

Increasing power in randomized controlled trials*

Conducting adequately powered randomized controlled trials in critically ill patients is a challenging business. Without even starting to consider issues of ethics and consent, the critical care researcher is limited by the relatively small and extremely heterogeneous available patient population. The result is that researchers often aim to detect an unrealistically large treatment benefit; consequently, we see too many negative trials in the critical care literature (1). Some authors have proposed that the solution to this is to consider intermediate or composite end points to trials, rather than seeking a reduction in mortality. However, it is vital that research remains focused on outcomes that are of genuine importance to patients and their families, and which have the potential to change practice. Translating the results of research into changes in clinical practice is difficult enough even when strong evidence of a mortality benefit exists (2, 3).

In this issue of *Critical Care Medicine*, Dr. Roozenbeek and colleagues (4) explore three strategies for increasing the statistical power of a randomized controlled trial, or alternatively, of reducing the required sample size at the same time maintaining the power: selective recruitment based on strict entry criteria; "prognostic targeting" to exclude patients with extreme (low or high) risk; and covariate adjustment.

In many ways, the conclusions of the study are unremarkable but the simulations presented give a greater insight into the magnitude of potential increases in power and the effects on study recruitment and efficiency of applying these different approaches, using real data from random-

ized controlled trials and cohort studies in acute traumatic brain injury.

First, if you know (or can accurately hypothesize) which patients your new treatment will benefit, then you should recruit only these patients. Although this approach may seem obvious, many would presume that targeting recruitment to the correct patients would only reduce the total sample size but not the duration of the study, as the reduced sample size would be offset by a reduced recruitment rate. However, as these simulations nicely demonstrate, this is not the case. Excluding patients with no potential to benefit is a genuinely "efficient" strategy, in that it not only reduces the sample size but also the study duration. This is because the presence of patients with no potential to benefit dilutes the observed treatment effect in the overall intention-to-treat population.

Second, if you cannot accurately target your treatment to those who will benefit (and even if you can), adjusting analyses for strong predictors of outcome will increase the study power. Covariate adjustment as a means to increase power is a recommended approach to analysis in most textbooks on controlled trials. This is one area in which critical care is at an advantage relative to many specialties. There is extensive literature on risk factors for mortality in both general critical care admissions (5), and also specific patient groups including acute traumatic brain injury (6, 7).

What does this mean for the critical care researcher planning a new randomized controlled trial? Unfortunately, the authors acknowledge that their results, although presented in terms of a "reduction in sample size" cannot actually be directly applied at the stage of selecting the sample size for a new study. Although the simulation results suggested potential sample size reductions of 16% to 30%, to be able to accurately estimate the sample size reduction for any particular new study would require this type of simulation modeling to be repeated, using accurate data representative of the specific

patient group of interest to avoid adding yet another unverifiable assumption to the sample size calculation. In practical terms, these results give us some assurance that a slightly underpowered study may be redeemed by the application of careful and appropriate risk adjustment.

How should I decide which covariates to adjust for? Covariates for adjustment in a randomized controlled trial should be selected *a priori*, based on an established strong relationship with the outcome of interest (8); or if it is not possible to specify the exact variables, then the process for selecting variables should be specified and must be completely objective so as to prevent any possible *post hoc* manipulation of results (9). Covariates should not be selected (as is often the case) based on spurious significance tests for imbalance between the trial arms (10). Crucially, all covariates to be included in the analysis must be measured before the point of randomization (or, at the very least, any intervention) to ensure that the covariates are not themselves influenced by the treatment allocation.

By taking advantage of the high-quality data available in critical care, we can hope to increase power in randomized controlled trials and improve the available evidence for new treatments, devices, and organizational interventions.

David A Harrison, PhD

Intensive Care National Audit
and Research Centre
London, UK

REFERENCES

- Ospina-Tascón GA, Büchele GL, Vincent JL: Multicenter, randomized, controlled trials evaluating mortality in intensive care: Doomed to fail? *Crit Care Med* 2008; 36: 1311–1322
- Kalassian KG, Dremiszov T, Angus DC: Translating research evidence into clinical practice: New challenges for critical care. *Crit Care* 2002; 6:11–14
- Kahn JM, Rubenfeld GD: Translating evidence into practice in the intensive care unit: The need for a systems-based approach. *J Crit Care* 2005; 20:204–206
- Roozenbeek B, Maas AIR, Lingsma HF, et al: Baseline characteristics and statistical power

*See also p. 2683.

Key Words: critical care; models; statistical; randomized controlled trials as topic; risk adjustment; sample size

The author has not disclosed any potential conflicts of interest.

