

Inpatient hyperglycemia management: The voyage continues!*

We have known for some time now the strong association between hyperglycemia and increased risk of complications in hospitalized patients (1–3). We have also known that in-hospital hyperglycemia confers increased risk of mortality not only in patients with diabetes, but especially in those who manifest hyperglycemia for the first time during critical illness (1, 4). These findings were supported in the sentinel clinical trial by van den Berghe et al, in which critically ill surgical patients randomized to a tight glucose target of 80 to 110 mg/dL experienced significant reductions in morbidity and mortality when compared with a glucose range of 180 to 200 mg/dL (5). This trial was the genesis for the concept and promotion of tight glucose control (TGC) in all critically ill patients (6, 7). Subsequent attempts to further define the impact of TGC have, however, produced inconsistent results, finding not only minimal or no benefit in mortality (8, 9), but also exposing the increased incidence of hypoglycemia. So, although intensive insulin therapy is designed to achieve TGC, it also increases the risk of hypoglycemia, which is thought to be an independent risk factor for mortality (10, 11).

More recently, the benefit of TGC has been further challenged by the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation trial (12). In this well-designed multicentered study, Finfer et al randomized 6104 critically ill patients to TGC (blood glucose [BG] 81–108 mg/dL) or a BG range of 144 to 180 mg/dL with a primary end point of 90-day mortality. Surprisingly, the tight control group was found to have a 14-fold increase in 90-day

all-cause mortality compared with the control population. None of the secondary outcome measures (including 28-day mortality) were different between the two groups. Nonetheless, the authors concluded that it could not be considered safe to target BGs in the 81 to 108-mg/dL range for critically ill patients. Although no causality for this increase in 90-day mortality has been established, some have argued that the high rate of hypoglycemia (6.8% in the intensive group compared with 0.5% in the conventional group) could have been a factor contributing to the deaths. Following these results, the American Diabetes Association and the American Association of Clinical Endocrinologists convened a consensus panel to review the data on inpatient hyperglycemia management. The panel issued revised recommendations advising that targets of 140 to 180 mg/dL might be safer in critically ill patients unless under the care of expert teams with validated protocols in which case a target of 110 to 139 mg/dL might be appropriate. Given the increased risk for hypoglycemia, the panel felt that a BG of <110 mg/dL, as they had previously recommended (6), could no longer be considered safe (13).

In this issue of *Critical Care Medicine*, it is in this context that the report by Falciglia et al (14) makes an important contribution to our understanding of critical illness hyperglycemia. In their elegantly crafted retrospective cohort study of 259,040 veterans, the authors considered clinically important factors, including patient age, admission diagnosis, mean central laboratory-derived BGs, and other laboratory values using a well-validated method to predict mortality. They sought to determine the independent contribution of mean glucose to mortality risk in all intensive care unit patients using the normoglycemic (70–111 mg/dL) cohort for comparison and found that hyperglycemia was associated with increased mortality independent of severity of illness in all patients. The adjusted odds of mortality (odds ratio [95% confidence interval]) for mean glucose increased within the selected ranges: 111 to 145 (1.31 [1.26–1.36]); 146 to 199 (1.82 [1.74–1.90]);

200 to 300 (2.13 [2.03–2.25]); and >300 (2.85 [2.59–3.14]). However, and more importantly, adjusted mortality in critically ill patients presenting with hyperglycemia was found to vary with admission diagnosis rather than with disease severity, type of intensive care unit, diabetes status, or length of stay. The adjusted odds of mortality related to hyperglycemia were significantly higher in patients with sudden-onset conditions such as acute myocardial infarction, arrhythmia, unstable angina, stroke, pulmonary embolus (Table 3) and even greater in patients without diabetes (Fig. 2) (14). This new evidence may explain some of the confounding results of the clinical trials and meta-analyses to date (8, 9, 12). Certainly the two Leuven trials reflected differences in the medical and surgical populations (5, 15). Also, because Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation included all comers to medical and surgical intensive care units, secondary analysis may yield differences in outcomes in subsets of patients.

The Falciglia study suggests that one shoe may not fit all critically ill patients when it comes to blood sugar targets. The challenge is to determine what constitutes optimal glucose control. In this study, unadjusted mortality was lowest in the reference glucose range of 70 to 110 mg/dL (Appendices 1 and 2). When adjusted for relevant factors, mortality was lowest in the range of 111 to 145 mg/dL. These data would suggest that an optimal target range lies between 70 and 145 mg/dL, although Figure 1B appears to show that hypoglycemia may be contributing to higher mortality in some. An analysis of the data from patients experiencing hypoglycemia would be very helpful in this context. Despite this, the authors' focus on hyperglycemia reminds us that normal blood glucose levels are associated with improved survival. Considering the multiple combinations of factors that characterize unstable, critically ill patients, these findings reveal that glucose targets are only part of the dilemma. The clinical community is still left with finding the means to achieve glycemic con-

*See also p. 3001.

Key Words: critical care; hyperglycemia; mortality; glycemic control; diagnosis

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tol while mitigating iatrogenic hypoglycemia. As we continue in our quest to determine how “tight” the blood glucose needs to be in critically ill patients, we must consider two attributes inexorably linked to any TGC strategy: timely BG testing and well-validated intravenous insulin protocols, a position endorsed by the American Diabetes Association/American Association of Clinical Endocrinologists consensus panel (13). Clearly more evidence is needed, and the design of any future clinical trial will need to consider admission diagnosis. This journey has only just begun. While we await more data, we should not abandon course; we must continue our efforts to treat hyperglycemia in critically ill patients, albeit with target ranges and protocols that minimize the risk for hypoglycemia.

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REFERENCES

1. Umpierrez GE, Isaacs SD, Bazargan N, et al: Hyperglycemia: An independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab* 2002; 87:978–982
2. Dellinger R, Levy M, Carlet J, et al: Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; 36: 296–327
3. Grey NJ, Perdrizet GA: Reduction of nosocomial infections in the surgical intensive care unit by strict glycemic control. *Endocr Pract* 2004; 10(Suppl 2):46–52
4. Kosiborod M, Rathore SS, Inzucchi SE, et al: Admission glucose and mortality in elderly patients hospitalized with acute myocardial infarction: Implications for patients with and without recognized diabetes. *Circulation* 2005; 111:3078–3086
5. Van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; 345:1359–1367
6. Garber AJ, Moghissi ES, Bransome ED, et al: American College of Endocrinology Position Statement on inpatient diabetes and metabolic control. *Endocr Pract* 2004; 10: 77–82
7. Clement S, Braithwaite SS, Magee MF, et al: The Diabetes in Hospital Writing Committee: Management of diabetes and hyperglycemia in hospitals (technical review). *Diabetes Care* 2004; 27:553–591
8. Brunkhorst FM, Engel C, Bloos F, et al: Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; 358:125–139
9. Wiener RS, Weiner DC, Larson J: Benefits and risks of tight glucose control in critically ill adults: A meta-analysis. *JAMA* 2008; 300: 933–944
10. Krinsley JS, Grover A: Severe hypoglycemia in critically ill patients: Risk factors and outcomes. *Crit Care Med* 2007; 35:1–6
11. Kosiborod M, Inzucchi SE, Goyal A, et al: Relationship between spontaneous and iatrogenic hypoglycemia and mortality in patients hospitalized with acute myocardial infarction. *JAMA* 2009; 301:1556–1564
12. The NICE-SUGAR Investigators: Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; 360: 1283–1297
13. Moghissi ES, Korythowski MT, DiNardo M, et al: American Association of Clinical Endocrinologists and American Diabetes Association Consensus Statement on inpatient glycemic control. *Endocr Pract* 2009; 15:1–17
14. Falciglia M, Freyberg RW, Almenoff PL, et al: Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. *Crit Care Med* 2009; 37:3001–3009
15. Van den Berghe G, Wilmer A, Hermans G, et al: Intensive insulin therapy in the medical ICU. *N Engl J Med* 2006; 354:449–461

Triaging severe pneumonia: What is the “score” on prediction rules?*

Community-acquired pneumonia results in substantial morbidity, mortality, and cost (1–4). Patients with severe community-acquired pneumonia, usually defined by admission to the intensive care unit (ICU), have mortality rates as high as 13% to 37% (4–8) and accrue four times the cost of non-ICU patients (4). Clinical prediction rules have been used to identify patients with severe disease for purposes of prognostication and resource allocation, specifically assessing eligibility for ICU admission.

Multiple prediction rules are available, including the Infectious Disease Society of America/American Thoracic Society (IDSA/ATS) criteria, Pneumonia Severity Index, British CURB-65, Australian SMART-COP, and Spanish CURXO-80 (9–13). Prediction rules like the Pneumonia Severity Index and CURB-65 have been useful for standardizing clinical assessments and identifying low-risk patients with pneumonia who might be appropriate for outpatient therapy (10). These rules have been far less useful at discriminating between moderate (ward) and high-risk (ICU) patients. Granted, these prediction rules vary widely in their ease of use, resource requirements, accuracy, sensitivity, specificity, and responsiveness over time. Validated and clinically useful assessment tools are sorely needed to help acute care

physicians better prognosticate and allocate scarce resources. Therefore, the IDSA/ATS criteria were revised in 2007 and (empirically) recommended ICU admission when one of two major or three or more of nine minor criteria were fulfilled (9). The major criteria (need for invasive mechanical ventilation or vasopressors) have been validated (14), although it is hardly arguable that these patients would not warrant ICU admission. The IDSA/ATS expert panel also suggested that equally weighted combinations of the nine minor criteria might help predict which other patients could still benefit from ICU admission. The use of these minor criteria were validated in Singapore by Phua et al (15); they found them more specific than the Pneumonia Severity Index and more sensitive than the CURB-65 for predicting mortality and ICU admission.

*See also p. 3010.

Key Words: severe community-acquired pneumonia; intensive care; prediction models; severity scoring; mortality; IDSA/ATS screening criteria; resource allocation

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In this issue of *Critical Care Medicine*, the article by Brown et al (16) is a well-conducted relatively large single-center North American observational study that importantly adds to this literature because it further validates the use of the minor criteria for identifying patients with severe community-acquired pneumonia who are best cared for in an ICU and it also demonstrates that the criteria can be captured from routinely collected data stored in electronic health records. Despite its strengths, however, it represents yet another attempt at tweaking our ability to try to figure out which patients with pneumonia might benefit from ICU admission. In part this is the result of the usual shotgun approach—trying to have one prediction rule generated at the time of initial assessment that fits all purposes. Future approaches, as done by Brown et al (16), should eliminate patients who require mechanical ventilation or vasopressor support because it is self-evident these patients need ICU admission and no prediction rule will influence site of care. Instead, future rules should focus on predicting who will deteriorate after admission to the ward. There may be distinct subsets within this population suggesting a one-size-fits-all approach will still not work; for example, those who deteriorate because pneumonia: 1) adversely affects a comorbid illness such as exacerbating stable heart failure or chronic obstructive pulmonary disease; 2) progresses as a result of a virulent or resistant pathogen; or 3) leads to complications, either local (empyema) or systemic (multisystem organ failure). Regardless, rather than predicting who needs to go to the ICU at admission, better algorithms might be developed for predicting who is going to decompensate and require more aggressive management.

Indeed, the most useful approach might be the one that uses serial assessments at admission, at 12 to 24 hrs, and later as clinically indicated. Up to now, scores on admission have been used in isolation. One measurement of severity seems unlikely, to us, to reflect a dynamic illness such as pneumonia. It is during the postadmission phase that patients may initially appear to be doing quite well but then decompensate. Serial assessments of severity have rarely been studied but hold great promise (17).

No severity of illness scoring system will likely deliver on all fronts. We believe

that the best chance of success will be some combination of biomarkers (e.g., procalcitonin, C-reactive protein, advanced metabolomics or proteomics), better measures of functional status and frailty (e.g., confusion, a loosely defined sign, was a powerful predictor of severe community-acquired pneumonia in both the studies by Phua et al [15] and Brown et al [16]), and a pneumonia-specific scoring system designed to not only predict mortality, but risk of decompensation. We have a long way to go before we can fill this obviously tall order. In our experience, we have yet to see any tool or algorithm that can trump the clinical judgment of a seasoned and adequately resourced acute care physician who serially assesses his or her patient with decompensation-prone pneumonia.

Until the mentioned research agenda has been completed, the work of Brown et al suggests that IDSA/ATS criteria are useful in identifying patients with severe community-acquired pneumonia. These criteria may aid both triage and prognostication and help avoid delays in appropriate ICU admission. Brown et al suggest a threshold of four minor criteria compared with the three criteria proposed by IDSA/ATS expert panel, because this was most accurate in correctly classifying severe community-acquired pneumonia in their study, although this accuracy came at the cost of a far lesser sensitivity (30% vs. 54%). At the expense of “overadmitting” to our ICUs while ensuring those at greatest risk of decompensation are not left out on the wards, we (and others [15]) would agree that the IDSA/ATS threshold of three minor criteria seems more appropriate. Nevertheless, one-time use of IDSA/ATS minor criteria to predict ICU admission should be considered a fairly blunt and hopefully temporary measure. Until demonstrably better and more useful clinical prediction rules become available, we will still be going back to the bedside on a regular basis to decide which patient might decompensate and so benefit from more aggressive management and ICU admission. The astute physician, at least for now, “scores” higher than any prediction rule.

