do not resuscitate (DNR) order on ICU admission (OR, 0.30; 95% CI, 0.11-0.80; $P = 0.02$), DNR on discharge (OR, 0.60; 95% CI, 0.45-0.79; $P < 0.001$), or change from full code status to DNR during their ICU stay (OR, 0.62; 95% CI, 0.46-0.82; $P < 0.001$). For those who experienced a change in code status, this took 3.8 days longer (interquartile range, 1.9-5.6 days) compared to patients without LEP ($P < 0.001$). Documentation of a family conference was higher for patients with LEP (OR, 2.53; 95% CI, 1.86-3.43; $P < 0.001$). Patients with LEP were more likely to receive invasive mechanical ventilation (OR, 1.26; 95% CI, 1.07-1.48; $P = 0.005$), but less likely to receive noninvasive mechanical ventilation. They also were more likely to be restrained (OR, 1.36; 95% CI, 1.11-1.65; $P = 0.003$), despite lower rates of nurse-assessed delirium, agitation, and pain. Patients with LEP were less likely to have a comfort measures only set ordered; for those who did, it took 19.1 days longer to place the order compared to patients without LEP. ICU and

hospital LOS were significantly longer for patients with LEP (0.6 days and 2.5 days, respectively), and patients with LEP were more likely to be discharged home. There were no differences between groups in terms of ICU or hospital mortality or rates of palliative care consultation.

■ COMMENTARY

This is the first study to highlight that code status, advance directives, life support decisions, patient symptoms, and end-of-life care in the ICU are different for patients with LEP compared to patients who speak primarily English. The findings that patients with LEP demonstrate lower rates of and delayed initiation of DNR orders and comfort measures before death could imply either that more patients with LEP desire to die with full support rather than withdraw/withhold life support or that communication and other barriers exist that prevent healthcare providers from effectively assessing and implementing comfort care measures for LEP patients at the end of life. In reality, both scenarios may be true depending on the patient/surrogate involved. The factors that support the study's findings are likely complex and intricately interconnected. Patients with LEP are a heterogeneous group regarding cultural norms, religious tenets, and languages. Given this wide range, it is likely inevitable that communication barriers will surface, especially in end-of-life discussions, which already are unique, multifaceted, and emotional. Although the investigators adjusted for severity of illness, education, sex, and insurance status, other factors such as cultural concerns, religious beliefs, trust and perception of medical providers, and communication barriers likely contribute to the differences seen between the two groups. Future reforms in improving end-of-life care for ICU patients will need to recognize the group of patients with LEP distinctly; increase awareness and respect for religious, cultural, and health literacy variations that may influence care decisions at the end of life; and focus on ensuring appropriate language interpretation during all aspects of patient care, from assessment to decision-making. ■

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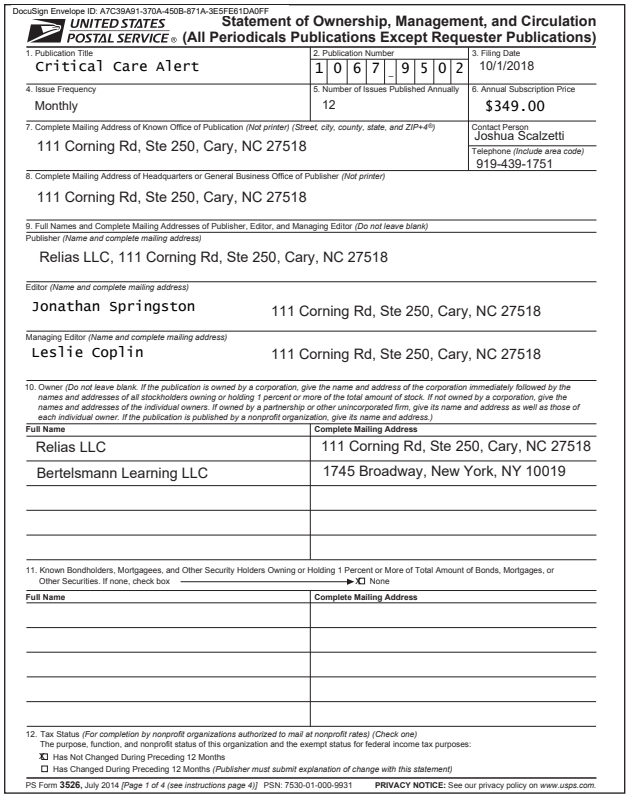