Copyright © 2009 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/CCM.0b013e3181ad7b62

- in randomized controlled trials: Selection, prognostic targeting, or covariate adjustment? *Crit Care Med* 2009; 37:2683–2690
5. Moreno RP, Jardim AL, Godinho de Matos R, et al: Principles of risk-adjustment in the critically ill patient. In: 25 Years of Progress and Innovation in Intensive Care Medicine. Kuhlen R, Moreno R, Ranieri M, Rhodes A (Eds). Berlin, Medizinisch Wissenschaftliche Verlagsgesellschaft, 2007, pp 409–417
 6. MRC CRASH Trial Collaborators: Predicting outcome after traumatic brain injury: Practical prognostic models based on a large cohort of international patients. *BMJ* 2008; 336:425–429
 7. Steyerberg EW, Mushkudiani N, Perel P, et al: Predicting outcome after traumatic brain injury: Development and international validation of prognostic scores based on admission characteristics. *PLoS Med* 2008; 5:e165
 8. Raab GM, Day S, Sales J: How to select covariates to include in the analysis of a clinical trial. *Control Clin Trials* 2000; 21: 330–342
 9. Pocock SJ, Assmann SE, Enos LE, et al: Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: Current practice and problems. *Stat Med* 2002; 21:2917–2930
 10. Senn S: Testing for baseline balance in clinical trials. *Stat Med* 1994; 13:1715–1726

Point-of-care glucose testing in critically ill patients: Visual logistics and a glycemic variability hypothesis*

In this issue of *Critical Care Medicine*, the paper by Dr. Meynaar et al (1) represents a step in the right direction. It focuses on critically ill patients, presents a systematic approach to glucose meter evaluation, and applies locally smoothed median absolute difference (LS MAD) curves (2–4) to evaluate bedside testing. LS MAD curves provide compact visual representation of performance by means of “visual logistics”—readily interpretable and clinically relevant graphics that reveal accuracy simultaneously at different decision levels, which for glucose include hypoglycemia, tight glucose control (TGC), hyperglycemia, and critical limits (5). LS MAD curves facilitate comprehension of performance without lengthy explanation and also show that most glucose meter systems do not provide consistent enough measurements (2–4) for therapeutic decisions in the extremely high or

low glucose range where Dr. Meynaar et al captured too few paired observations to arrive at a conclusion.

Dr. Meynaar and colleagues explored how an empirically derived “correction factor” of 1.086 [$(1.086) \times (\text{meter whole-blood glucose}) \Rightarrow \text{central laboratory serum glucose}$] modulates the shape of the LS MAD curve (shown in their Figs. 2a and 2b). However, glucose meters are not intended for comparison to mainframe analyzers without a correction factor (e.g., International Federation of Clinical Chemistry recommended 1.11 for plasma equivalent). Thus, improvement in the LS MAD curve after filtering raw data is expected. However, the curve still exceeded by a substantial margin the error tolerance of 5 mg/dL (0.28 mmol/L) that we recommend. Additionally, Dr. Meynaar et al did not show nonparametric confidence intervals (2–4) with the LS MAD curves. If they had, wide bands would have appeared over ranges where there were few paired observations. Smaller bandwidth, e.g., 15 mg/dL (0.83 mmol/L) (2–4), would have revealed jagged LS MAD curves symptomatic of underlying erratic performance.

The paper by Dr. Meynaar and colleagues presented International Organization for Standardization (ISO) 15197 difference plots (with a similar correction argument) but did not explain sources of erroneous results. The ISO failure rates were 20.0% for ≤ 75 mg/dL (≤ 4.16 mmol/L), and 5.2% > 75 mg/dL (> 4.16 mmol/L), violating the error rate limit of 5% for each range considered separately. Therefore, neither qualified the bedside device for critical care, despite consistent use of arterial samples. Additionally, the

authors did not state whether there were Class I (meter glucose above TGC interval, reference value below it) or Class II (converse) discrepant values (2–4). Class I discrepancies are especially dangerous. For example, if a patient’s “true” glucose were 71 mg/dL (3.94 mmol/L), a discrepant meter value of 145 mg/dL (8.05 mmol/L) could trigger insulin administration that precipitates hypoglycemia, the bane of TGC (6) and an argument for the use of less aggressive TGC intervals when the accuracy of the handheld device is in doubt. These metrics are all part of the “toolbox” we recommend for the evaluation of glucose meter systems used in critical care.

Glucose meter accuracy varies throughout the physiologic glucose range. This variation should be considered when evaluating devices for clinical application. A paradox arises because test strips typically are optimized for the “sweet spot” of normal or near-normal glucose levels, but not adequately accurate for intensive insulin therapy decisions at abnormal glucose levels in lower and higher ranges. Hence, meter inaccuracy limits the aggressiveness of the TGC protocol, which is an important point we can glean from the study by Dr. Meynaar and colleagues. The Food and Drug Administration-approved package inserts should display LS MAD curves so that critical care practitioners can identify quickly unacceptable ranges in relationship to intended clinical uses and settings. Manufacturers should obtain these results from multicenter studies that reflect large numbers of paired observations.

*See also p. 2691.

Key Words: bandwidth; discrepant values; erroneous results; hypothesis; ISO 15197 guideline; locally smoothed median absolute difference curve; outcomes

This study was supported, in part, by the Point-of-Care Testing Center for Teaching and Research, School of Medicine, University of California, Davis, and by a National Institute of Biomedical Imaging and Bioengineering Point-of-Care Technologies Research Network Center grant (Dr. Kost, PI, National Institutes of Health Grant 1U54 EB007959). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Biomedical Imaging and Bioengineering or the National Institutes of Health.

The authors have not disclosed any potential conflicts of interest.