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REFERENCES

- Adams PF, Hendershot GE, Marano MA: Current estimates from the National Health Interview Survey, 1996. *Vital Health Stat* 1999; 10:1-203
- Almirall J, Bolibar I, Vidal J, et al: Epidemiology of community-acquired pneumonia in adults: A population-based study. *Eur Respir J* 2000; 15:757-763
- Fine MJ, Smith MA, Carson CA, et al: Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. *JAMA* 1996; 275:134-141
- Angus DC, Marrie TJ, Obrosky DS, et al: Severe community-acquired pneumonia: Use of intensive care services and evaluation of American and British Thoracic Society Diagnostic criteria. *Am J Respir Crit Care Med* 2002; 166:717-723
- Dremsizov T, Clermont G, Kellum JA, et al: Severe sepsis in community-acquired pneumonia: When does it happen, and do systemic inflammatory response syndrome criteria help predict course? *Chest* 2006; 129:968-978
- Restrepo MI, Mortensen EM, Velez JA, et al: A comparative study of community-acquired pneumonia patients admitted to the ward and the ICU. *Chest* 2008; 133:610-617
- Rodriguez A, Lisboa T, Blot S, et al: Mortality in ICU patients with bacterial community-acquired pneumonia: When antibiotics are not enough. *Intensive Care Med* 2009; 35: 430-438
- Valencia M, Badia JR, Cavalcanti M, et al: Pneumonia severity index class V patients with community-acquired pneumonia: Characteristics, outcomes, and value of severity scores. *Chest* 2007; 132:515-522
- Mandell LA, Wunderink RG, Anzueto A, et al: Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007; 44(Suppl 2):S27-S72
- Fine MJ, Auble TE, Yealy DM, et al: A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997; 336:243-250
- Lim WS, van der Eerden MM, Laing R, et al: Defining community acquired pneumonia severity on presentation to hospital: An international derivation and validation study. *Thorax* 2003; 58:377-382
- Charles PG, Wolfe R, Whitby M, et al: SMART-COP: A tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. *Clin Infect Dis* 2008; 47:375-384
- Espana PP, Capelastegui A, Gorordo I, et al: Development and validation of a clinical prediction rule for severe community-acquired pneumonia. *Am J Respir Crit Care Med* 2006; 174:1249-1256
- Liapikou A, Ferrer M, Polverino E, et al: Severe community-acquired pneumonia: Validation of the Infectious Diseases Society of America/American Thoracic Society guidelines to pre-

dict an intensive care unit admission. *Clin Infect Dis* 2009; 48:377–385

15. Phua J, See KC, Chan YH, et al: Validation and clinical implications of the IDSA/ATS minor criteria for severe community-acquired pneumonia. *Thorax* 2009; 64:598–603

16. Brown SM, Jones BE, Jephson AR, et al: Validation of the Infectious Disease Society of America/American Thoracic Society 2007 guidelines for severe community-acquired pneumonia. *Crit Care Med* 2009; 37:3010–3016

17. Chen CZ, Fan PS, Lin CC, et al: Repeated Pneumonia Severity Index measurement after admission increases its predictive value for mortality in severe community-acquired pneumonia. *J Formos Med Assoc* 2009; 108: 219–223

Do it right?*

Right ventricular dysfunction in myocardial infarction may cause or contribute to cardiogenic shock (CS). Whereas right ventricular infarction resulting from occlusion of the proximal right coronary artery is a rare cause of CS (1), secondary right ventricular dysfunction in association with left ventricular failure is thought to be common; however, this phenomenon has not been investigated systematically so far. The main mechanisms for the involvement of the right ventricle in predominantly left-sided heart failure include an increase in right ventricular afterload through an increase in pulmonary arterial pressure and a decrease in right coronary perfusion resulting from systemic hypotension. Urgent revascularization is the therapeutic cornerstone in the treatment of patients with CS. Traditionally, besides inotropic therapy, treatment of patients with predominant right ventricular failure in the course of complicated myocardial infarction has focused on aggressive volume resuscitation. There are no data on optimal filling pressures in this setting, but a generally held belief is that right atrial pressures should be kept at 15 to 20 mm Hg. However, right ventricular overload can induce changes in the right ventricular geometry with consecutive left ventricular impairment (2) and generally distinctive hemodynamic monitoring is mandatory. Because the inotropic reserve of the right ventricle is limited, a reduction in pulmonary vascular resistance is a major therapeutic target in acute right sided cardiac failure. In a small case se-

ries, nitric oxide inhalation led to a significant fall in pulmonary vascular resistance associated with a raise in cardiac output (3). For right ventricular dysfunction resulting from predominant left ventricular failure, no specific treatment modalities are advocated. Levosimendan (LS) is a calcium sensitizer with inotropic and vasodilatory properties. In case series, LS has been shown to improve left ventricular performance in patients with CS on top of other inotropes (4, 5). Furthermore, in an observational study, LS led to a significant fall in pulmonary vascular resistance and mean pulmonary arterial pressure in patients with acute respiratory distress syndrome (6).

In this issue of *Critical Care Medicine*, the work of Russ et al (7) is on this promising dual-acting drug in the setting of refractory CS. Particularly, this study addressed the influence of LS on right ventricular function using a novel parameter, the right ventricular cardiac power index (rvCPI). In the study, 56 patients with myocardial infarction complicated by CS were investigated. All patients were treated with percutaneous coronary intervention and with standard inotropic therapy. After 24 hrs, 25 consecutive patients, who were deemed to have an insufficient hemodynamic response to inotropic therapy, received LS as a bolus and continuous infusion for 24 hrs on top of norepinephrine and dobutamine. All patients were instrumented with a pulmonary artery catheter. LS exerted a positive hemodynamic response in terms of a significant increase in left and right ventricular power index and a significant fall in systemic vascular resistance and pulmonary vascular resistance. The mean arterial pressure and the pulmonary capillary wedge pressure were not significantly affected in this setting. The positive hemodynamic response was sustained beyond the end of the LS infusion. rvCPI was lower at baseline and initially the response to LS infusion was significantly

blunted in patients with inferior myocardial infarction. After the bolus infusion of LS, 44% and 68% of patients required a fluid challenge and norepinephrine had to be uptitrated in 32% and 44% of patients within 3 and 24 hrs, respectively.

This observational study raises some interesting questions. Considering that a normal rvCPI is in the range of 0.13 W/m², rvCPI was not depressed in most patients at baseline, although mean pulmonary arterial pressure and the pulmonary vascular resistance were modestly elevated. In the course of LS infusion, the mean rvCPI increased to somewhat supernormal values and interestingly, those patients who showed no meaningful increase under LS challenge had a worse outcome. One simple explanation for this finding could be that in the course of CS, an either left or right ventricular inotropic reserve translates into a better clinical outcome. On the other hand, because under LS infusion rvCPI increased above normal values, a compensational role of the right ventricle in the setting of predominant left ventricular failure could be discussed.

The most intriguing finding of this series is the depressed rvCPI in patients with inferior myocardial infarction, although the authors report that there was no “extensive right ventricular impairment” on two-dimensional echocardiography. This interesting finding suggests that there might be subclinical right ventricular involvement in all patients with inferior myocardial infarction. For long, the right ventricle has been somewhat mysterious. Although the range of right ventricular involvement in inferior myocardial infarction varied from 40% to 70% (8, 9) in echo and scintigraphic studies and between 15% and 34% in autopsy studies (10, 11), only 3% to 8% are clinically apparent (12, 13). Also important from the present series, this subclinical involvement seems to be prognostically important.

*See also p. 3017.

Key Words: cardiogenic shock; right ventricular; levosimendan; right ventricular power index

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The use of LS was safe in this setting and with invasive hemodynamic monitoring, LS was able to improve right ventricular performance on top of norepinephrine and dobutamine. Caution should be drawn on volume management because many patients require additional fluid challenges during LS infusion, especially when a bolus infusion is given. In some patients, the positive hemodynamic response is balanced by the need for higher vasopressor doses to compensate the vasodilatory actions of the drug. Whether the positive hemodynamic action of LS translates into a better clinical outcome cannot be obtained from this study. It should be recognized also that the safety and efficacy of LS in patients with isolated or predominant right heart failure cannot be obtained from the present series. This awaits further studies.

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REFERENCES

- Jacobs AK, Leopold JA, Bates E, et al: Cardiogenic shock caused by right ventricular infarction: A report from the SHOCK registry. *J Am Coll Cardiol* 2003; 41:1273–1279
- Brookes C, Ravn H, White P, et al: Acute right ventricular dilatation in response to ischemia significantly impairs left ventricular systolic performance. *Circulation* 1999; 100:761–767
- Inglessis I, Shin JT, Lepore JJ, et al: Hemodynamic effects of inhaled nitric oxide in right ventricular myocardial infarction and cardiogenic shock. *J Am Coll Cardiol* 2004; 44:793–798
- Russ MA, Prondzinsky R, Christoph A, et al: Hemodynamic improvement following levosimendan treatment in patients with acute myocardial infarction and cardiogenic shock. *Crit Care Med* 2007; 35:2732–2739
- Delle Karth G, Buberl A, Geppert A, et al: Hemodynamic effects of a continuous infusion of levosimendan in critically ill patients with cardiogenic shock requiring catecholamines. *Acta Anaesthesiol Scand* 2003; 47:1251–1256
- Morelli A, Teboul JL, Maggiore SM, et al: Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: A pilot study. *Crit Care Med* 2006; 34:2287–2293
- Russ MA, Prondzinsky R, Carter JM, et al: Right ventricular function in myocardial infarction complicated by cardiogenic shock: Improvement with levosimendan. *Crit Care Med* 2009; 37:3017–3023
- Wackers FJ, Lie KI, Sokole EB, et al: Prevalence of right ventricular involvement in inferior wall infarction assessed with myocardial imaging with thallium-201 and technetium-99 pyrophosphate. *Am J Cardiol* 1978; 42:358–362
- Tobinick E, Schelbert HR, Henning H, et al: Right ventricular ejection fraction in patients with acute anterior and inferior myocardial infarction assessed by radionuclide angiography. *Circulation* 1978; 57:1078–1084
- Ratloff NB, Hackel DB: Combined right and left ventricular infarction: Pathogenesis and clinicopathologic correlations. *Am J Cardiol* 1980; 45:217–221
- Isner JM, Roberts WC: Right ventricular infarction complicating left ventricular infarction secondary to coronary heart disease. Frequency, location, associated findings and significance from analysis of 236 necropsy patients with acute or healed myocardial infarction. *Am J Cardiol* 1978; 42:885–894
- Cohn JN, Guiha NH, Broder MI, et al: Right ventricular infarction. Clinical and hemodynamic features. *Am J Cardiol* 1974; 33:209–214
- Lorell B, Leinbach RC, Pohost GM, et al: Right ventricular infarction. Clinical diagnosis and differentiation from cardiac tamponade and pericardial constriction. *Am J Cardiol* 1979; 43:465–471

Propofol infusion syndrome: Difficult to recognize, difficult to study*

“If you hold a cat by the tail, you learn things you cannot learn any other way.”—Mark Twain

When first described 17 yrs ago, propofol infusion syndrome (PRIS) was thought to be limited to pediatric patients receiving particularly high doses of propofol (1). As the population at risk for this often fatal process expanded to include adults and patients receiving lower doses of propofol (2, 3),

the components from the initial reports have remained surprisingly constant: progressive metabolic acidosis, lipemia, rhabdomyolysis, and progressive shock and cardiac instability, including bradycardia and a right bundle branch block pattern on the electrocardiogram. In this issue of *Critical Care Medicine*, Iyer et al (4) report their experience with PRIS among patients with refractory status epilepticus, a group commonly treated with high-dose propofol (4, 5).

Like most other reported series of patients with PRIS, Iyer et al retrospectively reviewed medical records to identify 41 patients with refractory status epilepticus, including 31 patients treated with propofol and ten patients treated with midazolam, lorazepam, or pentobarbital.

Fourteen of the 31 patients receiving propofol (45%) developed at least one feature of PRIS, including unexplained metabolic acidosis (n = 6), bradycardia (n = 6), hypotension (n = 5), new right bundle branch block (n = 2), and creatine kinase elevation (n = 1). Three patients with PRIS features developed cardiac arrest (three of 14 [21%]), and two patients died. The cumulative dose, peak infusion rate, and total infusion time for propofol were greater in patients developing PRIS compared with those receiving propofol without PRIS features. There were no deaths or serious arrhythmias in the group not receiving propofol.

As suggested by Samuel Clemens (Mark Twain), different approaches or perspectives are sometimes required to

*See also p. 3024.

Key Words: propofol; adverse drug events; sedation; intensive care unit; metabolic acidosis; bradycardia; status epilepticus

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provide a better understanding of certain problems; so it is with PRIS. Most multiple-patient studies to date have been retrospective series, providing data on patients in whom PRIS was identified not during their care, but only during a later review of their charts specifically looking for PRIS. Although we tend to distrust retrospective research in favor of randomized, controlled trials, all clinicians involved in the prescribing and administration of propofol need to be aware of the important data obtained from these studies.

The risk to patients receiving higher doses and prolonged infusions of propofol reported by Iyer and colleagues is consistent with the majority of documented PRIS cases. To further complicate our efforts to identify PRIS, recent reports have suggested that propofol administered for hours rather than days and at doses that are not excessive may also be associated with PRIS, or at least some components of the syndrome (3, 6, 7).

A recent prospective study monitored 461 general intensive care unit patients receiving propofol, suggesting that PRIS (defined as cardiac dysfunction and metabolic acidosis along with at least one other PRIS feature: rhabdomyolysis, hypertriglyceridemia, or renal failure) occurs infrequently with an incidence of 3.7% (8). This infrequency and the overlap between the features of PRIS and the common manifestations of underlying critical illness (such as acidosis, creatine kinase release, and shock) make recognition of this iatrogenic event difficult.

Fong et al recently described a PRIS scoring system based on Medwatch data from >1100 patients (9). They identified six factors that seemed to predict mortality from PRIS: Rhabdomyolysis, metabolic acidosis, cardiac dysfunction, renal failure, age <18 yrs, and the presence of both rhabdomyolysis and hypotension. Unfortunately, study methodology limited evaluation of potentially important risk factors such as propofol dose and duration and concomitant corticosteroid use. This important first effort may not be as generalizable as first hoped with a recent validation study of 321 patients yielding disappointing results (10). Lack-

ing a validated scoring system, how can clinicians best monitor their patients?

Routine monitoring for biochemical markers such as serum lactate, creatine kinase, myoglobin, and triglycerides has been advocated for early detection of PRIS (11, 12). Unfortunately, even twice-daily evaluations of these laboratory studies (with immediate discontinuation of propofol if derangements are detected) may not be protective (13). The development of a right bundle branch block with convex-curved ST segment elevation in the right precordial leads of the electrocardiogram (similar to those seen in Brugada syndrome) has been linked to PRIS and may have been seen in two of the three cardiac arrests reported by Iyer et al (4, 14, 15). Whether prospective electrocardiographic evaluations can improve outcomes in patients treated with propofol has yet to be determined.

Although PRIS is classically described as a catastrophic event associated with unexpected and irreversible cardiovascular collapse, recent reports have identified patient recovery if recognized early (6, 7). Like with many clinical issues, PRIS appears to be a syndrome with a spectrum of severity, an uncertain mechanism (although several have been proposed), and with multiple risk factors that vary by report. Given the high mortality associated with this often inconspicuous disorder, we need to have a low threshold to consider PRIS, to monitor for its features, and to switch to alternate medications for sedation if PRIS is suspected. A great deal of additional research is required before we fully understand PRIS, but Iyer and colleagues provide a little catnip, moving us in the right direction.