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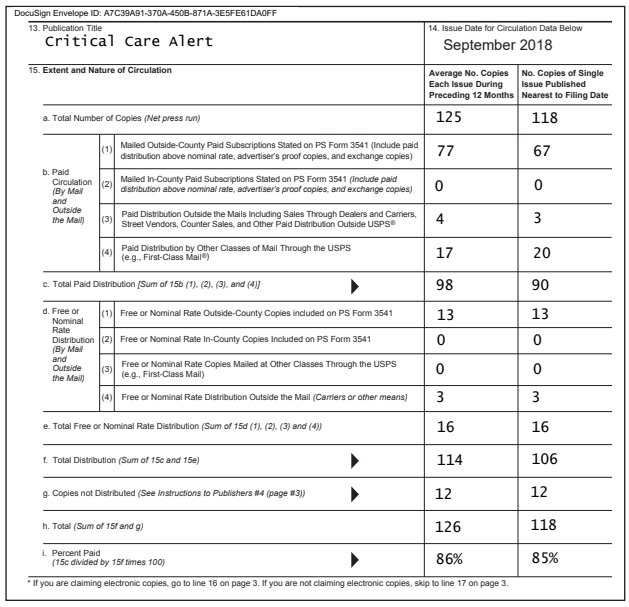

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c. Total Paid Distribution *[Sum of 15b (1), (2), (3), and (4)]* ▶			98	90
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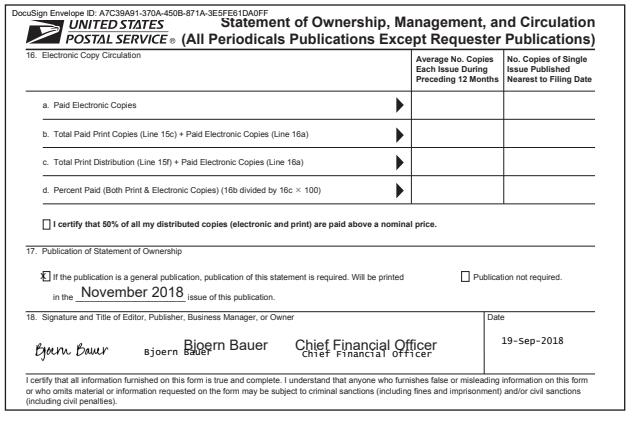
f. Total Distribution *(Sum of 15c and 15e)* ▶			114	106
g. Copies not Distributed *(See Instructions to Publishers #4 (page #3))* ▶			12	12
h. Total *(Sum of 15f and g)*			126	118
i. Percent Paid *(15c divided by 15f times 100)* ▶			86%	85%

* If you are claiming electronic copies, go to line 16 on page 3. If you are not claiming electronic copies, skip to line 17 on page 3.



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CME/CE QUESTIONS

1. **What did Holcomb et al show in a large randomized, clinical trial regarding plasma to platelets to red blood cell ratio?**
   a. Improved 30-day mortality with 1:1:1
   b. Improved 24-hour mortality with 1:1:1
   c. Fewer deaths due to exsanguination at 24 hours in the 1:1:1 group
   d. Increased ICU-free days in the 1:1:1 group

2. **Which is the true statement?**
   a. The Assessment of Blood Consumption score may be used in nontrauma patients with hemorrhagic shock.
   b. Liver disease is more common in nontrauma massive hemorrhage.
   c. 1:1:1 blood component resuscitation improves mortality in obstetric hemorrhages.
   d. Most massive transfusion protocol activations result in > 10 units of packed red blood cells transfused.

3. **In the low-dose nocturnal dexmedetomidine study by Skrobik et al, which of the following were found in patients who were randomized to dexmedetomidine compared to placebo?**
   a. Patients experienced improved sleep quality as measured by polysomnography.
   b. Patients exhibited more incidences of bradycardia and hypotension.
   c. Patients required equivalent amounts of propofol and antipsychotics.
   d. Patients required fewer intravenous infusions of fentanyl.

4. **Low-dose nocturnal infusion of dexmedetomidine in critically ill patients has been shown to:**
   a. decrease antipsychotic use.
   b. decrease frequency of delirium.
   c. improve sleep quality.
   d. decrease length of stay in the ICU.

5. **In the study by Barwise et al, which of the following statements is *true* regarding patients with limited English proficiency (LEP) compared to those without LEP?**
   a. They were more likely to have existing advance directives prior to admission to the ICU.
   b. They were more likely to have their code status changed to do not resuscitate in the ICU.
   c. They were more likely to have comfort care measures orders placed while in the ICU.
   d. They were more likely to receive mechanical ventilation while in the ICU.

6. **In the Barwise et al study, compared to patients who speak English proficiently, the care of patients with LEP in the ICU is notable for:**
   a. increased use of restraints.
   b. increased nursing-reported rates of delirium.
   c. increased nursing-reported rates of pain.
   d. increased use of continuous IV sedation.

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.