Copyright © 2009 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/CCM.0b013e3181ad7927

We showed (2) that virtually no commercial glucose meters are sufficiently accurate, a fact that intensive care unit staff often recognize, as Dr. Meynaar et al (1) did, but may not realize on a daily basis. Inaccuracy of glucose measurement limits the choice of glucose target ranges. For example, safety demands the maintenance of a buffer against hypoglycemia, and this buffer necessarily must expand when using inaccurate devices. Inaccurate meters also present problems when used with less robust TGC protocols. Protocols or nursing orders that depend on only the most recent value, as opposed to protocols that use ≥ 2 previous values or continuous monitoring, are prone to overreact. If a TGC protocol reacts to only the current measurement, it will tend to be jumpy and oscillatory (undamped feedback system).

These considerations lead us to hypothesize that poor glucose meter performance a) magnifies glycemic variability that adversely affects outcomes in TGC, and b) is detrimental especially to underserved populations where both bedside and laboratory staff may use, often exclusively, handheld glucose meters for critical therapeutic decisions. We include low-resource settings because of the striking increase in the prevalence of diabetes worldwide and the potential damage that measurement errors may cause. Glucose meters often are deployed in developing countries for “off-label” diagnosis, although they are not licensed for this purpose. Hence, this hypothesis provides a mechanism at two levels—the individual patient and the health system. Measurement inaccuracy is not the only potential source failure in TGC (6).

Numerous confounding factors affect test strip chemistry, such as hematocrit, oxidizing substances, PO_2 , matrix effects, sample type (capillary, venous, or arterial), partial filling (7, 8), as well as pathophysiological states (e.g., regional hypoperfusion where sampling), and contribute to measurement error that can exacerbate glycemic variability. The connection of variability specifically with glucose measurement inaccuracy is that *the greater the absolute differences à la the LS MAD curve, the more variability will be introduced*. Thus, the *sine qua non* for minimizing variability and patient risk are “flat line” LS MAD curves consistently below the error tolerance of 5 mg/dL, no erroneous results on the ISO 15197 plot, and especially, no Class I discrepant values. Additionally, when at the

bedside, the critical care team should look for unexpected temporal patterns—shifts up or down that suggest technical or quality control failures.

A number of researchers have suggested an association between glucose variability and adverse outcomes. Ali et al (9) found that high blood glucose variability, in terms of the glucose lability index, was associated with an increased risk of mortality in septic patients with lower average glucose levels. Importantly, septic patients were the only group found by meta-analysis to benefit from TGC (6). Hirshberg et al (10) discovered that hyperglycemia and increasing blood glucose variability were associated with nosocomial infections, and also that both blood glucose variability and hyperglycemia were associated with increased mortality. Dossett et al (11) showed that in the surgical intensive care unit, nonsurvivors had larger successive changes in blood glucose values than survivors.

Krinsley (12) showed that increasing glycemic variability conferred a strong independent risk of mortality in a heterogeneous population of critically ill patients, especially when fluctuations occurred within the euglycemic range of 70 to 99 mg/dL (3.89–5.50 mmol/L). In a study of septic patients, Waeschle et al (13) determined that variability in blood glucose, recorded as standard deviation, was associated with higher mortality rate. Egi et al (14) determined that the mean blood glucose, as well as standard deviation, were associated with mortality in the intensive care unit and hospital. In a separate study, this group (15) found that isolated hyperglycemia was associated with an increased mortality in nondiabetic patients but not in diabetic patients.

These phenomena underscore the need for new point-of-care technologies so accurate as to render the bedside result the reference throughout the hospital and health system. It is worth noting that one multiplex glucose meter system that compensates for abnormal hematocrit and confounding substances generates LS MAD curves within the tolerance limit (3, 4). The portion of the LS MAD curve < 5 mg/dL covers a broad range reasonable for most, but not all, decision levels (3, 4). The “breakout” points where performance deteriorates were 186 mg/dL (3) and 179 mg/dL (4) (10.32 mmol/L and 9.94 mmol/L), with none in the low range and no discrepant values. Therefore, we recommend that critical care practitioners seek the most accurate

system available for intensive care, surgery, the burn unit, and other high-risk settings, to help improve outcomes and balance expenses for the health system as a whole.