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REFERENCES

1. Parke TJ, Stevens JE, Rice ASC, et al: Metabolic acidosis and fatal myocardial failure

- after propofol infusion in children: Five case reports. *BMJ* 1992; 305:613–616
2. Cremer OL, Moons KG, Bouman EA, et al: Long-term propofol infusion and cardiac failure in adult head-injured patients. *Lancet* 2001; 357:117–119
3. Merz TM, Regli B, Rothen HU, et al: Propofol infusion syndrome—A fatal case at a low infusion rate [Letter]. *Anesth Analg* 2006; 103:1050
4. Iyer VN, Hoel R, Rabinstein AA: Propofol infusion syndrome in patients with refractory status epilepticus: An 11-year clinical experience. *Crit Care Med* 2009; 37:3024–3030
5. Miller LC, Drislane FW: Treatment of status epilepticus. *Expert Rev Neurother* 2008; 8:1817–1827
6. Burkow BK, Johnson ME, Packer DL: Metabolic acidosis associated with propofol in the absence of other causative factors. *Anesthesiology* 2004; 101:239–241
7. Liolios A, Guerit JM, Scholtes JL, et al: Propofol infusion syndrome associated with short-term large-dose infusion during surgical anesthesia in an adult. *Anesth Analg* 2005; 100:1804–1806
8. Roberts R, Devlin JW, Schumaker G, et al: Incidence of the propofol infusion syndrome in critically ill adults [Abstract 699]. *Crit Care Med* 2008; 36:A180
9. Fong JJ, Sylvia L, Ruthazer R, Schumaker G, et al: Predictors of mortality in patients with suspected propofol infusion syndrome. *Crit Care Med* 2008; 36:2281–2287
10. Roberts R, Devlin JW, Schumaker G, et al: Failure of a FDA Medwatch-derived scoring system to predict mortality in patients with suspected propofol infusion syndrome [Abstract 698]. *Crit Care Med* 2008; 36:A180
11. Kam PC, Cardone D: Propofol infusion syndrome. *Anaesthesia* 2007; 62:690–701
12. Koch M, De Backer D, Vincent JL: Lactic acidosis: An early marker of propofol infusion syndrome? *Intensive Care Med* 2004; 30:522
13. Veldhoen ES, Hartman BJ, van Gestel JP: Monitoring biochemical parameters as an early sign of propofol infusion syndrome: False feeling of security. *Pediatr Crit Care Med* 2009; 10:e19–21
14. Vernooij K, Delhaas T, Cremer OL, et al: Electrocardiographic changes predicting sudden death in propofol-related infusion syndrome. *Heart Rhythm* 2006; 3:131–137
15. Junttila MJ, Gonzalez M, Lizotte E, et al: Induced Brugada-type electrocardiogram, a sign for imminent malignant arrhythmias. *Circulation* 2008; 117:1890–1893

Sedating America: The state of sedative use in intensive care units*

In the 25 years since investigators started to titrate sedation and analgesia to specific end points, there has been an explosion of guidelines and protocols for the use of these agents. Some have been broad-based such as those developed by the Society of Critical Care Medicine (1–3), whereas others have been developed by individual hospitals and intensive care units (ICUs). These guidelines and protocols were developed to aid in the care of mechanically ventilated patients, perform serial neurological examinations, decrease length of stay, and modulate healthcare costs. They were also used to meet compliance with government regulations for sedation and pain management.

There has been an explosion in the literature of the number of investigations into new agents, old agents used in new ways, combination of agents, and delivery protocols as to how these agents should be delivered. *Goggle Scholar* has over 28,500 hits for sedation in the ICU. Physicians, nurses, and pharmacists are bombarded with industry and academic seminars and workshops on this topic at every local and international professional meeting; but as of today, there have been very few reviews of how all these guidelines and education programs have changed practice.

As early as 1997, investigators looked at ICU sedation guidelines and the impact of pharmacist interventions on sedation practice and on individual clinical outcomes (4). The vast majority of these studies have usually been single ICU or small groups of specific specialty ICUs, thus not giving a national or broad picture, but only a snapshot of individual practice.

The vast majority of literature also covers sedation practice based on agent A versus agent B with set practice goals

based on individual pharmacokinetic and pharmacodynamics specific to given compounds. In this issue of *Critical Care Medicine*, it is stimulating to see that a group of individuals from several institutions has taken the vast effort to mine the data from Project Impact over a 6-year period (5).

Results from 174 ICUs and 109,671 mechanically ventilated patients were reviewed from a validated broad-based database from across a wide demographic of community and academic medical centers in multiple geographic areas (6). The results show that formulations of propofol were the more commonly used sedative agents. This has great implications in sedation research, first in that many new agents are classically compared in ongoing research studies with benzodiazepines, which are not indicative of current sedation practices. It is important that costly new agents be compared with agents that are in current use and not historical agents to show true advantages over current sedation practice.

The use of propofol formulations also illustrates how highly titratable drugs with short half-lives can gain use even in sedation of patients over a long term. This fact illustrated use preference in ICU practitioners of titratable drugs not only for blood pressure and arrhythmia management, but across multiple clinical problems. This use is driven by nursing who, as bedside advocates, are constantly working to balance comfort and reduction of delirium with length of stay. This reinforces the culture of the ongoing ICU in which physiological parameters are under tight control. This control issue is the basis of practice in the modern ICU and has roots in the practice of anesthesiology, the parent of sedation and pain protocols.

The other important factor that was presented by this study was that mortality was different based on the agent use. This supports a growing literature on how sedation may modulate cellular immunity and the systemic inflammatory response.

Several studies show that formulations of propofol may have the ability to change the release of cytokines (7, 8) in mechanical ventilation of acute lung injury. This factor opens many new doors in research to closely study how current drugs and the many new agents in the research pipeline may affect patient outcomes.

Future research will also evaluate many more parameters as to how wide-based guidelines impact not only pain, sedation, and delirium, but how we modulate outcomes and costs systemwide. The economic downturn worldwide should not slow this research, but act as a spark to accelerate it.

As national and international societies develop guidelines and protocols, the study in this issue may reinforce the need that they are trialed first, before publication. This would address clinician concerns early on and mold the protocols to better mirror widespread practice. Input from the ground troops of the bedside can clearly act to improve these recommendations so that they can be used broadly and not only in selected academic centers with their large staffs and safety nets. As always, this study also reinforces the need to look at data collection databases to aid us early on to change and develop new practices. Only by studying the trends can we implement change and not be tied to the past.

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REFERENCES

1. Shapiro BA, Warren J, Egol AB, et al: Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: An executive summary. Society of Critical Care Medicine. *Crit Care Med* 1995; 23: 1596–1600
2. Jacob J, Fraser GL, Coursin DB, et al: Clinical practice guidelines for the sustained use in intensive care units in the critically ill adult. *Crit Care Med* 2002; 30:119–141

*See also p. 3031.

Key Words: intensive care unit; sedation; United States; propofol; healthcare costs protocols

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3. Cohen IL, Gallagher TJ, Pohlman AS, et al: The management of the agitated ICU patient. *Crit Care Med* 2002; Suppl:S97–S123
4. Devlin JW, Nolbrook AM, Fuller HD: The effect of ICU sedation guidelines and pharmacist interventions on clinical outcomes and drug cost. *Ann Pharmacother* 1997; 31: 689–695
5. Wunsh H, Khan JK, Kramer AA, et al: Use of intravenous infusion sedation among mechanically ventilated patients in the United States. *Crit Care Med* 2009; 37:3031–3039
6. Cook S, Visscher WA, Hobbs C, et al: Project Impact: Results from a pilot validity study of a new observational database. *Crit Care Med* 2002; 30:2765–2770
7. Tahao Y, Mikawa K, Nishina K, et al: Attenuation of acute lung injury with propofol in endotoxemia. *Anesth Analg* 2005; 100:810–816
8. Haitsma JJ, Lachmann N, Papadakos PJ: Additives in intravenous anesthesia modulates pulmonary inflammation in a model of LPS-induced respiratory distress. *Acta Anaesthesiol Scand* 2009; 53:176–182

Red blood cell deformability is critical for oxygen utilization in sepsis*

Red blood cell (RBC) transfusion is usually employed to increase oxygen transport in sepsis in the hope that adequate oxygen supply will assure optimal oxygen use and thereby minimize organ dysfunction. This assumption may not be entirely true since it does not take into consideration the frequent alterations in blood cell rheology in critically ill septic patients (1). These alterations can be influenced by many factors, including alterations in intracellular calcium and adenosine triphosphate concentrations, a decrease in some RBC membrane components such as sialic acid, and changes in 2,3 diphosphoglycerate. These changes in RBC function may contribute to the frequent alterations in septic microcirculatory blood flow, and therefore to cellular dysoxia (1).

Several studies have demonstrated alterations in RBC deformability in animal models of septic shock and in septic humans. The latter were well studied by Baskurt et al (2), who concluded that RBCs became more spherical in septic patients than in healthy volunteers and attributed this alteration to a significant decrease in sialic acid membrane content.

In this issue of *Critical Care Medicine*, Reggiori et al (3) were very auspicious in determining RBC rheologic abnormalities in septic patients that might jeopardize oxygen availability to the tissues.

Furthermore, these alterations in RBC deformability were more marked if white blood cells were stimulated by tumor necrosis factor. Rheologic features (deformability and aggregation) were determined within the first 24 hrs after intensive care unit admission by using a laser-assisted optical rotational cell analyzer (LORCA). The authors could conclude that RBC aggregation and deformability are altered early in intensive care unit septic patients, and that these alterations may, in fact, contribute to organ failure in sepsis and septic shock. Several reports have indicated an association between sepsis and RBC deformability (4, 5), and these observations are supported by studies demonstrating structural and chemical alterations of RBC in sepsis or when red blood cells are subjected to biochemical factors associated with sepsis (6). Local changes in tissues in a septic organism and leukocyte-mediated effects might be responsible for these alterations in RBC structure and mechanical behavior. It is not always easy to determine whether the hemorheologic alteration is the cause or the result of a pathophysiologic process. Sepsis syndrome represents one of the most striking disturbances of the general homeostasis; both clinical and experimental studies have indicated that sepsis is characterized by significantly impaired RBC deformability and increased aggregation. Such alterations in RBCs may well contribute to the generalized vascular problems encountered in sepsis syndrome (7).

In fact, Fernandes et al (8) showed that blood transfusion does not lead to acute improvement in systemic or regional oxygenation, and may hamper right ventricular ejection by increasing pulmonary vascular resistance in sepsis.

Furthermore, in patients undergoing cardiac surgery transfusion of red blood cells that had been stored for more than 2 wks, transfusion was associated with a significantly increased risk of postoperative complications as well as reduced short-term and long-term survival (9). The effects of prolonged storage on red blood cells include decreased deformability, which can impede microvascular blood flow, and depletion of 2,3-diphosphoglycerate which shifts the oxyhemoglobin dissociation curve to the left and reduces oxygen delivery to the tissues. Accordingly, Marik and Sibbald (10) reported worsening of gastric oxygenation when RBCs were stored for more than 15 days because of increased sphericity which could lead to capillary obstruction and deterioration of splanchnic oxygenation, and therefore increased mucosal permeability and augmented bacteria translocation.

I agree with Drs. Jha and Gutierrez (11) who add a cautionary note against blood transfusions in septic patients. Until now, there has been no reason to transfuse septic patients without coronary disease whose hemoglobin levels are greater than 7g/dL, despite the increased survival observed by Dr. Rivers (12) in his early goal-directed therapeutic protocol.

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REFERENCES

1. Piagnerelli M, Boudjeitia M, Vanhaeverbeek M, et al: Red blood cell rheology in sepsis. *Intensive Care Med* 2003; 29:1052–1061
2. Baskurt OK: Pathophysiological significance

*See also p. 3041.

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- of blood rheology. *Turk J Med Sci* 2003; 33:347–355
3. Reggiori G, Occhipinti G, De Gasperi A, et al: Early alterations of red blood cell rheology in critically ill patients. *Crit Care Med* 2009; 37:3041–3046
 4. Astiz ME, DeGent GE, Lin RY, et al: Microvascular function and rheologic changes in hyperdynamic sepsis. *Crit Care Med* 1995; 23:265–271
 5. Powell RJ, Machiedo GW, Rush BF: Decreased red blood cell deformability and impaired oxygen utilization during human sepsis. *Am Surg* 1993; 59:65–68
 6. Todd JC, Mollitt DL: Effect of sepsis on erythrocyte intracellular calcium homeostasis. *Crit Care Med* 1995; 23:459–465
 7. Piagnerelli M, Boudjeltia KZ, Gulbis B, et al: Anemia in sepsis: The importance of red blood cell membrane changes. *Transf Alt in Transf Med* 2007; 9:143–149
 8. Fernandes CJ Jr, Akamine N, De Marco FVC, et al: Red blood cell transfusion does not increase oxygen consumption in critically ill septic patients. *Crit Care* 2001; 5:362–367
 9. Koch CG, Li L, Sessler DI, et al: Duration of red cell storage and complications after cardiac surgery. *NEJM* 2008; 358:1229–1239
 10. Marik PE, Sibbald WJ: Effect of stored blood transfusion on oxygen delivery in patients with sepsis. *JAMA* 1993; 269:3024–3027
 11. Jha V, Gutierrez G: Should blood be transfused to raise mixed venous oxygen saturation? (Editorial) *Chest* 2007; 131:1267
 12. Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377

How strong is weakness?*

Intensivists have become increasingly interested in the recovery and longer-term outcome of critically ill patients surviving the intensive care unit (ICU). Because of its prevalence, acquired neuromuscular weakness (1, 2) is possibly one of the more relevant problems for these survivors. Not only are many survivors affected but the manifestations of weakness, in terms of ambulation and functional independence, seems to persist for months or even years (3). However, much remains unknown regarding essential details of this syndrome.

