adequate surveillance for neurologically devastated patients and pathway-driven management particularly if patient family intent is unknown (13).

Malinoski et al (6) have demonstrated the effects of DMGs on OTPD in this prospective trial. Causality is difficult to demonstrate in this type of study; however, the desire for organs from patients meeting DMGs was much higher from the transplant centers standpoint than those donors who failed to achieve DMGs. What were notable were the rates of thoracic organ transplantation when DMGs were met prior to recovery (Table 5). The physiologic consequences of brain death and cardiopulmonary dysfunction have led to attempts at management standards and hormonal resuscitation to improve their recovery (8). Using DMGs as a guide to normalize physiologic parameters does make good clinical sense and provides a common language for often poorly defined end points. The current study only discusses standard criteria donors and much work remains to be done on those donors in the expanded/extended criteria donor and donation after cardiac death groups. As management strategies continue to evolve, more aggressive intensive care unit care is likely the result. Ethical considerations are valid concerns (14), especially when discussing the sensitive area of "pre-consent" management. Intensive care unit professionals will be vital to ongoing research and management strategies with this very difficult to manage subset of patients. Malinoski and his coauthors are to be commended for their addition to the growing literature regarding this topic.

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The many facets of procalcitonin in the critically ill population*

The use of biomarkers in critically ill patients is increasing, and now it is incorporated into daily management of inflammatory diseases, mainly severe sepsis. A myriad of old and new biomarkers have been studied, but blood leukocytes, C-reactive protein (CRP), and procalcitonin (PCT) are those most used in clinical practice; however, their accuracy for the triage of diagnosis and therapeutic interventions of severe sepsis is heterogeneous (1). Blood leukocytes, for example, are influenced by almost every inflammatory stimulus, turning it less useful for the management of severely ill patients. CRP and PCT are widely used for both diagnosis and antibiotic guidance. PCT can reflect the severity of systemic inflammatory response syndrome to infection, probably because it is more specific to differentiate between infectious and sterile causes of systemic inflammatory response syndrome (2), although it can also be increased in noninfectious diseases (e.g., cardiogenic shock and acute pancreatitis) (3, 4).

CRP and PCT followed opposite directions on sepsis biomarkers issue. Natural history, kinetics, and response to treatment with CRP were elucidated (5). Daily monitoring of CRP levels can identify intensive care unit (ICU)-acquired infections early, and its patterns of response to treatment (rapid, slow, or no decay) are also associated with prognosis (6). However, there were no clinical trials using this biomarker to guide patient's management. On the other hand, PCT was studied in clinical trials evaluating antibiotic stewardship, mostly of pneumonia. Serum PCT is known to rise early in severe sepsis, mainly by pneumonia and bloodstream infections (7–10). Unlike CRP, serial

*See also p. 2781.

Key Words: critical care; infection; procalcitonin; sepsis; shock

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measurements of PCT were not fully elucidated in the critically ill population (8). In this issue of *Critical Care Medicine*, Reynolds and colleagues (11) filled part of this gap investigating the natural history of this biomarker in a cohort of critically ill patients.

Reynolds and co-workers (11) conducted a prospective, three-center, observational study, in which PCT levels were followed for the first 10 days after ICU admission (11). The authors closely observed sequential measurements in a heterogeneous group of critically ill patients analyzing longitudinal changes of PCT according to the type of admission, the presence of infection, and the influence of shock. Medical and surgical patients presented similar timely peak and baseline levels; infected patients had higher PCT levels for 10 days, mainly when associated with shock. Prevalent infection, as said infection present on the day of ICU admission or within 48 hrs before, was associated with higher PCT peak values and longer decay over the 10-day period when compared with ICU-acquired infection (incident). Gram-positive infections were associated with slower PCT decay, although there were no differences on the magnitude of PCT levels between culture-positive or culture-negative infections, or between Gram-positive or Gram-negative bacterial etiologies.

New evidences of PCT behavior in critically ill patients have emerged. The first amazing point is the impact of shock on PCT levels. Infected patients with shock presented higher levels than infected patients without shock and also shock patients without infection. We should closely regard two points. The presence of shock can leverage PCT to much higher levels, suggesting that this biomarker is also driven by inflammatory stimuli, such as bacterial intestinal translocation or the release of damage-associated molecular pattern molecules after ischemia-reperfusion lesions (12). Another observation is that patients with shock also presented significantly higher serum levels than their brackets with no shock, even without infection. After 7 days, PCT levels were similar, regardless of the presence of infection or shock. Although PCT usually shows high specificity for severe infections, data recorded by Reynolds and colleagues suggest a role of inflammatory response magnitude on PCT kinetics. To reinforce this observation, it is known that exogenous PCT can induce the release of cytokines and inhibit neutrophil function, probably by a lipopolysaccharide-independent mechanism (13). So, it is possible to link PCT levels with the severity of infection.

Another interesting evidence was the lower level of PCT associated with infections acquired after 4 days of ICU stay. PCT values have already been shown to be lower after the second bloodstream infection associated with sepsis, when compared with the first episode (14). Reynolds et al (11) showed a more discrete slope of PCT changes of patients with ICU-acquired infections, when they were compared to patients admitted with infections. One can point to two possible explanations for this result. First, ICU-acquired infections could be diagnosed and treated earlier than prevalent infections, and the prompt management of infections with antibiotics could avoid the increasing levels of biomarkers. Another possibility would be an effect of "immune fatigue," or immune paralysis, as the infected host is no longer able to respond to a new inflammatory event to the same degree as previous events (15).