Gerald J. Kost, MD, PhD, MS

Nam K. Tran, PhD

Jorge R. Sifontes

Dan M. Mecozzi, BS

Richard F. Louie, PhD

Point-of-Care Testing Center
for Teaching and Research

University of California,

Davis-LLNL Point-of-Care

Technologies Center

Davis, CA

Victor J. Abad, MA

Charlottesville, VA

REFERENCES

1. Meynaar IA, van Spreuwel M, Tangkau PL, et al: Accuracy of AccuCheck glucose measurements in intensive care patients. *Crit Care Med* 2009; 37:2691–2696
2. Kost GJ, Tran NK, Abad VJ, Louie RF: Evaluation of point-of-care glucose testing accuracy using locally-smoothed median absolute difference curves. *Clin Chim Acta* 2008; 389: 31–39
3. Kost GJ, Tran NK, Louie RF, et al: Assessing the performance of handheld glucose testing for critical care. *Diabetes Tech Ther* 2008; 10:445–451
4. Kost GJ, Tan NK, Sifontes JR, et al: Point-of-care testing for underserved populations: LS MAD curves, glycemic variability, and the first global performance cooperative. *Point of Care* 2009; 8:45–52
5. Kost GJ: Critical limits for urgent clinician notification at US medical centers. *JAMA* 1990; 263:704–707
6. Wiener RS, Wiener DC, Larson RL: Benefits and risks of tight glucose control in critically ill adults. A meta-analysis. *JAMA* 2008; 300: 933–944
7. Kost GJ, Vu HT, Lee J, et al: Multicenter study of oxygen-insensitive handheld glucose point-of-care testing in critical care/hospital/ambulatory patients in the United States and Canada. *Crit Care Med* 1998; 26:581–590
8. Tang Z, Louie RF, Lee JH, et al: Oxygen effects on glucose meter measurements with glucose dehydrogenase- and oxidase-based test strips for point-of-care testing. *Crit Care Med* 2001; 29:1062–1070
9. Ali NA, O'Brien JM, Dungan K, et al: Glucose variability and mortality in patients with sepsis. *Crit Care Med* 2008; 36:2316–2321
10. Hirshberg E, Larsen G, Van Duker H: Alterations in glucose homeostasis in the pediatric thorough care unit: Hyperglycemia and glucose variability are associated with increased mortality and morbidity. *Pediatr Crit Care Med* 2008; 9:361–366
11. Dossett LA, Cao H, Mowery NT, et al: Glucose

- variability is associated with mortality in the surgical intensive care unit. *Am Surg* 2008; 74:679–685
12. Krinsley JS: Glycemic variability: A strong independent predictor of mortality in critically ill patients. *Crit Care Med* 2008; 36: 3008–3013
 13. Waeschle RM, Moerer O, Hilgers R, et al: The impact of the severity of sepsis on the risk of hypoglycaemia and glycaemic variability. *Crit Care* 2008; 12:R129. Available at: <http://ccforum.com/content/12/5/R129>. Accessed August 14, 2009
 14. Egı M, Bellomo R, Stachowski E, et al: Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology* 2006; 105:244–252
 15. Egı M, Bellomo R, Stachowski E, et al: Blood glucose concentration and outcome of critical illness: The impact of diabetes. *Crit Care Med* 2008; 36:2249–2255

Two decades of simulation-based training: Have we made progress?*

The transformation of a student into a successful physician is a highly complex educational process. It starts with the phase of knowledge acquisition. Next, procedural competency is attained. Then, by deliberate practice of each component of the skills to be mastered along with immediate feedback, expertise is achieved. This concept was well described by Fitts and Posner (1). They described an initial cognitive phase of knowledge acquisition that leads to the intermediate integrative phase of procedural competence and then to the final autonomous phase of practice at expert level. In discussing methods of learning and assessment of a graduating physician, Miller (2) used a pyramid with four levels stacked within it to illustrate his point. The bottom of this pyramid can be conceptualized as knowledge where the student “knows” the information. Knowledge is acquired from textbooks, journals, lectures, discussions, and others. This knowledge can be easily assessed by various well-established objective tests. The next higher level is the student’s ability to “know how” to use this knowledge to analyze a patient’s history, physical findings, laboratory, imaging, and other data to arrive successfully at a diagnosis and management plan. This may be regarded as achievement of competence. The third higher level consists of

the student’s ability to “show how” he does it (performance), during an objective assessment; but unlike tests of knowledge, tests of performance are more difficult to perform. The top level is what a graduate “does” (action) when practicing independently. This action level is even more difficult to test. Over the past several decades, many different modalities—such as patient management problems, inanimate models like Resusci-Anni, human examination volunteers, and standardized patients—have been employed to assess “performance” and “action” levels of Miller’s pyramid, with the goal to mimic as closely as possible the real patient situation.

Performance-based assessment and advanced level of simulation-based training have become common in clinical practice and in medical education as a consequence of external events including the publication of the 1999 Institute of Medicine report on medical errors (3). As close to reality as they may be, simulation models still are not real patients. Therefore, training and assessment through these simulation models should meet certain criteria. They should have validity and reliability. The skills learned and mastered should be directly transferrable to real patient situations and should be resistant to decay.

Intense research trials on simulation-based training have led to numerous publications that attempt to show that training by simulation does meet the above criteria. A few of them are listed below. Aggarwal et al (4) demonstrated shortening of the learning curve in laparoscopic cholecystectomy with the use of virtual reality simulator-based training. Seymour et al (5), in a randomized double-blind study, showed that the use of virtual reality simulation with the goal to reach a specific target set of criteria im-

proved residents’ operating room performance. These two studies answered the question about skill transferability. Kuduvali et al (6), prospectively studying simulation-based difficult airway management training, demonstrated retention of learned skills for at least 6 to 8 wks and for up to 6 to 8 mos depending on the complexity of the scenario. Wayne et al (7), studying simulation-based advanced cardiac life support training, found no decay in learned skills at 14 mos. These two studies answered the question about skill retention. On the basis of evidence of benefit, major medical specialties and professional organizations (8–10) have become endorsers and supporters of simulation-based education.

In this issue of *Critical Care Medicine*, Barsuk et al (11) describe their study which shows that simulation-based mastery learning reduces complications during central venous catheter (CVC) insertion in a medical intensive care unit. In their well-planned and well-executed observational cohort study of educational intervention, they evaluated CVC insertion ability of 103 residents from their Internal Medicine and Emergency Medicine training programs over a 1-yr period. Twenty-seven residents, assigned to their medical intensive care unit during the first 4 mos of the study who did not receive any formal training in CVC insertion, acted as the control group. Seventy-six other residents, who underwent simulation-based educational training in CVC insertion to what the investigators considered to be mastery level of skill acquisition 1 to 2 mos before their medical intensive care unit rotation, formed the intervention group. All study subjects were surveyed daily about the CVCs they inserted including CVC quality indicators and the subject’s level of confidence in

*See also p. 2697.