One of these unknowns is defining where the weakness of deconditioning ends and pathologic strength loss of ICU-acquired weakness begins. Although this seems the most basic of questions, this is an area of current controversy in the field. Several studies have demonstrated the increased morbidity and mortality associated with ICU-acquired weakness (1, 4). However, because some strength loss seems pervasive in our patients and still others are unable to be examined, ICU practitioners' expectations of normal recovery may be low. As a result, simple and clear definitions of weakness are critical. ICU-acquired paresis or weakness in several studies (1, 4) has been

characterized as an average muscle strength that only allows limb movement against gravity and no additional resistance. This equates to average muscle strength of ≤ 4 according to one common scale of muscle strength, the Medical Research Council scale. Although this approach was successful in identifying groups at significantly different risk for poor outcomes, it remains an arbitrary level. It is plausible to think that more modest strength loss can lead to debility or that isolated muscle group weakness could also be important.

In this regard, Tarek Sharshar and colleagues have made significant progress in helping to further describe the impact and relevance of acquired weakness after significant mechanical ventilator use. In this issue of *Critical Care Medicine*, Sharshar et al (5) explore the association of strength after awakening and in-hospital mortality. In this study, the authors observed that not only was the arbitrary level of strength defined as ICU-acquired paresis (Medical Research Council scale score of < 4) associated with increased mortality but more subtle levels of strength loss as well. For every single point drop in the Medical Research Council score of a patient, the odds of hospital mortality rose $\sim 3\%$. This observation held after adjustment for severity of illness. This suggests that any strength loss seems to increase a patient's risk during the vulnerable period of recovery from critical illness and adds weight to our patients' complaints that they are changed after ICU care, regardless of whether they are profoundly paretic or not.

This manuscript, while advancing our understanding on this point, also illustrates problems facing researchers in this field, the lack of consensus among investigators in this field, and what this strength loss really means. How does strength loss result in increased mortality? Based on our own and this group's data, it does not seem that those subjects who die in hospital do so imminently, making it unlikely that the increased mortality observed is due to immediate consequences of weakness. It is more likely that weakness leads to altered recovery that lays the seeds for other complications like nosocomial infection, as these authors suggest. Second, this lack of consensus is apparent when trying to look across other studies of acquired weakness. It is apparent that many studies use a variety of definitions to describe this syndrome. In fact, many of the largest series beyond those referenced here have almost exclusively used electrodiagnostics like muscle stimulation or nerve conduction studies (6–8). Thus, very limited information is available. Finally, the timing of strength assessment can be tricky in the ICU with the competing needs of life-support devices and altered consciousness. In the present study and our own, we measured strength at the first focused moment after awakening (4, 5), whereas in the other major series, they waited a full 7 days after this point (1, 9). Simply by changing the timing of the examination in their own cohort, the prevalence of ICU-acquired paresis dropped from 65% at awakening to 38% 7 days later. What are we to do with pro-

*See also p. 3047.

Key Words: critical care; intensive care unit-acquired weakness; paresis; polyneuropathy; myopathy; measurement; mechanical ventilation

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found weakness that resolves in less than a week? What does this represent?

Should we continue to give patients with transient weakness the same diagnosis as those whose syndrome continues for weeks? Should we continue to only define the weakest of patients as “at risk.” The answer to both of these questions is likely “no,” but we clearly need consensus on this diagnosis and a better understanding of how this weakness leads to death and delayed functional recovery before we can decide what to do. Despite these problems, the work by Sharshar and colleagues advances our understanding of this syndrome. In isolation, these data challenge us to not be comfortable with even the slightest amount of strength loss in our ICU survivors. In other words, when it comes to mortality risk for ICU survivors, no amount of strength loss is too small.

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REFERENCES

1. De Jonghe B, Sharshar T, Lefaucheur JP, et al: Paresis acquired in the intensive care unit: A prospective multicenter study. *JAMA* 2002; 288:2859–2867
2. de Letter MA, Schmitz PI, Visser LH, et al: Risk factors for the development of polyneuropathy and myopathy in critically ill patients. *Crit Care Med* 2001; 29:2281–2286
3. Herridge MS, Cheung AM, Tansey CM, et al: One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003; 348:683–693
4. Ali NA, O'Brien JM Jr, Hoffmann SP, et al: Acquired weakness, handgrip strength and mortality in critically ill patients. *Am J Respir Crit Care Med* 2008; 178:261–268. Epub 2008 May 29
5. Sharshar T, Bastuji-Garin SB, Stevens RD, et al: Presence and severity of intensive care unit-

acquired paresis at the time of awakening are associated with increased intensive care unit and hospital mortality. *Crit Care Med* 2009; 37: 3047–3053

6. De Jonghe B, Cook D, Sharshar T, et al: Acquired neuromuscular disorders in critically ill patients: A systematic review. Groupe de Reflexion et d'Etude sur les Neuromyopathies En Reanimation. *Intensive Care Med* 1998; 24:1242–1250
7. Lacomis D, Petrella JT, Giuliani MJ: Causes of neuromuscular weakness in the intensive care unit: A study of ninety-two patients. *Muscle Nerve* 1995; 21:610–617
8. Hermans G, Wilmer A, Meersseman W, et al: Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in the medical intensive care unit. *Am J Respir Crit Care Med* 2007; 175: 480–489
9. De Jonghe B, Bastuji-Garin S, Durand M, et al: Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. *Crit Care Med* 2007; 35: 2007–2015

Education is what remains after medical emergency teams are trained*

Many hospitalized patients (estimated between 370,000 and 750,000) have a cardiac arrest with attempted resuscitation yearly (1, 2). Survival is poor with <30% dismissed with neurologic recovery (1, 2). Delays in treatment are common and result in lower survival and neurologic outcomes (2). Studies that have reviewed in-hospital cardiac arrest profiles have shown that these patients often exhibit physiologic deterioration hours before cardiopulmonary arrest (3, 4).

In a response to improve access to intensive care for these patients with physiologic deterioration, rapid response teams were created (5, 6). Early randomized trials showed a survival benefit when these teams were utilized. Unfortunately,

the heterogeneity of other outcome data available—including patients with diverse disease states, the dynamic interplay of rapid response teams with traditional caring staff, and inefficient ward monitoring—has resulted in controversy regarding the utility and benefit of these teams (7).

Despite this controversy, there is no argument that early recognition of physiologic deterioration with targeted care is required to improve outcomes. Within this statement is derived the first problematic concept—early recognition of physiologic deterioration. Early signs of deterioration are common (7.7 times more than late signs) and nurses account for approximately 86% of the detections (8). Unfortunately, 17.8% of all early signs and 9% of late signs of physiologic deterioration in one study were considered by nurses as usual or typical for the patient (8). These data underscore the importance of education in improving outcomes of in-hospital cardiac arrest at a very basic level.

In this issue of *Critical Care Medicine*, Campello and colleagues (9) report their institutional experience after

a medical emergency team program was implemented. Early after the program was started, the number of cardiac arrest deaths per 1000 admissions declined (3.65–2.45) as well as the total number of in-hospital deaths per 1000 patients (5.35–4.45). Unfortunately, 2 yrs after the program was implemented, the in-hospital deaths per 1000 patients increased above the level before the program was started and the cardiac arrest deaths per 1000 patients were no longer significantly reduced. A careful examination of their data provided the authors insight into the reduction of the observed medical emergency team efficacy.

First, the authors examined factors that influenced the survival of these patients. The strongest factor reducing in-hospital mortality was the number of interventions started before the medical emergency team arrived. These measures were not insignificant as they comprised basic and advanced life-support interventions, such as chest compressions, basic airway management, peripheral venous access, intravenous drugs, and electrocardiographic monitoring. The fact that these measures were used increasingly

*See also p. 3054.

Key Words: heart arrest; education; ventricles; outcomes; risk factors

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before the emergency team was activated suggests that early signs of clinical deterioration were not recognized or acted upon over time. A similar possibility is that ward education of the medical emergency team's role in the acute management of these patients also waned. These data highlight the need not only of continued education of these emergency teams but of the entire hospital staff that care for patients.

The second important concept derived from this institutional experience is that of temporal worsening of disease complexity. With population aging, more patients are living with chronic illnesses. In the three studied time periods in the study by Campello et al (9), the average age increased as well as comorbidities of heart disease, renal disease, and diabetes. There was also a trend toward more cancer. This population shift provided a difficult scenario in which the patients were more ill and complicated at a time when education and staff awareness had atrophied. Given these findings, the title of "a plea" for periodic and continual education is well justified. Also, these unique concepts derived from their data may provide insight into the variable results

that underlie the controversy of rapid response team efficacy.

Albert Einstein said: "Education is what remains after one has forgotten everything he learned in school." Rapid response team education begins and continues after the program is implemented. Education must include fundamental aspects of care to all those who encounter these patients. Without continual education, the complexity and time-dependent staff awareness and knowledge will not be sufficient to treat the increasingly complex in-hospital cardiac arrest patients.

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REFERENCES

1. Eisenberg MS, Mengert TJ: Cardiac resuscitation. *N Engl J Med* 2001; 344:1304–1313
2. Chan PS, Krumholz HM, Nichol G, et al: Delayed time to defibrillation after in-hospital cardiac arrest. *N Engl J Med* 2008; 358:9–17
3. Hillman KM, Bristow PJ, Chey T, et al: Ante-

cedents to hospital deaths. *Intern Med J* 2001; 31:343–348

4. Buist MD, Jarmolowski E, Burton PR, et al: Recognising clinical instability in hospital patients before cardiac arrest or unplanned admission to intensive care. A pilot study in a tertiary-care hospital. *Med J Aust* 1999; 171:22–25
5. Hillman K, Chen J, Cretikos M, et al: Introduction of the medical emergency team (MET) system: A cluster-randomised controlled trial. *Lancet* 2005; 365:2091–2097
6. Priestley G, Watson W, Rashidian A, et al: Introducing Critical Care Outreach: A ward-randomised trial of phased introduction in a general hospital. *Intensive Care Med* 2004; 30:1398–1404. Epub 2004 Apr 27
7. Tee A, Calzavacca P, Licari E, et al: Bench-to-bedside review: The MET syndrome—The challenges of researching and adopting medical emergency teams. *Crit Care* 2008; 12:205
8. Harrison GA, Jacques TC, Kilborn G, et al: The prevalence of recordings of the signs of critical conditions and emergency responses in hospital wards—The SOCCER study. *Resuscitation* 2005; 65:149–157
9. Campello G, Granja C, Carvalho F, et al: Immediate and long-term impact of medical response teams on cardiac arrest prevalence and mortality: A plea for periodic basic life-support training programs. *Crit Care Med* 2009; 37: 3054–3061

Hypothermia: Is it just for ventricular fibrillation?*

The challenges in the management of the cardiac arrest victim extend from the initial restoration of a perfusing rhythm through the postresuscitative period. Survival to hospital discharge in North America remains poor overall at <10%, with better survival, about 20%, for ventricular fibrillation (VF) (1). However, the principal challenge of the postresuscitative period is the achievement of good neurologic function.

Although the utilization of hypothermia for neurologic protection in the setting of cardiac bypass and vascular surgery has been used for decades, its usefulness in the postresuscitative phase of cardiac arrest was not recognized until several years ago. Two landmark trials, published back to back in 2002 in the *New England Journal of Medicine*, were responsible for the recognition of hypothermia as a treatment modality in the post resuscitative period. In Australia (2), 77 patients resuscitated from an initial rhythm of VF but still in a comatose state were randomized to receive therapeutic hypothermia to a temperature of 33°C, or usual therapy with a state of normothermia. This trial demonstrated a 49% survival to hospital discharge with a good neurologic outcome in hypothermia-treated patients, compared with 26% survival in the normothermia group. Similar results were found in a larger multicenter

trial in Europe, the Hypothermia After Cardiac Arrest Study Group trial (3), that randomized 275 patients resuscitated from VF or pulseless ventricular tachycardia to therapeutic hypothermia or normothermia, with 55% of hypothermia-treated patients attaining a favorable neurologic outcome at 6 mos compared with 39% of normothermia patients. As a result of these trials, therapeutic hypothermia for 12 to 24 hrs was given a class 2A indication for unconscious patients resuscitated from VF arrest by the American Heart Association in the 2005 guidelines and a 2B indication for non-VF arrest (4).

Cerebral protection from therapeutic hypothermia is thought to relate to altering signaling pathways at the cellular level, affecting oxidative injury, inflammation, and programmed cell death (5–7). One would think that these mechanisms should not be related to the

*See also p. 3062.

Key Words: hypothermia; cardiac arrest; ventricular fibrillation; cardiopulmonary resuscitation; sudden cardiac death

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rhythm cause for cardiac arrest, whether due to VF/ventricular tachycardia or pulseless electrical activity (PEA). However, a small retrospective study found no difference in outcome among PEA/asystole patients treated with hypothermia (8). Furthermore, registry data from Europe suggested improved survival to hospital discharge for patients with PEA or asystole treated with hypothermia, yet no difference in overall unfavorable outcome, namely, death or poor neurologic function (9). There are inherent difficulties with registry data, including selection bias; therefore, the question remains whether therapeutic hypothermia (TH) benefits victims of cardiac arrest due to PEA or asystole.

In this issue of *Critical Care Medicine*, this was a key question investigated by Don and colleagues (10). In Seattle, a TH protocol was instituted in November 2002. Outcomes in 204 cardiac arrest patients treated after this date were compared with 287 patients treated before this date. During the TH period, 60% of victims were resuscitated from PEA or asystole, compared with 66% in the pre-TH period. The authors found, in an intention-to-treat analysis, that hypothermia was not of benefit in survival or good neurologic outcome if the cardiac arrest was related to PEA or asystole. Specifically, for VF cardiac arrest, a good neurologic outcome was improved from 15.9% to 35.0% ($p = .003$) with the institution of the hypothermia protocol after November 2002. For non-VF cardiac arrest, good neurologic outcome was not significantly improved. Survival to hospital discharge was also markedly improved in VF victims from 38.7% to 54.3% ($p = .04$) but not in PEA/asystole victims (19.1%–21.1%, $p = .65$).

Of the 204 patients treated in the TH period, only 134 patients (66%) actually received this treatment. The authors have

performed their statistics based on an intention to treat; thus, the patients who did not receive hypothermia in the TH period are kept in the analysis. Although it is a strength of the study to include these nonhypothermia-treated patients from the TH period, it is also a potential weakness. In particular, the data are unclear as to whether there may have been a difference in the proportion of non-VF patients who actually received hypothermia compared with those who did not among the 204 patients treated in the TH period. We do know, however, that the PEA and asystole patients did have a significant lowering of their esophageal temperatures by intention to treat, with 78% achieving a goal temperature $<34^{\circ}\text{C}$, similar to VF patients (74%), among patients with temperature data.