Some limitations were observed in Reynolds' study. The authors could not infer any relation between PCT serial patterns with prognosis. It is not known if PCT oscillates with treatment interventions, such as surgeries or inflammatory drugs, such as steroids. Because the authors did not collect a list of patients' interventions through ICU stay, it is not possible to evaluate PCT variations according to outcome. Another limitation about this study was the absence of the correlation of PCT with sepsis severity, as systemic inflammatory response syndrome, sepsis, severe sepsis, and septic shock could present a grade of PCT changes over time (8). The association of infection and shock on this study could only represent a surrogate for this outcome, but it cannot substitute sepsis grading system. The positivity of culture examinations and the classification of bacterial infections according to the Grain stain in the face of CPT values were analyzed, but the authors could not do the same with the etiology and the site of infection, such as pneumonia and peritonitis. One reason for this limitation was the relative small subgroup of infected patients, turning it jeopardized by this small sample.

Reynolds and colleagues brought new evidence of PCT changes over the first days of ICU stay, and they opened a window of opportunities for the better knowledge of PCT behavior in the critically patient. It became clear that the case mix population influence serial measurements of this biomarker, making it probably more useful for critically ill patients admitted with infection and shock.

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Sedation, nighttime, icebergs, and the Titanic*

In this issue of *Critical Care Medicine*, Seymour et al (1) seek to determine whether patients enrolled at one center involved in the Awakening and Breathing Controlled (ABC) trial received higher doses of a benzodiazepine or propofol at night and whether daytime and nighttime sedative dosing was associated with delirium, coma, or a delay in liberation from mechanical ventilation (2, 3). Deep sedation still occurs frequently in the intensive care unit (ICU) despite its association with a longer duration of mechanical ventilation and ICU stay, a greater prevalence of delirium, and higher mortality (4–7). Studies linking successful strategies focused on increasing patient wakefulness (such as protocolized titration, daily sedation interruption, or paired spontaneous awakening-spontaneous breathing trials) with improved outcomes often get simplified in our memory, with recollection of only the specific intervention that was investigated (2, 8, 9).

Just as the disaster that befell the Titanic during the fifth night of its journey, April 14, 1912, had less to do with the iceberg and more to do with factors such as the design of the ship, the number of lifeboats, a failure to heed warnings of the presence of icebergs, and the lack of response from nearby ships; many factors other than nighttime increases in sedative dosing may explain the outcomes observed in this single-site secondary analysis (10). These factors include patient-specific variables, drug-related issues, and environmental confounders (11).

Using data from the first 5 days that patients participated in the study, benzodiazepine and propofol doses were increased in 40% and 41%, respectively, of the patient nights (11 PM to 7 AM) compared to the hourly doses administered during the prior day (7 AM to 11 PM) (3). After adjusting for random allocation to the ABC study intervention, the investigators found that higher doses of a benzodiazepine or propofol, and the increased administration of either at night, were associated with a greater likelihood for coma. However, while higher daytime doses and nocturnal increases in benzodiazepine dosing were associated with delirium and failed spontaneous breathing trials, greater daytime propofol doses and increases at night were not. The specific pharmacokinetic and pharmacodynamic properties of sedatives play an important, and frequently complex, role in defining the outcome of therapy and should be considered when individualizing sedation therapy in the ICU (12, 13).

Despite the use of a daily spontaneous awakening protocol among half the patients, coma and/or delirium defined 75% of the 485 patient days that were included in the analysis (3). This is consistent with prior studies such as Kress et al who showed that patients in the control arm (without scheduled sedation interruption) were awake on only 9% of ICU days or Brook et al who showed that patients not managed with a nurse-driven sedation protocol spent more time on the ventilator, in the ICU, and in the hospital (8, 9).

Although nocturnal increases in sedation may impact outcome, sedation that is administered during the daytime remains important. In this study, the proportion of nights when lorazepam dosing decreased (45%) exceeded the nights when dosing increased (41%), and the size of the dose increases at night were small for both lorazepam (0.2–0.5 mg/hr) and propofol (4–9 μg/kg/min). Based on the mean doses presented in Figure 1, these dosing increases represent only a 10% increase for lorazepam and 14% increase for propofol. With lorazepam and midazolam known to accumulate in a time-dependent fashion when administered as a continuous infusion, the nighttime period (8 hrs) was only half as long as the daytime period (16 hrs), making nocturnal dosing changes less important than dosing increases during the day (12, 14). In fact, the analysis demonstrated that increases in benzodiazepine dosing during the daytime period had an association with spontaneous breathing trial failure and delirium that was far stronger than that observed at night, and unlike the outcomes that were associated with benzodiazepine dosing increases at night, daytime benzodiazepine increase was also associated with greater extubation failure.

While the average doses of lorazepam (4–5 mg/hr) and propofol (40–50 μg/kg/hr) administered from this site appear higher than the doses reported in the parent study, it should be noted that these averages represent sedation administration over only the first 5 study days (2). Sedation-associated coma and delirium are both dose-related; the administration of higher doses likely lead to a higher prevalence of both these undesirable outcomes (2, 3, 6, 7, 15). A common target

***See also p. 2788.**

Key Words: coma; delirium; mechanical ventilation; nocturnal; sedation

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