Key Words: medical education; simulation based training; central venous catheterization; performance assessment; skill transferability; skill retention; laparoscopic surgery

The author has not disclosed any potential conflicts of interest.

Copyright © 2009 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/CCM.0b013e3181ad7897

procedure performance. Their results showed that 164 (40%) of 407 catheters had been inserted by the study subjects with 42 (26%) of 164 CVCs inserted by the controls and 122 (74%) of 164 CVCs inserted by the simulator-trained subjects. The simulator-trained subjects had lower number of needle passes, arterial punctures, catheter position adjustments, and higher success rates than the controls, all of which were statistically highly significant. Both groups reported similar confidence levels in procedure performance. The authors conclude that simulation training in CVC insertion with deliberate practice to mastery level results in improved bedside performance.

This study used a much larger sample size than many others published to date. Their conclusions are compelling. Some of the weaknesses of this study have been acknowledged and explained by the authors themselves. One other criticism relates to study design. Because the stated aim of this study was to determine whether simulation-based training was superior, the only difference between the control and the intervention groups should have been the use of the simulator; but the control group had absolutely no formal training in CVC insertion. On the other hand, the simulator-trained group had a ≥ 4 hrs of formal instruction with feedback and direct faculty contact along with the use of the simulator and ultrasound equipment. In actuality, this study is a comparison of a group of residents with formal training in CVC insertion including the use of simulation and ultrasound equipment with another group that had no formal training of any kind. Whether the improved performance by the intervention group is solely due to the use of the simulator has not really been answered by this study.

Britt et al (12) in their paper on simulation-based CVC insertion training to proficiency level stated that, even though the training session met the goals, many trainees were unsuccessful in performing the initial patient procedure without assistance. They further stated that, although simulation training increased the comfort level, it did not obviate the need for supervision of initial CVC insertions. In contrast, in the study by Dr. Barsuk et al, training was provided to achieve mastery level. It seems that this level of training resulted in transferability of learned skills and obviated the need for supervision.

Even though a total of 407 CVC insertions took place during the study period, only 164 (40%) were performed by the 103 study subjects for an average of 1.6 insertions per subject. This is too small an experience per study subject. With such minimal experience per study subject, it is difficult to predict that there will be long-term retention of the learned procedural skills.

By nature, research in medical education suffers from small sample sizes and limited study durations. In research on simulation-based training, equipment with different levels of sophistication have been used, thereby making it difficult to compare studies. Better designed prospective multicenter studies with proper standardization of simulation equipment and procedures are still needed to help us understand the true benefits of simulation-based procedural training in medical education.

Samuel K. Appavu, MD, FCCM

University of Illinois College of
Medicine-Rockford
Rockford, IL

REFERENCES

1. Fitts PM, Posner MI: Human Performance. Reprint of ed. Brooks/Cole Pub Co. Westport, CT, Greenwood Press, 1979
2. Miller GE: Assessment of clinical skills/competence/performance. *Acad Med* 1990; 65:S63-S67
3. Kohn LT, Corrigan JM, Donalson MS (eds): To Err Is Human: Building a Safer Health System. Washington, DC, National Academy Press, 1999
4. Aggarwal R, Ward J, Balasundaram I, et al: Proving the effectiveness of virtual reality simulation for training in laparoscopic surgery. *Ann Surg* 2007; 246:771-779
5. Seymour WE, Gallagher AG, Roman SA, et al: Virtual reality training improves operating room performance: Results of a randomized double blinded study. *Ann Surg* 2002; 236: 458-464
6. Kuduvali PM, Jervis A, Tighe SQM, et al: Unanticipated difficult airway management in anesthetized patients: A prospective study of the effect of mannequin training on management strategies and skill retention. *Anesthesiology* 2008; 63:364-369
7. Wayne DB, Siddall VJ, Butler J, et al: A longitudinal study of internal medicine residents' retention of advanced cardiac life support skills. *Acad Med* 2006; 81:S9-S12
8. Sachdeva AK, Pellegrini CA, Johnson KA: Support for simulation based surgical education through American College of Surgeons—Accredited Education Institutes. *World J Surg* 2008; 32:196-207
9. McLaughlin S, Fitch MT, Goyal DG, et al: Simulation in graduate medical education 2008: A review for emergency medicine. *Acad Emerg Med* 2008; 15:1117-1129
10. Scott DJ, Dunnington GL: The new ACS/APDS skills curriculum: Moving the learning curve out of the operating room. *J Gastroenterol Surg* 2008; 12:213-221
11. Barsuk JH, McGaghie WC, Cohen ER, et al: Simulation-based mastery learning reduces complications during central venous catheter insertion in a medical intensive care unit. *Crit Care Med* 2009; 37: 2697-2701
12. Britt RC, Reed SF, Britt LD: Central line simulation: A new training algorithm. *Am Surg* 2007; 73:680-682; discussion 682-683

Ventilator-associated pneumonia and mortality: The controversy continues*

The question as to whether ventilator-associated pneumonia (VAP) has attributable mortality in critically ill patients continues to perplex clinicians, researchers, and public health officials. Yet there is a divergence between evidence and accepted dogma. The overwhelming perception in the medical media is that VAP causes substantial mortality, and, invariably, literature on VAP leads with this. Although this may seem to be an arcane piece of trivia, this information is important from many different perspectives. It is important to patients, their families, and public health officials who wish to know how safe the health care system is. It is important to clinicians who struggle to put in place effective preventive measures and to better treat VAP when it occurs. Finally, it is important to researchers who are studying VAP, because it is necessary to know the impact of VAP when determining sample size calculations for trials of VAP prevention, diagnosis, and treatment studies.