This study also confirms that survival from PEA and asystole is poor compared with cardiac arrest due to VF. The causes for cardiac arrest due to asystole and PEA are diverse, and the underlying medical problems leading to arrest are more difficult to treat. It may be that any benefit of hypothermia in this real-world setting is not sufficient to counteract the very poor prognosis of these victims from the outset. We also do not know if the pathophysiology of cerebral metabolism and dysfunction is different in PEA/asystole victims. Perhaps a different target temperature is needed in such patients. It may also be that hypothermia has a smaller benefit compared with VF victims, which is not discernible in this sample size. Therefore, a prospective, randomized, multicenter trial in PEA/asystole cardiac arrest patients would be very helpful. However, we should also recognize that this study did not show any detrimental effects of hypothermia, and therefore the class 2B recommendation from the American Heart Association

2005 guidelines (4) would still seem appropriate until future trials can be performed.

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REFERENCES

1. Nichol G, Thomas E, Callaway CW, et al: Regional variation in out-of-hospital cardiac arrest incidence and outcome. *JAMA* 2008; 300:1423–1431
2. Bernard SA, Gray TW, Buist MD, et al: Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; 346:557–563
3. Hypothermia after Cardiac Arrest Study Group: Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002; 346:549–556
4. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2005; 112(24 Suppl):IV-84–IV-88
5. Dine CJ, Abella BS: Therapeutic hypothermia for neuroprotection. *Emerg Med Clin North Am* 2009; 27:137–149, ix
6. Bernard S: Induced hypothermia in intensive care medicine. *Anaesth Intensive Care* 1996; 24:382–388
7. Colbourne F, Sutherland G, Corbett D: Post-ischemic hypothermia: A critical appraisal with implications for clinical treatment. *Mol Neurobiol* 1997; 14:171–201
8. Oddo M, Schaller M-D, Feihl F, et al: From evidence to clinical practice: Effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest. *Crit Care Med* 2006; 34:1865–1873
9. Arrich J, The European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group: Clinical application of mild therapeutic hypothermia after cardiac arrest. *Crit Care Med* 2007; 35:1041–1047
10. Don CW, Longstreth WT Jr, Maynard C, et al: Active surface cooling protocol to induce mild therapeutic hypothermia after out-of-hospital cardiac arrest: A retrospective before-and-after comparison in a single hospital. *Crit Care Med* 2009; 37:3062–3069

Tracheostomy in the surgical intensive care unit: Perception and reality*

A controversy in critical care medicine that seems unable to be put to rest is who precisely should undergo a tracheostomy in the intensive care unit (ICU), and when should it happen. Numerous studies have been performed attempting to answer this question, with many demonstrating some benefit to early tracheostomy vs. prolonged mechanical ventilation (1–5), while others have not (6, 7). Despite the fact that tracheostomy has become a routine tool of the intensivist for patients with respiratory failure, the lack of consensus in the literature regarding who really is a candidate for tracheostomy is somewhat disheartening.

In this issue of *Critical Care Medicine*, Freeman and colleagues (8) have taken a slightly different approach to analyzing this challenging clinical conundrum. Previous work by this group (9) demonstrated that their tracheostomy rate was rather high, and that many patients who may be meeting criteria for liberation from mechanical ventilation according to the results of their spontaneous breathing trial (SBT) were not only kept on mechanical ventilation but were ultimately being subjected to a tracheostomy. The purpose of the present study was to determine the extent to which nonclinical factors were contributing to tracheostomy practice, including interindividual practitioner variability. The authors also wished to explore if there were any “disconnects” between what clinicians said they were doing and actual practice, as well as to determine the value of a streamlined tracheostomy consult form.

Freeman et al found that their rate of tracheostomy was much higher than that in a comparable group of patients from the Project Impact database (54.2% vs. 13.9%). Although the authors point out that there was significant turnover in attending intensivists, and that each patient was being managed on average by two intensivists, these are not the truly impactful data from this study.

Most importantly, they found multiple profound disconnects between what they said they did and what they actually did. In their survey, a majority of respondents estimated that only one quarter of patients would not be extubated after a successful SBT; in fact, more than two thirds of patients were not extubated after a successful SBT. Along the same lines, most respondents felt that fewer than one fourth of patients who pass a SBT would go on to tracheostomy, whereas in reality this rate was greater than 40%. The authors then go on to try and determine the exact mechanism of this faulty perception, but this is primarily hypothesis-generating.

The authors also found that when they implemented a tracheostomy consult note, the rate of tracheostomy went up (52% precohort vs. 65% postcohort), although the implications of these results are somewhat unclear given the fact that the Acute Physiology and Chronic Health Evaluation II scores also went up (from 18 to 19, $p = .025$). The counterintuitive results from implementing a consult note such as this merit further investigation.

A strength of this study is the fact that they compared their results with a large database (Project Impact) to provide some sense of what a reasonable tracheostomy rate may be in a unit such as theirs. Some weaknesses include: 1) the fact that there is no mention of adherence to protocols such as daily sedation vacation (10); 2) no documentation of follow-up outside the ICU stay; and 3) no record of the reasons why patients who passed their SBT were not extubated. Documenting what happens to patients once they leave the ICU, as well as their

hospital mortality, is absolutely crucial if a rational determination is to be made as to the true value of tracheostomy in the ICU.

So what are we to glean from the most recent expedition by Freeman et al into this highly important, but persistently murky, area of critical care? At first glance, one may state that this study simply showed that their tracheostomy rate was high, and there was worrisome variability in practice among the attending intensivists; the practicing clinician can therefore take nothing away from reading their report. On the contrary, this manuscript, more than most in the ICU tracheostomy literature, points out a potential solution to a vexing clinical dilemma: The answer to selection for and timing of tracheostomy will not be solved by more randomized trials, but rather with quality improvement research. The authors began by asking relevant clinical questions: “Do we believe that patients who successfully undergo a SBT should be extubated? Yes.” and “Should patients who pass a SBT remain on the ventilator and undergo a tracheostomy? No!” They then looked at their own practice and discovered that they did not even agree with what they said they wanted to do. That is the “eureka” moment of this manuscript. Although this lack of compliance with guidelines (internal or external) is not unique in critical care medicine (11), asking and answering these questions should be done in most ICUs, and in the minds of some should not be considered research (12).

As modern intensivists, we can either assume that we are practicing appropriate medicine without looking at our practices—“flying blind,” as it were—or we can do what is right; we can gather data, and when we find discrepancies between where we are and where we should be, we must be held accountable (13). The final step is to implement appropriate, continuous, iterative quality-improvement plans (14) so that our perception of patient care meets reality.

*See also p. 3070.

Key Words: tracheostomy; surgical intensive care unit; protocol; compliance; spontaneous breathing trial; survey

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REFERENCES

1. Arabi YM, Alhashemi JA, Tamim HM, et al: The impact of time to tracheostomy on mechanical ventilation duration, length of stay, and mortality in intensive care unit patients. *J Crit Care* 2009; E-pub Ahead of Print
2. Schneider GT, Christensen N, Doerr TD: Early tracheostomy in elderly patients results in less ventilator-associated pneumonia. *Otolaryngol Head Neck Surg* 2009; 140:250–255
3. Ahmed N, Kuo YH: Early versus late tracheostomy in patients with severe traumatic head injury. *Surg Infect (Larchmt)* 2007; 8:343–347
4. Combes A, Luyt CE, Nieszkowska A, et al: Is tracheostomy associated with better outcomes for patients requiring long-term mechanical ventilation? *Crit Care Med* 2007; 35:802–807
5. Savel RH, Goldstein EB, Riedinger D, et al: Early tracheostomy in the elderly surgical ICU (SICU) patient is associated with decreased ICU and hospital length of stay. *Crit Care Med* 2006; 34:A124
6. Blot F, Similowski T, Trouillet JL, et al: Early tracheostomy versus prolonged endotracheal intubation in unselected severely ill ICU patients. *Intensive Care Med* 2008; 34:1779–1787
7. Clec'h C, Alberti C, Vincent F, et al: Tracheostomy does not improve the outcome of patients requiring prolonged mechanical ventilation: A propensity analysis. *Crit Care Med* 2007; 35:132–138
8. Freeman BD, Kennedy C, Coopersmith CM, et al: Examination of non-clinical factors affecting tracheostomy practice in an academic surgical intensive care unit. *Crit Care Med* 2009; 37:3070–3078
9. Freeman BD, Kennedy C, Robertson TE, et al: Tracheostomy protocol: Experience with development and potential utility. *Crit Care Med* 2008; 36:1742–1748
10. Girard TD, Kress JP, Fuchs BD, et al: Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled Trial): A randomised controlled trial. *Lancet* 2008; 371:126–134
11. Rubenfeld GD, Cooper C, Carter G, et al: Barriers to providing lung-protective ventilation to patients with acute lung injury. *Crit Care Med* 2004; 32:1289–1293
12. Savel RH, Goldstein EB, Gropper MA: Critical care checklists, the Keystone Project, and the Office for Human Research Protections: A case for streamlining the approval process in quality-improvement research. *Crit Care Med* 2009; 37:725–728
13. Levy MM: Society of Critical Care Medicine President's address: Making a difference. *Crit Care Med* 2009; 37:1541–1544
14. Lipshutz AK, Fee C, Schell H, et al: Strategies for success: A PDSA analysis of three QI initiatives in critical care. *Jt Comm J Qual Patient Saf* 2008; 34:435–444

Defining new risk factors for out-of-hospital cardiac arrest: A hot opportunity for discovery*

A significant amount of research and effort has gone into the understanding of patients at risk of sudden death. Available data have defined subsets of patients at risk such as those with inherited channelopathies or structural heart disease, prior ventricular arrhythmias, in the setting of moderate to severe left ventricular dysfunction and heart failure, and after a myocardial infarction (1–5). Although the cardiac arrest incidence in these subgroups is high, the actual number of events per year is low compared with the number of events that occur in those without these risk factors (1). These population-based findings highlight the need to understand novel risk factors in the general population and those individuals

considered at “low” risk to greatly impact cardiac arrest rates in the community. Predicting which asymptomatic or “low”-risk patients will present with sudden cardiac arrest remains an enigma. Currently, it is unclear if large-scale population-based screening can enhance risk detection. Potential population screening tools will need to be cost-effective, readily available, cross sex and race boundaries, and have an acceptable sensitive and specificity.

In this issue of *Critical Care Medicine*, Empana et al (6) investigated the effects of a heat wave in Paris, France, on out-of-hospital cardiac arrest and ST segment elevation myocardial infarction. In this observational study, patients aged ≥ 20 yrs treated by mobile intensive care units from January 1, 2000, through December 21, 2005, were studied. An important inclusion criterion was only witnessed arrest. Patients were excluded for arrests clearly not resulting from cardiac causes and death before or on arrival of the mobile intensive care unit. Rates of out-of-hospital cardiac arrest and ST segment elevation

myocardial infarction were determined for the 2 weeks in August 2003 during a severe heat wave and were compared with the same period from prior years without a heat wave.

The authors make a vital observation in this carefully conducted study. During the devastating heat wave in France, the number of out-of-hospital cardiac arrests increased two and a half times compared with those rates experienced in prior years and in the time period after the heat wave. Interestingly, they observed no difference in the frequency of ST segment elevation myocardial infarction between the weeks of the heat wave and corresponding weeks of nonheat wave years. The data separation from coronary atherosclerosis is critical and provides insight into the environmental stress influence on arrhythmia susceptibility. As expected, those individuals at greatest risk during this period were the elderly.

Although the study is limited to define if hyperthermia is causal of the arrest, there are many intriguing possibilities that may underlie the observed association. During the heat wave, both an in-

*See also p. 3079.

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crease in core body temperature and dehydration resulting from sweat losses can lead to a decrease in central blood volume. This volume loss results in heart rate elevation to maintain perfusion and augments heat loss by increasing skin blood flow. In patients with impaired macro- and microperfusion, relative hypotension resulting from central volume loss coupled by tachycardia may result in ischemia-provoked arrhythmia. In individuals in whom these compensatory mechanisms fail, shock develops. Although the root cause of the mortality was shock, the end consequence of the severe loss of perfusion is cardiac arrest. From these data, it is difficult to sort out the relevance and prevalence of shock as a contributing factor of arrest. In general, the elderly are at particular risk of inadequate compensation and resultant shock, a characteristic that may explain their elevated hazard in this study.

There are many other potential mechanisms. In dehydrated patients, ingestion of large amounts of water with poor salt intake can induce symptomatic electrolyte loss and in susceptible individuals result in ventricular arrhythmias. Hyperthermia increases atherosclerosis plaque instability and resultant ischemia (7). Although ST segment elevation myocardial infarction was not elevated, many patients who present in cardiac arrest have diffuse atherosclerosis with ischemia of the microcirculation as the likely arrhythmia mechanism.

These data do prompt the question if temperature elevation in itself is arrhythmogenic in susceptible individuals. In a small case series, fever was found to be associated with idiopathic ventricular fibrillation. In one patient, mapping of the tachycardia resulted in localization of ventricular fibrillation to a Purkinje fiber trigger (8). Similarly, in patients with Brugada syndrome, which is characterized by a loss of function of the cardiac sodium channel, fever is a potent stimu-

lant of the electrocardiographic phenotype and ventricular arrhythmias (9, 10). Perhaps when considering the broad spectrum of genetic variance in the population, the environmental stress of heat in those with sodium channel deficits or relatively lower levels of sodium channel function is enough to place many at risk of arrhythmias who otherwise may not have been a risk. Similarly, heat and sodium channel dysfunction coupled with any of the mentioned potential mechanisms may provide the environment and genetic coupling that is required for sudden death.

The authors are to be congratulated in their efforts to further classify those who are at risk for sudden cardiac arrest. Strengths of this study include a large sample size, clearly defined events, and on-site, highly trained medical staff to make diagnoses. Limitations include the limited ability to draw conclusions regarding cause and effect from the results of an observational study. Although limiting the patients to those who experienced a witnessed arrest improves the accuracy of the report, it underestimates the true number of arrests that occurred. Furthermore, because the majority of events were alerted by firefighters, those individuals who were not in public settings, and may have been at most risk for heat wave-related injury, were less likely to be witnessed. This latter limitation impacts the study demographics and the relative risks of the study population. Nonetheless, the study provides an important observation that will hopefully aid in new discovery of mechanisms of risk.