The difficulty with assessing the influence of VAP on mortality stems from the fact that it is a complication of critical illness. The critically ill populations in whom VAP occurs have variable levels of intrinsic mortality related to diagnoses, comorbid conditions, and the severity of illness. Thus, the concept of attributable mortality of VAP arises, which is defined as total mortality (with VAP) minus the mortality of the underlying population without VAP (1). For the determination of attributable mortality, the only evidence available comes from observational studies comparing groups of patients with and without VAP. Although many of these studies have been reported, their

interpretation has been hampered by methodological concerns such as the influence of systematic bias.

In this issue of *Critical Care Medicine*, Dr. Melsen and colleagues (2) convey the results of a systematic review of observational studies that report on the mortality associated with VAP. The authors included all studies of VAP that reported on the mortality of patients with and without VAP. Fifty-two studies reporting on >17,000 patients met the inclusion criteria and were included.

There was significant heterogeneity among the included studies. However, in the subgroup analysis of specific populations, namely those with acute respiratory distress syndrome (ARDS) and trauma, the heterogeneity disappeared. When all studies were included, VAP was associated with a relative risk of mortality of 1.27 (95% confidence interval [CI], 1.15–1.39), but in trauma and ARDS patients there was no associated mortality (relative risk of 1.09 [95% CI, 0.87–1.37] and 0.86 [95% CI, 0.72–1.04], respectively).

The major strength of this study is its comprehensiveness and the large sample size of included studies and patients. In addition, the study is well done and the methods for the meta-analysis are as recommended in the literature (3). Furthermore, the authors scored the quality of the studies and had an *a priori* hypothesis for the heterogeneity observed. In regard to quality, only a third of the studies met the authors' criteria for high quality. Heterogeneity remained when the studies were pooled by diagnostic criteria, duration of mechanical ventilation, matching of cohorts, and quality. The heterogeneity disappeared when ARDS and trauma patients were analyzed.

Given these strengths, does this Herculean task of sorting through the extensive literature on VAP answer the question as to whether VAP is responsible for significant mortality? Unfortunately, the answer remains no. First, the question of attributable mortality for VAP should be reframed: Does VAP have attributable

mortality given the adequate and timely use of the therapeutic options available at the time? This is a shifting baseline given the ever-changing microbiology of VAP, increasing antimicrobial resistance, and different treatment regimens (4). Numerous studies demonstrate worse outcomes in the treatment of VAP when antibiotic therapy is delayed or inappropriate, yet a minority of VAP mortality studies report this let alone control for it (5). Second, unmatched studies of VAP mortality are confounded by a wide variety of biases, and in this systematic review, 36 of the 52 included studies were unmatched. The list of possible biases is long and beyond the scope of this editorial. Three of the most important ones are time of exposure bias (patients who are more ill spend more time in the ICU and have an increased chance of contracting VAP), premorbid illness bias (illnesses that predispose to VAP may have worse outcomes in the ICU), and ascertainment bias (without a reference standard for VAP only severe cases may be recognized). All of these would increase the chances of VAP occurring or being recognized in the most ill patients, and thus VAP may be an epiphenomenon of mortality and not a causal one.

Given the number of potential biases, it is not surprising that there was significant heterogeneity among all the studies. It is arguable as to whether uncontrolled studies should be included in any critical review of VAP mortality. In this review, a significant mortality difference was present in the matched studies, but again there was significant heterogeneity. Furthermore, the degree of matching was variable and methodological quality was low in >40% of the matched studies. Another source of variability may lie in the grouping of hospital and ICU mortality into the same analysis. Because VAP is likely associated with prolonged length of stay in the ICU (6), patients with VAP may be more likely to die in the ICU irrespective of the VAP and there may be dissociation between hospital and ICU mortality.

*See also p. 2709.

Key Words: ventilator-associated pneumonia; mortality; systematic review

The author has not disclosed any potential conflicts of interest.

Copyright © 2009 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/CCM.0b013e3181aff7db

The authors are to be commended for their efforts given the limitations of these studies. What can we conclude from this systematic review? The answer is that combining a variety of studies with different diagnostic criteria, variable quality, different designs (matched and unmatched), and high degree of heterogeneity does not produce results that we can be confident of. Furthermore, the finding that VAP was not associated with attributable mortality in the ARDS and trauma populations, in which there was little heterogeneity, should give rise to further thought. At the minimum, this systematic review should lead us to question accepted dogma and ask whether appropriately treated VAP does cause significant attributable mortality. In this respect, the debate continues (7).

Because observational data in regard to the attributable mortality of VAP are all that we will ever have, studies of more methodological rigor are required if we

are going to answer this important question. Case control studies need to be better matched for the prognostic factors of VAP outcome. No studies have conducted a propensity analysis of VAP mortality, and this may be useful in view of the large number of factors that may influence mortality (8). Furthermore, better definition of the groups being compared, along with better diagnostic modalities, are required. Without these, the controversy will continue without resolve.

John Muscedere
Queen's University
Kingston, Ontario, Canada

REFERENCES

1. Schumacher M, Wangler M, Wolkewitz M, et al: Attributable mortality due to nosocomial infections: A simple and useful application of multistate models. *Methods Inf Med* 2007; 46:595–600
2. Melsen W, Rovers M, Bonten M: Ventilator-associated pneumonia and mortality: A sys-

tematic review of observational studies. *Crit Care Med* 2009; 37:2709–2718

3. Stroup D, Berlin J, Morton S, et al: Meta-analysis of observational studies in epidemiology: A proposal for reporting. *JAMA* 2000; 283:2008–2012
4. Guidelines for the management of adults with hospital-acquired, ventilator-associated and healthcare associated pneumonia. *Am J Respir Crit Care Med* 2005; 171: 388–416
5. Kollef MH: Broad-spectrum antimicrobials and the treatment of serious bacterial infections: Getting it right up front. *Clin Infect Dis* 2008; 47(suppl 1):S3–S13
6. Safdar N, Dezfulian C, Collard HR, et al: Clinical and economic consequences of ventilator-associated pneumonia: A systematic review. *Crit Care Med* 2005; 33:2184–2193
7. Carlet J: Dying from or with a nosocomial pneumonia in the intensive care unit? *Crit Care Med* 2001; 29:2392–2394
8. Rubin DB: Estimating causal effects from large data sets using propensity scores. *Ann Intern Med* 1997; 127:757–763

Pulmonary artery catheter redux: Physical findings in acute respiratory distress syndrome/acute lung injury*

Using a physical examination to gain information that otherwise would require a pulmonary artery catheter (PAC) would avoid the cost and the complications associated with a PAC. In lieu of a PAC, central venous pressure and central venous saturation (ScvO₂) obtained via a central venous catheter (CVC) might supplement the examination sufficiently to obviate any need for a PAC, although the cannulation complications are the same for both types of catheters. In this issue of *Critical Care Medicine*, Grissom and colleagues (1) used data from patients with acute respiratory distress syndrome (ARDS) or acute lung injury (ALI) culled

from the PAC arm of the Fluid and Catheter Treatment Trial (FACTT) (2), to test three hypothesis: 1) whether capillary refill time >2 secs, skin mottling over the knees, and cool extremities could predict a cardiac index (CI) <2.5 or a mixed venous saturation (SvO₂) <60%; 2) whether this prediction would be enhanced by adding urine output and central venous pressure; and 3) whether ScvO₂ was a useful predictor of SvO₂. Their results indicate that these three clinical findings, clinical findings (CF), and ScvO₂ “are not useful predictors of a low CI or low SvO₂” and that ScvO₂ could not reliably predict SvO₂. These results engender three questions: 1) Could these results be spurious because of study design or the patient population? 2) In view of the repeatedly negative results from studies of the contribution of PAC to outcome, why try to predict a low CI or SvO₂ from CF, urine output, and central venous pressure? 3) Are there physiologic reasons why these values for CI and SvO₂ should be important?

Before fully accepting these negative findings, we should recognize that they

may reflect an underpowered study. Although the number of patients is adequate, there are numerous limitations in the data that potentially could cause large variability and bias. Most of these limitations are discussed by the authors. Particularly important are the potential sources of bias in data collection: The examiners were not blinded to the CI or SvO₂, there were no objective criteria for the CF, and interrater reliability was not determined. Imprecision in the analyses could arise from the small number of patients who had either a CI <2.5 (8%) or ScvO₂ <70% (16%) so that small errors in measurements or CF leading to misclassifications could markedly affect the results. Further loss of power might have occurred because ARDS/ALI patients comprise a heterogeneous group. Although the criteria for ARDS/ALI are widely accepted, they identify a syndrome, not a disease, with diverse etiologies and phenotypes. It is well known that clinical estimates of left atrial pressure are inaccurate and that there is considerable disagreement in interpreting chest radiographs, both leading to imprecise

*See also p. 2720.

Key Words: pulmonary artery catheter; ARDS/ALI; clinical examination; cardiac index; central venous oxygen saturation

The author has not disclosed any potential conflicts of interest.

Copyright © 2009 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/CCM.0b013e3181b3a06a

classifications. What seems to be less well known is that there is no physiologic reason why the PO_2/FIO_2 ratio should be invariant with respect to FIO_2 ; in fact, multiple studies have shown that it does vary both with FIO_2 and the level of respiratory support. Finally, as noted, 29% of patients in the PAC group of the FACTT study did not meet ALI or ARDS criteria because the pulmonary artery occlusion pressure (PAOP) was >18 mm Hg. All of these factors dilute the possibility of finding relations between CF, central venous pressure, urine output, and CI or SvO_2 , even if one exists. However, this begs the question of whether there is physiologic rationale for believing that a CI of 2.5 or an SvO_2 of 60% is an important cut point for prognosis or treatment. Obviously, even if these values are important, slight deviations could not have much impact. That is, it would be extraordinary if CIs of 2.49 and 2.51 were associated with markedly different outcomes. More likely, these cutoff values represent points on probability distributions relating CI and SvO_2 to outcomes. They could, in theory, have been determined as values that yield maximum separation of the distributions of positive and negative outcomes, for example, adequate and inadequate perfusion, from their receiver operating characteristic curves. However, to my knowledge such data do not exist. Thus, these values are apparently arbitrary even though they may have some relation to outcomes.