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REFERENCES

1. Myerburg RJ, Mitrani R, Interian A Jr, et al: Interpretation of outcomes of antiarrhythmic clinical trials: Design features and population impact. *Circulation* 1998; 97: 1514–1521
2. Moss AJ, Hall WJ, Cannom DS, et al: Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996; 335: 1933–1940
3. Buxton AE, Lee KL, Fisher JD, et al: A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med* 1999; 341: 1882–1890
4. Moss AJ, Zareba W, Hall WJ, et al: Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002; 346:877–883
5. Bardy GH, Lee KL, Mark DB, et al: Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; 352:225–237
6. Empana JP, Sauval P, Ducimetiere P, et al: Increase in out-of-hospital cardiac arrest attended by the medical mobile intensive care units, but not myocardial infarction, during the 2003 heat wave in Paris, France. *Crit Care Med* 2009; 37:3079–3084
7. Guinea GV, Atienza JM, Fantidis P, et al: Increases of corporal temperature as a risk factor of atherosclerotic plaque instability. *Ann Biomed Eng* 2008; 36:66–76
8. Pasquie JL, Sanders P, Hocini M, et al: Fever as a precipitant of idiopathic ventricular fibrillation in patients with normal hearts. *J Cardiovasc Electrophysiol* 2004; 15: 1271–1276
9. Amin AS, Meregalli PG, Bardai A, et al: Fever increases the risk for cardiac arrest in the Brugada syndrome. *Ann Intern Med* 2008; 149:216–218
10. Morita H, Zipes DP, Morita ST, et al: Temperature modulation of ventricular arrhythmogenicity in a canine tissue model of Brugada syndrome. *Heart Rhythm* 2007; 4:188–197

Is resident education a casualty or beneficiary of rapid response systems?*

“Reading papers is not the purpose of showing how much we know and what we are doing but is an opportunity to learn” (1). This quote by William J. Mayo is particularly pertinent because there is a great deal to learn from the manuscript by Sarani et al (2) published in this issue of *Critical Care Medicine*. Their work is one of only two publications (3) to examine the consequences of a rapid response system on resident education. Despite inconclusive and contradictory findings about the effectiveness of rapid response systems on patient outcome (4–8), political forces have deemed them important (9), and many hospitals have implemented these systems with little concern for the potentially negative impact they may have on resident education. To err on the side of a proactive approach to patient care while the effectiveness of these systems is investigated has its merits. However, over the years it will take to determine efficacy, cohorts of residents will be completing their training, and the impact of rapid response systems on their education must be considered concurrently. Regrettably, not even the Consensus Conference on Emergency Medical Teams (10), which lists 18 physicians as authors, considered the potential effect these teams may have on resident education. In this report, trainee doctors are only cited in a table listing barriers to implementation. Similarly, nursing journals describe how to develop rapid response systems but fail to give guidance on incorporating residents (11–13).

Sarani et al (2) demonstrate that if developed appropriately, a rapid response

system can protect resident autonomy, improve development of clinical skills, and enhance the educational experience. It has previously been reported that nearly half of internal medicine residents do not feel confident leading resuscitations (14). This may be the result of the horizontal nature of in-hospital resuscitations that require residents to orchestrate the actions of a larger team in which each team member has a specialized role. This type of resuscitation stands in contrast with the vertical, sequential approach taught during all advanced life support courses (15). Because most problems requiring a rapid response system can be appropriately managed by the primary team (16), the system used by the University of Pennsylvania (2), which places the resident from the primary team in charge, is proper and maintains continuity of care. In addition to a better understanding of individual patients, maintaining continuity of care has great educational value, because it allows the resident to witness how critical illness develops and plays out.

One potential explanation for the conflicting data (4–8) regarding rapid response systems may be that in teaching hospitals, residents are immediately available, provide a greater degree of continuity of care, and are capable of treating most problems when rapid response is summoned. It should be noted that Sarani et al (2) did not actually measure patient outcome, but rather assessed perceptions about patient safety. This is a significant limitation of an otherwise excellent work, because perceptions do not always equate with reality.

The perception of improved patient safety may be the result of the presence of an attending physician. Attending physician “back up” of the residents provides the patient with a safety net and the entire team with an experienced resource. The attending physician also provides a clear command presence in a time of crisis, which has been shown to improve team performance (17) and may limit

confrontations between residents and nurses that have been shown to correlate with poor patient outcomes (18).

Another important aspect of the University of Pennsylvania (2) system was the integration of the resident into the activation process. This allows the resident to put a consistent team of experienced individuals at the bedside, which may improve patient care while simultaneously decreasing resident stress. Much of the potential benefit of the rapid response system will be lost, however, if institutions implement processes that exclude involvement of the resident team. Worse yet would be implementation of a rapid response system in a manner antagonistic to the primary physician or resident team. The unfortunate result in that case will be a conflict in which no patient will benefit.

From the standpoint of a resident advocate, the development of a rapid response system that respects the educational needs of the resident, allows for autonomy with appropriate attending support while simultaneously placing an effective multidisciplinary team at the bedside has great educational potential. However, failure to respect the needs of the residents may result in even less well-trained, less confident residents in the future. Because residents frequently do not accurately assess their own performance (19), incorporation of a debriefing session by the attending physician may provide education about resuscitative medicine that heretofore has been sorely lacking.

In addition to resident education, the education of nurses is likewise paramount. There appears to be a growing knowledge gap about basic resuscitation between floor nurses and critical care nurses. This disparity is disappointing. Nursing leadership should try to close this gap by instituting nurse-to-nurse debriefing as part of the rapid response system. Hearing feedback directed to the resident by attending faculty may enhance the nurse’s understanding; however, a nurse may be in a better position to educate another nurse, because the

*See also p. 3091.

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specific roles of residents and nurses are different. One unintended consequence of a rapid response system is that a two-tiered approach to nursing care will be codified when eliminating knowledge gaps should be the ultimate goal.

Currently, those with critical care experience typically staff rapid response systems. Although their critical care experience is valuable, given the wide variety of clinical problems in differing age groups and the need to render care in resource-poor, atypical environments, critical care knowledge should be considered just a minimum prerequisite. Members of these teams would be better served if their education were modeled after paramedic training, which integrates knowledge, advanced technical skills, and comfort in different environments.

In closing, if a rapid response system is developed using the model set forth by Sarani et al (2), the resident education will be a beneficiary. However, if the needs of the resident are not considered, education will surely be a casualty of a rapid response system.

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REFERENCES

1. Aphorisms & Quotations for the Surgeon. Schein M (Ed). Shrewbury, UK, Publishing Limited, 2003, p 70
2. Sarani B, Sonnas S, Bergey MR, et al: Resident and nurse perceptions of the impact of a medical emergency team on education and patient safety in an academic medical center. *Crit Care Med* 2009; 37:3091-3096
3. Jacques T, Harrison GA, McLaws ML: Attitudes towards and evaluation of medical emergency teams: A survey of trainees in intensive care medicine. *Anesth Intensive Care* 2008; 36:90-95
4. Buist MD, Moore GE, Bernard SA, et al: Effects of a medical emergency team on reduction of incidence of and mortality from unexpected cardiac arrests in hospital: A preliminary report. *BMJ* 2002; 324:387-390
5. MERIT Study Investigators: Introduction of the medical emergency team (MET) system: A cluster-randomized control trial. *Lancet* 2005; 365:2091-2097
6. Sharek PJ, Parast LM, Leong K, et al: Effect of a rapid response team on hospital-wide mortality and code rates outside the ICU in a children's hospital. *JAMA* 2007; 298:2267-2274
7. Chan PS, Khalis A, Longmore LS, et al: Hospital-wide code rates and mortality before and after implementation of a rapid response team. *JAMA* 2008; 300:2506-2513
8. Winters BD, Cuong J, Hunt EA, et al: Rapid response systems: A systematic review. *Crit Care Med* 2007; 35:1238-1243
9. Berwick DM, Calkins DR, McCannon CJ, et al: The 100,000 lives campaign: Setting a goal and a deadline for improving health care quality. *JAMA* 2006; 295:324-327
10. DeVita MA, Bellomo R, Hillman K, et al: Findings of the first consensus conference on medical emergency teams. *Crit Care Med* 2006; 34:2463-2478
11. Halvorsen L, Garolis S, Wallace-Scroggs A, et al: Building a rapid response team. *AACN Advanced Critical Care* 2007; 18:129-140
12. Jamieson E, Ferrell C, Rutledge DN: Medical emergency team implementation: Experiences of a mentor hospital. *Medsurg Nurs* 2008; 17:312-316
13. Donaldson N, Shapiro S, Scott M, et al: Leading successful rapid response teams: A multisite implementation evaluation. *J Nurs Admin* 2009; 39:176-181
14. Hayes CW, Rhee A, Detsky ME, et al: Residents feel unprepared and unsupervised as leaders of cardiac arrest teams in teaching hospitals: A survey of internal medicine residents. *Crit Care Med* 2007; 35:1668-1572
15. Schenarts PJ: Incorporating leadership training, a horizontal approach to resuscitation and performance feedback into advanced life support. *Crit Care Med* 2007; 35:1781-1782
16. Prado R, Albert RK, Mehler PS, et al: Rapid response: A quality improvement conundrum. *J Hosp Med* 2009; 4:255-257
17. Hoff WS, Reilly PM, Rotondo MF, et al: The importance of a command physician in trauma resuscitation. *J Trauma* 1997; 43:772-777
18. Baldwin DC Jr, Daugherty SR: Interprofessional conflict and medical errors: Results of a national multi-specialty survey of hospital residents in the US. *J Interprof Care* 2008; 22:573-586
19. Brewster LP, Risucci DA, Joehl RJ, et al: Comparison of resident self-assessments with trained faculty and standardized patient assessments of clinical and technical skills in a structured educational model. *Am J Surg* 2008; 195:1-4

Estrogen therapy after traumatic brain injury: Time for clinical trials?*

The hypothesis that female hormones might be neuroprotective is drawn from clinical data suggesting that males have worse outcomes post neurologic

insults than females with similar injuries (1). Experimentally, brain injuries are exacerbated in female animals after ovariectomy, an effect attenuated by hormone replacement (2). The neuroprotective actions of estrogens, in particular, have been reported in response to chemical toxins, excitotoxicity, ischemia, heatstroke, oxidative stress, β -amyloid toxicity, and mechanical strain. The neuroprotective mechanisms of estrogen are largely attributed to improved cerebral blood flow, stabilization of the blood-brain barrier, and

reductions of both inflammation and cell loss (3).

In this issue of *Critical Care Medicine*, the paper by Dr. Chen et al (4) explored the use of Premarin, a compound drug consisting primarily of conjugated estrogens, to protect against fluid percussion injury elicited in male rodents. Premarin therapy attenuated fluid percussion injury-induced cerebral contusion, apoptosis, activated inflammation, and motor and cognitive deficits. Surprisingly, Premarin therapy also promoted both neurogenesis and angiogenesis in the peri-ischemic tis-

*See also p. 3097.

Key Words: traumatic brain injury; premarin; estrogen; therapy; gender

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sue adjacent to the contusion. The neuroprotective actions of Premarin seemed to be mediated by estrogen receptor- α , as pharmacologic blockade of estrogen receptor- α occluded the neuroprotective actions of Premarin therapy. The authors concluded that Premarin therapy attenuates fluid percussion injury-induced cell loss and neural deficits in male rodents. This reported investigation is intriguing as it not only demonstrates an estrogen therapeutic drug action but also identifies an estrogen receptor for targeted therapy after traumatic brain injury (TBI). This study also demonstrates the potential healing benefits of estrogen therapy via neurogenesis and angiogenesis. Importantly, their work indicates that estrogen therapy in the context of TBI deserves further attention, despite some published contradictory findings (5, 6).

The study by Dr. Chen et al (4), however, has several limitations. First, although the exclusive use of male animals in this study eliminated the confounding effect of fluctuating levels of endogenous estrogen in females, the use of ovariectomized female animals could have provided important supportive data. Second, Premarin was only administered immediately after fluid percussion injury, an unrealistically rapid dosing for neuroprotective therapeutic agents after TBI. Furthermore, as rightly pointed out by the authors, the study is also limited by the use of animals within a restricted age range and the lack of Premarin dose-response experiments. These latter omissions may be particularly important as estrogen responsiveness is dynamic, altered by reproductive age and endogenous release; and peak plasma concentrations of exogenous estrogen that are early, prolonged, or supraphysiological might be associated with worsening of neurologic insult (7). Despite these caveats, Dr. Chen et al (4) should be commended as the large battery of tests applied in their study all support the premise that estrogen is truly neuroprotective and importantly, that estrogen therapy has positive actions on cognitive outcome after TBI. Furthermore, to our knowledge, this study is the first to demonstrate that Premarin, a drug with a well-known pharmacologic profile in humans, exhibited therapeutic efficacy after TBI.

How does estrogen protect the brain at the cellular level from such a wide variety of neurologic insults? Cerebral blood flow is improved by estrogen stimulating estrogen receptor- α on both

smooth muscle and endothelial cell layers of the cerebral blood vessels (8). In particular, estrogen acts at the cerebrovasculature to increase the production of local vasodilating factors (i.e., nitric oxide and prostacyclin), to improve mitochondrial energy production at the same time reducing reactive oxygen species, and to elicit anti-inflammatory actions evident by reduced nuclear factor- κ B activity. Vasogenic edema is reduced by estrogen after TBI by maintaining integrity of the blood-brain barrier, possibly through inhibition of membrane lipid peroxidation and changes in expression of water channels, termed aquaporins, located at the endothelial-astrocytic interface (9). Also intriguing is the number of diverse actions of estrogen directly on cells of the brain parenchyma. Cell survival is promoted by estrogen administration after brain injury due to improved intracellular calcium homeostasis, via actions on calcium channels and N-methyl-D-aspartate receptors, increased production and release of growth factors, and induction of anti-apoptotic transcriptional mechanisms (1, 3, 10).

Although a large and growing body of literature suggests that estrogen therapy will be beneficial in humans post TBI, several outstanding issues might be resolved from further preclinical investigations (11). These include dose and timing of estrogen administration, identification of ages most likely to benefit from estrogen therapy, administration of estrogen alone or in combination with other hormones (such as progesterone), and the ideal drug delivery method (7, 9, 12, 13). Outstanding controversies in the literature are likely compounded by animal investigations with inadequate investigator blinding, limited information of age responsiveness to hormones, and poorly controlled or nonreporting of critical physiologic parameters (i.e., temperature). Despite these ongoing concerns, the majority of animal literature supports estrogen therapy after TBI. Given the potential neuroprotective benefits of estrogen therapy, one could argue that it is time for human clinical trials with controlled Premarin administration after TBI. These clinical trials will inevitably rely on pharmacokinetic studies with frequent sampling of blood and cerebrospinal fluid (via external ventricular drain) to monitor estrogen levels, given the complex dose-response relationship with exogenous administration (7).

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REFERENCES

1. Herson PS, Koerner IP, Hurn PD: Sex, sex steroids, and brain injury. *Semin Reprod Med* 2009; 27:229–239
2. Fukuda K, Yao H, Ibayashi S, et al: Ovariectomy exacerbates and estrogen replacement attenuates photothrombotic focal ischemic brain injury in rats. *Stroke* 2000; 31:155–160
3. Soustiel JF, Palzur E, Nevo O, et al: Neuroprotective anti-apoptosis effect of estrogens in traumatic brain injury. *J Neurotrauma* 2005; 22:345–352
4. Chen S-H, Chang C-Y, Chang H-K, et al: Premarin stimulates estrogen receptor- α to protect against traumatic brain injury in male rats. *Crit Care Med* 2009; 37:3097–3106
5. Bruce-Keller AJ, Dimayuga FO, Reed JL, et al: Gender and estrogen manipulation do not affect traumatic brain injury in mice. *J Neurotrauma* 2007; 24:203–215
6. Lebesgue D, LeBold DG, Surles NO, et al: Effects of estradiol on cognition and hippocampal pathology after lateral fluid percussion brain injury in female rats. *J Neurotrauma* 2006; 23:1814–1827
7. Strom JO, Theodorsson A, Theodorsson E: Dose-related neuroprotective versus neurodamaging effects of estrogens in rat cerebral ischemia: A systematic analysis. *J Cereb Blood Flow Metab* 2009; 29:1359–1372
8. Duckles SP, Krause DN: Cerebrovascular effects of oestrogen: Multiplicity of action. *Clin Exp Pharmacol Physiol* 2007; 34:801–808
9. O'Connor CA, Cernak I, Vink R: Both estrogen and progesterone attenuate edema formation following diffuse traumatic brain injury in rats. *Brain Res* 2005; 1062:171–174
10. Lapanantasin S, Chongthammakun S, Floyd CL, et al: Effects of 17 β -estradiol on intracellular calcium changes and neuronal survival after mechanical strain injury in neuronal-glia cultures. *Synapse* 2006; 60:406–410
11. Singh M, Sumien N, Kyser C, et al: Estrogens and progesterone as neuroprotectants: What animal models teach us. *Front Biosci* 2008; 13:1083–1089
12. Toung TJ, Chen TY, Littleton-Kearney MT, et al: Effects of combined estrogen and progesterone on brain infarction in reproductively senescent female rats. *J Cereb Blood Flow Metab* 2004; 24:1160–1166
13. Gibson CL, Gray LJ, Bath PM, et al: Progesterone for the treatment of experimental brain injury; a systematic review. *Brain* 2008; 131:318–328

Intensive care unit (short) and 1-year (long-term) prognosis: Data are in for patients with ischemic stroke*

In this issue of *Critical Care Medicine*, the study by Golestanian et al (1) is a welcomed contribution on the understanding of the natural history of the disease for patients with ischemic stroke, a frequent, costly, and usually devastating medical condition. This work is a result of an in depth analysis of a multicentered, retrospective cohort abstracted from large administrative databases (Centers for Medicare and Medicaid Services and Healthcare Management Organization—Medicare Plus Choice) with a cumulative sample size of >30,000 observations in patients ≥ 65 yrs. These observations provide the best unbiased estimate of many useful and important clinical parameters.

Healthcare administrators and clinicians alike understand the limitations of previously reported data obtained from single institutions with smaller sample sizes and with a blurred distinction of the underlying stroke mechanism (unclear separation of ischemic stroke from other forms of cerebrovascular accidents), so . . . What are facts we can learn from this work? How is this information going to help me when I am treating my patients? With this information, do I now feel that I have the supporting evidence to communicate news and perspectives of outcome to family members in the waiting area of my intensive care unit (ICU)?

Regarding ICU prognosis (26% of all admissions in the study), the data show, and I am confident to say, that mechanically ventilated patients have a higher mortality (odds ratio, 5.6) (2). The older the patient is, the higher the experienced mortality (>80 yrs old: odds ratio, 1.9;

>85 yrs old: odds ratio, 3) (3). The more comorbidities the patient has, the higher the ICU use and mortality. All these descriptors are not surprising to a practicing intensivist. They have biologic plausibility! The important contribution of this work is the definition of the magnitude of their independent effects. The presence of congestive heart failure, arrhythmias, or valvular disease was independently associated with a 40% increased mortality risk (4). Briefly, patients with ischemic stroke admitted to the ICU have a 21% short-term probability of death and 40% long-term mortality risk (5).

Regarding 30-day survivors' long-term prognosis (1 yr), it is worth mentioning that gastrostomy feeding identifies a population with increased risk of death (odds ratio, 2.6) (Mechanical ventilation was associated with a mortality of an odds ratio of 1.9.) (6). It is important to communicate to family members that in this cohort, only 30% of patients were able to be discharged home; the majority of them were left with moderate to severe disability, requiring assistance for activities of daily living or discharged to skilled nursing facilities (70%).

I found interesting and puzzling the strong association of hypothyroidism and mortality. The mechanism of such association is fertile ground for elucubration.

Unfortunately, all this wealth of information cannot be extrapolated to all clinical scenarios as a result of the characteristics of the population sampled. The population studied was predominantly older (>65 yrs old: 100%), educated (and Centers for Medicare and Medicaid Services and Healthcare Management Organization-insured), Caucasians (80%), and females (60%). These findings may not apply to other demographics, i.e., the inner-city, minority, and uninsured, that may develop their stroke at an early age, have difficult access to health care, and may have disease based on different pathophysiological mechanisms (i.e., autoimmune, cocaine use, or genetic fac-

tors). Differences in this population have been noted before for other conditions in the ICU (7). Furthermore, the impact of therapeutic interventions (i.e., thrombolysis) cannot be evaluated from the data provided.

The reader should also be aware and warned that because of the large sample size, some differences may achieve statistical significance, but the magnitude of the absolute "delta" has to be individually interpreted by providers. A significant *p* value does not necessarily imply or describe a clinically significant difference. Is this the case of the hypothyroidism association—frequently found in persons >65 yrs—with mortality? (8).

Finally, the meaningful outcome of interest functional status is not assessed in this study. A clinical spectrum poststroke that spans—in one end—the aphasia-free, functionally independent, cognitive spared survivor opposite to the persistent-vegetative-state (coma vigil), offers such a wide variability spectrum of quality of life that predictors of such variance need to be clarified by future research (9). In the meantime, we need to acknowledge the strength of the data presented in this work, incorporate this information into our knowledge base, and just say, for the ICU (short) and 1 yr (long-term) prognosis, data are in for victims of ischemic stroke.

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REFERENCES

1. Golestanian E, Liou J-I, Smith MA: Long-term survival in older critically ill patients with acute ischemic stroke. *Crit Care Med* 2009; 37:3107–3113
2. Berrouschot J, Rossler A, Koster J, et al: Me-

*See also p. 3107.

Key Words: stroke; cerebrovascular accidents; coma; mortality; outcomes; CMS; Healthcare Management Organization

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- chanical ventilation in patients with hemispheric ischemic stroke. *Crit Care Med* 2000; 28:2956–2961
3. Rordorf G, Koroshetz W, Efrid JT, et al: Predictors of mortality in stroke patients admitted to an intensive care unit. *Crit Care Med* 2000; 28:1301–1305
 4. Handschu R, Haslbeck M, Hartmann A, et al: Mortality prediction in critical care for acute stroke: Severity of illness-score or coma-scale? *J Neurol* 2005; 252:1249–1254
 5. Steiner T, Mendoza G, De Georgia M, et al: Prognosis of stroke patients requiring mechanical ventilation in a neurological critical care unit. *Stroke* 1997; 28:711–715
 6. Iizuka M, Reding M: Use of percutaneous endoscopic gastrostomy feeding tubes and functional recovery in stroke rehabilitation: A case-matched controlled study. *Arch Phys Med Rehabil* 2005; 86:1049–1052
 7. Freire AX, Bridges L, Umperiez GE, et al: Admission hyperglycemia and other risk factors as predictors of hospital mortality in a medical ICU population. *Chest* 2005; 128:3109–3116
 8. Canaris GJ, Manowitz NR, Mayor G, et al: The Colorado thyroid disease prevalence study. *Arch Intern Med* 2000; 160:526–534
 9. Schielke E, Busch MA, Hildenhagen T, et al: Functional, cognitive and emotional long-term outcome of patients with ischemic stroke requiring mechanical ventilation. *J Neurol* 2005; 252:648–654

Light from the EAST-SCCM*

In this issue of *Critical Care Medicine*, Napolitano et al (1) have performed a valuable service; in 34 succinct pages, they have reviewed and distilled a veritable mountain of evidence concerning thresholds for red cell transfusion. Based on best current evidence for the common clinical situations faced in the intensive care unit, their guidelines are applicable not only for traumatologists and surgeons but also for all intensivists. If followed, these guidelines, a substantial step forward from the vague, consensus-based recommendations of the past decade, will conserve resources, reduce morbidity, and save lives.

The guidelines depend heavily on the findings of the landmark Transfusion Requirements in Critical Care Trial, (2) now a decade old. This multi-centered, randomized, clinical trial found that a restrictive transfusion strategy was at least as effective and suggested a reduction in mortality compared with a more liberal one. In subgroup analysis, this survival advantage was greatest in younger patients and in those less severely ill. Reasonable conclusions could be drawn regarding some subgroups (those with cardiovascular disease) but were more difficult in others because of exclusion from the study (acute coronary syndromes) or small number of patients

(neurologic injury) or lack of clear identification for subgroup analysis (sepsis, acute lung injury) (3). Whereas controversy continues regarding the optimal transfusion strategies in these respective patient populations, Transfusion Requirements in Critical Care has provided at least a strong suggestion that 7 g/d of hemoglobin is plenty in most patients.

Among the areas discussed in the guidelines is septic shock. Because of its pathophysiology, including diminished oxygen extraction, loss of autoregulation, and increased oxygen demand, (4) some espouse aggressive transfusion. However, for those septic for 24 hrs or more, no survival benefit exists from therapies designed to increase oxygen demand (5, 6). Similarly, in established shock, red cell transfusion does not improve gastric pH (7–9) or improve sublingual capillary circulation or global oxygen transport (10).

For treating those in early shock, the publication of a multimodality, single-center study by Rivers et al (11) in 2001 renewed interest in goal directed therapy. In such patients undergoing surgery, previous, single-center studies using intravenous fluids, inotropes and transfusion had shown impressive survival benefit, although control group therapies were not well described (12, 13). In a medical population, the trial by Rivers et al found a 30% relative survival advantage for an intervention of inotropes and transfusion to maintain a central venous oxygenation of 70%. Based on this, the Surviving Sepsis Guidelines currently recommend to “transfuse packed red cells if necessary to hematocrit of >30%” (14).

The Eastern Association for the Surgery of Trauma—Society of Critical Care

Medicine (EAST-SCCM) guidelines eschew that recommendation, citing multiple studies from the large body of literature failing to find physiologic benefit from red cell transfusion in septic patients. They then discuss the limitations of the study by Rivers et al, including the inability to parse which intervention was of benefit, as well as a significant imbalance in fluid resuscitation between control and intervention groups. Simply put, it is not clear whether patients in this study actually benefited from red blood cell transfusion or simply from earlier overall fluid volume expansion and more aggressive resuscitation. Although the fluid protocol was identical, the goal-directed group received >40% greater volume than the control group in the first 6 hrs. The intravascular volume imbalance may be even larger. Whereas the text indicates that the fluid used was crystalloid, Figure 2 indicates that either crystalloid or colloid could be used for the intervention arm patients, and in public presentation (Laennec Society, Philadelphia 2004), Dr Rivers indicated that 5% albumin was the predominant resuscitation fluid used. As an unblinded study, intervention patients may have simply received a greater proportion of colloid. These patients achieved significantly higher blood pressures. The EAST-SCCM guideline authors advise against an increased transfusion threshold based on a broader reading of known risks (inflammatory activation, circulatory overload, transfusion-related acute lung injury, and development of acute respiratory distress syndrome) and questionable benefits (increased oxygen delivery).

The EAST guidelines do support aggressive, empirical transfusion in trauma

*See also p. 3124.

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and other surgical patients with uncontrolled hemorrhage and a rapidly evolving clinical course. One characteristic of modern transfusion thinking is the recognition that bleeding patients need blood, whereas nonbleeding patients generally do not. In acute hemorrhagic shock, red blood cells are often the most available and effective initial resuscitation fluid, and prudence suggests a liberal transfusion strategy until anatomical control is achieved and laboratory values stabilize.

The EAST-SCCM guidelines provide a service in making recommendations when the data are compelling that a conservative transfusion strategy will improve outcomes. The authors have also pointed out something equally important, namely, that in areas of continued controversy, the assumption that a more liberal transfusion strategy must be of benefit are based on shaky evidence, and that randomized clinical trials are necessary to establish the optimal transfusion strategy in the areas of sepsis, acute lung injury, acute respiratory distress syndrome, acute coronary syndromes, and neurologic injury. Until we have data from such studies, these guidelines provide the clearest direction available. We hope the guidelines will engender evidence-based debate over transfusion thresholds, further study of both short-term and long-term risks and benefits of transfusion, and that these efforts will generate more light than heat.

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REFERENCES

1. Napolitano LM, Kurek S, Luchette FA: Clinical practice guideline: Red blood cell transfusion in adult trauma and critical care. *Crit Care Med* 2009; 37:3124–3157
2. Hebert PC, Wells G, Blajchman MA, et al: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999; 340:409–17
3. Hebert PC: The TRICC trial: a focus on the sub-group analysis. *Vox Sang* 2002; 83 (Suppl 1):387–96
4. Cain SM, Curtis SE: Experimental models of pathologic oxygen supply dependency. *Crit Care Med* 1991; 19:603–12
5. Gattinoni L, Brazzi L, Pelosi P, et al: A trial of

- goal-oriented hemodynamic therapy in critically ill patients. SvO₂ Collaborative Group. *N Engl J Med* 1995; 333:1025–32
6. Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D: Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 1994; 330:1717–22
7. Marik PE, Sibbald WJ: Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA* 1993; 269:3024–9
8. Fernandes CJ Jr, Akamine N, De Marco FV, De Souza JA, Lagudis S, Knobel E: Red blood cell transfusion does not increase oxygen consumption in critically ill septic patients. *Crit Care* 2001; 5:362–367
9. Silverman HJ, Tuma P: Gastric tonometry in patients with sepsis. *Effects of dobutamine infusions and packed red blood cell transfusions Chest* 1992; 102:184–188
10. Sakr Y, Chierego M, Piagnerelli M, et al: Microvascular response to red blood cell transfusion in patients with severe sepsis. *Crit Care Med* 2007; 35:1639–44
11. Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377
12. Boyd O, Grounds RM, Bennett ED: A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. *JAMA* 1993; 270:2699–2707
13. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS: Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. *Chest* 1988; 94: 1176–86
14. Dellinger RP, Levy MM, Carlet JM, et al: Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med* 2008; 36:296–327

Toward new paradigms in critical care research*

Over 15% of hospital beds in the United States are in intensive care units, and critical care consumes >\$55 billion in healthcare costs in the United States each year (1). Yet, there has been

limited focus in investigating the pathophysiology and treatment of the multisystemic disorders that affect many critically ill patients. In part, this reflects the segmentation of critical care between various specialties, including internal medicine, anesthesiology, surgery, pediatrics, and emergency medicine. The organ and disease-specific organization of the National Institutes of Health also limits opportunities to explore entities such as critical illness in which interactions between multiple cell populations and organ systems play a major role.

In this issue of *Critical Care Medicine*, Cobb et al (2) present recommendations from the Fifth National Institutes of Health Symposium on the Functional Genomics of Critical Illness and Injury that are aimed at developing a strategic plan for critical care research in the United States. Key components of the initiative are directed at defining priorities in critical care research, delineating optimal care for critically ill patients with the goal of achieving greater standardization in the care provided to such patients, and enhancing communication between stakeholders in critical care, including federal

*See also p. 3158.

Key Words: sepsis; acute lung injury; cell biology; genetics; genomics; critical illness

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agencies, pharmaceutical and biotechnology companies, hospitals, critical care physicians, and professional societies.

A central component of this initiative to advance critical care research is the formation of the U.S. Critical Illness and Injury Trials Group, funded by the National Institute of General Medical Sciences. The U.S. Critical Illness and Injury Trials Group will provide a forum for the design of high-priority clinical trials examining important issues in critical care. As envisaged, the U.S. Critical Illness and Injury Trials Group will facilitate communication between basic scientists and clinicians. By incorporating powerful technologies such as genetics, genomics, proteomics, and systems biology, this endeavor should provide new understanding of the genesis of critical illnesses and transform clinical research, allowing entry criteria and patient recruitment to move beyond clinically defined syndromes and be based on specific cellular alterations. Reducing heterogeneity in clinical trials and identifying individuals with cellular abnormalities amenable to correction with targeted therapies has been often discussed but rarely incorporated into clinical trial design in critical care (3–8). We continue to use poorly defined syndromes such as sepsis or acute lung injury initiated by multiple etiologies and associated with activation of a diverse spectrum of cellular pathways, whereas our colleagues in other specialties such as oncology or rheumatology have moved to treating entities defined by specific genetic or cellular alterations, an approach that is associated with increased response and diminished toxicity to biologic modifiers, monoclonal antibodies, and other therapies. It is highly likely that interventions such as antibodies to tumor necrosis factor- α or the interleukin-1 receptor antagonist, that appeared to be ineffective in clinical trials for sepsis or acute lung injury, may have actually reduced morbidity and mortality in subsets of patients, but such effects were unable to be detected as a result of the background heterogeneity produced by clinically defined entry criteria, which did not account for source or nature of infection, underlying

illnesses, or activation of the biologic pathways being targeted by these agents.

A centrally important issue in advancing critical care research is identifying appropriate funding sources for such efforts. Although the U.S. Critical Illness and Injury Trials Group will help with clinical trial design, it will not provide funding for studies, leaving a potential financial chasm between the design and performance of clinical investigation in critical care that will need to be bridged. The National Institutes of Health are the primary federal agencies in the United States funding basic, translational, and clinical research. However, because of the organ and disease-specific nature of institutes within the National Institutes of Health, the priorities for critical care issues have often centered on specific entities such as acute lung injury or acute kidney failure rather than multisystemic critical care issues such as sepsis. Nevertheless, recent National Institutes of Health initiatives have permitted funding of clinical trials that are more broadly based such as early goal-directed therapy for sepsis (Protocolized Care for Early Septic Shock, NCT00510835, ClinicalTrials.gov). The increasing awareness of the importance of basic and clinical issues relating to critical care as well as congressional and public interest in developing new therapies for important diseases provides reason for optimism in terms of National Institutes of Health funding for clinically oriented research in critical care. Similarly, the pharmaceutical industry continues to be interested in developing new approaches for studying interventions in critical care and is likely to participate in the design and execution of clinical trials, especially those in which novel therapies can be more specifically directed toward critically ill patients with well-characterized genetic or cellular alterations capable of predicting higher likelihood of response and diminished toxicity.

There have been remarkable advances in our understanding of the genetics of human disease and how genetics conditions responses to environmental factors, including infection. The development of biomar-

kers, able to identify patients with alterations in specific cellular pathways who are likely to demonstrate significant response to targeted therapeutic interventions, is a rapidly advancing area. The approaches outlined by Cobb and colleagues are tremendously exciting because they provide a roadmap for transformative advances in critical care research and clinical trial design. Incorporating genetics, gene expression, and cell biology into clinical trials will have immediate benefits in enhancing understanding of the pathophysiology of critical illness. However, the most important effect of using such approaches will be in identifying novel therapies able to improve clinical outcomes among the patients we treat each day in the intensive care unit.

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REFERENCES

1. Halpern NA, Pastores SM, Greenstein RJ: Critical care medicine in the United States 1985–2000: An analysis of bed numbers, use, and costs. *Crit Care Med* 2004; 32:1254–1259
2. Cobb JP, Ognibene FP, Ingbar DH, et al: Forging a critical alliance: Addressing the research needs of the United States critical illness and injury community. *Crit Care Med* 2009; 37:3158–3160
3. Abraham E, Dinarello CA, Matthay MA, et al: Consensus conference definitions for sepsis, septic shock, acute lung injury, and ARDS—Time for a reevaluation. *Crit Care Med* 2000; 28:232–235
4. Dellinger RP, Abraham E, Bernard G, et al: Controversies in sepsis clinical trials. *J Crit Care* 2006; 21:38–47
5. Abraham E, Marshall JC: Sepsis and mediator-directed therapy: Rethinking the target population. *Mol Med Today* 1999; 5:56–58
6. Cobb JP, O'Keefe GE: Injury research in the genomic era. *Lancet* 2004; 363:2076–2083
7. Opal SM, Patzou E: Translational research in the development of novel sepsis therapeutics: Logical deductive reasoning or mission impossible? *Crit Care Med* 2009; 37(Suppl):S10–15
8. Carlet J, Cohen J, Calandra T, et al: Sepsis: Time to reconsider the concept. *Crit Care Med* 2008; 36:964–966

Anticonvulsant overdose: Can we shorten the coma?*

Antiepileptic drugs (AEDs) are more numerous and widely used than ever before. Indications have extended from epilepsy to include psychiatric conditions and migraine. In addition, there is off-label use typically to augment the effect of other medications and this can increase toxicity. More widespread use in psychiatric populations, who may be at higher risk for suicide as part of the underlying condition, may increase the likelihood of drug overdose. Furthermore, the US Food and Drug Administration recently reported increased suicidality, in a large database, in people with epilepsy taking these drugs (1).

In 2006, there were 16,796 toxic exposures to the protein-bound drugs phenytoin, valproic acid, and carbamazepine, as reported by the US Toxic Surveillance System. Twelve of these cases resulted in death. In these patients, the addition of 2.5% to 5% albumin to dialysate significantly enhanced clearance of valproate and carbamazepine (2). However, the efficacy of hemodialysis is variable. Phenytoin, the most highly protein-bound agent, was not significantly cleared, but there is evidence that combining activated charcoal hemoperfusion and high-flux hemodialysis reduced the half-life substantially (3).

US Poison Center data for 2004 showed >9000 ingestions of valproic acid. Use of valproic acid is associated with various life-threatening side effects, including rash, pancreatitis, and elevation of serum ammonia. High ammonia can cause a spectrum of neurologic problems from unsteadiness to encephalopathy with obtundation and death. The exact mechanism of valproate-induced hyperammonemia is unknown, but it appears to be different from that of chronic hepatic encephalopathy. Valproate seems to lead to a disruption of the urea cycle

(4, 5). It then produces hyperammonemia by shifting the excitatory neurotransmitter glutamate toward glutamine. There is possibly an osmolytic compensation for high glutamine, which increases cerebral edema and coma (6, 7).

The effects of overdose with older AEDs are known for the most part. However, few reports exist for the newer agents. For instance, topiramate can cause a significant metabolic acidosis, lamotrigine, a life-threatening rash, and Stevens-Johnson syndrome. Oxcarbazepine can cause hyponatremia, and there can be psychosis with levetiracetam (8). It is also worth mentioning that all of these drugs have recently become available as generic formulations and each drug may have multiple makers. This will undoubtedly cause confusion and possible overdose situations.

Complicating matters more is the complex and variable interaction that valproic acid has with other drugs. We do not know much about the effect of concomitant administration of these other AEDs with valproic acid. They are frequently used in combination either for refractory epilepsy or to augment the therapeutic effects in epilepsy or psychiatric disease. There is some evidence suggesting an exaggerated hyperammonemic response (9). This would be surprising when we consider that many other AEDs like carbamazepine, phenytoin, and phenobarbital normally induce hepatic elimination of valproate.

In this issue of *Critical Care Medicine*, the study by Licari et al (10) highlights important points regarding valproic acid overdose and its management. Length of coma and supportive intensive care unit care were reduced by 8 days for a patient when hemodialysis was initiated on day 1 of presentation. The patient who started hemodialysis on day 3 had a more complicated course, including seizures without a history of epilepsy. The paper also brings up points to consider in other cases of epilepsy drug overdose, because there is no antidote available. Toxic levels of some anticonvulsants, especially phenytoin and valproic acid, can be proconvulsant. In the setting of coma, the electroencephalographic finding consistent with metabolic abnormalities, especially hepatic encephalopathy, is triphasic waves. Seizures, or status epilepticus, can rarely be confused with these, because there is a similar morphology to the discharges. This is an important consideration in situations in which subclinical status is suspected in the setting of metabolic abnormality.

Studies that would help us understand the whole of AED therapy are hard to do. We know too little about the mechanisms of action in the brain of these drugs and less about what areas of the brain they affect. For instance, do some drugs control frontal lobe seizures better than temporal lobe? If so, are they more likely to cause toxic biochemical reactions in specific areas that can be treated with targeted antidotes?

Most of this has been studied with animal models and some with nuclear imaging. The progress made in personalized medicine is certainly promising and might reduce the possibility of AED toxicity in susceptible individuals. Genotyping in severe progressive epilepsy syndromes is providing some clues, for instance, in the avoidance of sodium channel blockers. However, we are not very far in terms of genotyping to predict risk or optimal treatment.

If we are to continue the wide use of these drugs in epilepsy and psychiatry, we would do well to increase preventive care and monitoring. The appropriate social and psychologic care might minimize errors, overdose, and cost. Given the US Food and Drug Administration reported signal for increased risk, clinicians need to regularly screen patients taking AEDs for suicide.

The next step might be to develop consensus guidelines for critical care management of overdose to optimize patient outcome. Perhaps this can be done by expert consensus like in the case of out-of-hospital triage for valproate overdose (11). In the meantime, case reports and experience seem to be our best source of information.

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***See also p. 3161.**

Key Words: antiepileptic drugs; overdose; hemodialysis; valproic acid; suicide

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REFERENCES

1. U.S. Food and Drug Administration, Center for Drug Evaluation and Research: Information for healthcare professionals: Suicidality and antiepileptic drugs. Available at: www.fda.gov/Cder/Drug/InfoSheets/HCP/antiepilepticsHCP.htm. Accessed April 1, 2009
2. Churchwell MD, Pasko DA, Smoyer WE, et al: Enhanced clearance of highly protein-bound drugs by albumin-supplemented dialysate during modeled continuous hemodialysis. *Nephrol Dial Transplant* 2009; 24:231–238
3. Eyer F, Feilgenhauer N, Pfab R, et al: Treatment of severe intravenous phenytoin overdose with hemodialysis and hemoperfusion. *Med Sci Monit* 2008; 14:CS145–CS148
4. Segura-Bruna N, Rodriguez-Campello A, Puente V, et al: Valproate-induced hyperammonemic encephalopathy. *Acta Neurol Scand* 2006; 114:1–7
5. Champe PC, Harvey RA, Ferrier DR: Lippincott's Illustrated Reviews: Biochemistry. Third Edition. Baltimore, MD, Lippincott Williams & Wilkins, 2005, pp 254–257
6. Kreis R, Ross BD, Farrow N, et al: Metabolic disorders of the brain in chronic hepatic encephalopathy detected with H-1 MR spectroscopy. *Radiology* 1912; 182:19–27
7. Garcia M, Huppertz H, Ziyeh S, et al: Valproate-induced metabolic changes in patients with epilepsy: Assessment with H-MRS. *Epilepsia* 2009; 50:486–492
8. Wade JF, Dang CV, Nelson L, et al: Emergent complications of the newer anticonvulsants. *J Emerg Med* 2008 Aug 30 [Epub ahead of print]
9. Zaret BS, Beckner RR, Marini AM, et al: Sodium valproate-induced hyperammonemia without clinical hepatic dysfunction. *Neurology* 1982; 35:136–137
10. Licari E, Calzavacca P, Warrillow SJ, et al: Life-threatening sodium valproate overdose: A comparison of two approaches to treatment. *Crit Care Med* 2009; 37:3161–3164
11. Manoguerra AS, Erdman AR, Woolf AD, et al: American Association of Poison Control Centers. *Clin Toxicol (Phila)* 2008; 46:661–676