The authors' goal of trying to predict CI from CF or SvO_2 from $ScvO_2$ seems ironic given that the FACTT study, in which at least one of the authors participated, and multiple other investigations (see Dr. Grissom and colleagues' article for references) have failed to show any benefit from PACs. Therefore, it would seem, *a priori*, that testing these hypotheses would have little value even if associations could be established. However, it is my contention that there has never been a trial that fully used PAC data either diagnostically or therapeutically. Specifically, PAC data, including the FACTT study, have been used to meet relatively arbitrary numeric goals rather than to yield a better understanding of the state of the cardiovascular system. To achieve the latter, the full set of hemodynamic data are indispensable, that is, central venous pressure, pulmonary artery pressure, PAOP, cardiac output, heart rate, and systemic blood pressure. Using these data in conjunction with the well-

validated basic physiology of venous return (3) and cardiac mechanics (4), it is possible to estimate the functional systemic and pulmonary blood volumes and the contractile state of both ventricles (5). Furthermore, when used in such an integrated manner these data can provide a guide to diagnosis, therapy, and data consistency, especially when changes over time are evaluated. Such information is unlikely to be helpful for all patients with a given syndrome such as ARDS/ALI or CHF but may have value in selected patients when a specific question is being asked that cannot be answered clinically or by therapeutic perturbation. Admittedly, even in such patients the PAC used in this manner still may not affect outcome, but most critical care practices are based on surrogate measurements thought to affect outcome rather than outcomes themselves. Therefore, despite the negative results of this study, there may be value in using the PAC or estimating PAC data from physical findings and a CVC in selected patients.

Some insight into why specific values of CI or SvO_2 might be useful prognostically or therapeutically in lieu of a full set of hemodynamic data might be gained by asking how they relate to organ perfusion. However, with the exception of the coronaries, organ perfusion is, at least to a first approximation, determined not by cardiac output but by the difference between mean arterial and venous pressures. Changes in cardiac output can affect mean arterial pressure, but such changes can be misleading because there are multiple instances when mean pressure and regional flow change in opposite directions. For example, in distance runners cardiac output may be >20 L/min, but most is going to muscle and skin to generate power and dissipate the resultant heat, whereas visceral blood flow is reduced. Furthermore, because the lower limit of autoregulation varies widely among organs, the high cardiac output often seen in septic shock also goes mostly to muscle and skin because of their high autoregulatory reserve whereas renal flow decreases in part because its autoregulatory reserve is low (i.e., maximum renal arterial dilation is comparatively limited). Similarly, it is possible to have a low cardiac output and normal or high mean arterial pressure because of high peripheral resistance and yet perfuse vital organs adequately, especially at rest, by reducing muscle and skin blood flow. Thus, the relations be-

tween regional blood flow and cardiac output depend on the mean arterial and venous pressures, regional resistances, and metabolic demands. Although a low cardiac output might increase the probability of organ hypoperfusion, it is not a *sine qua non*. Furthermore, intervening to increase cardiac output does not guarantee a more normal blood flow distribution.

Similarly considerations apply to SvO_2 . Oxygen consumption (VO_2) is related to cardiac output (Q), arterial oxygen content (CaO_2), and venous oxygen content (CvO_2) by

$$VO_2 = 10 Q (CaO_2 - CvO_2)$$

where the factor 10 corrects for the difference in the units of Q and oxygen content. If CaO_2 and VO_2 remain constant, any change in Q must be reflected by a reciprocal change in CvO_2 and, thus, SvO_2 regardless of any change in blood flow distribution. It is also readily proven that oxygen extraction approximates $1 - SvO_2$ if arterial blood is fully saturated. Thus, a low cardiac output in the presence of normal CaO_2 and VO_2 must result in a low CvO_2 and SvO_2 , but it reflects ischemia only if oxygen extraction by organ beds cannot increase to meet demands. That is, a low SvO_2 does not in itself indicate ischemia. For example, distance runners may have extremely low SvO_2 because the increase in muscle oxygen extraction exceeds the increase in muscle blood flow yet oxygen supply to muscles is adequate to sustain the requisite prolonged aerobic effort. Conversely, patients with septic shock may have a high Q and thus a high SvO_2 but may be hypoperfusing vital organs. Consequently, not only is a low CI or SvO_2 , not necessarily indicative of hypoperfusion, but also increasing them may not alter outcomes because most interventions alter blood flow distribution, not necessarily increasing it to hypoperfused organs.

So where does this leave us? First, when assessing the utility of a PAC, we should select a patient group for which there is a specific question and a high likelihood that there is no other way to answer it. Second, rather than setting precise numeric goals, investigators should interpret hemodynamic data collectively and as a continuum in terms of the underlying physiology, avoiding the mentality that says, "if it's high, make it lower; if it's low, make it higher; and otherwise give steroids." Third, studies trying to relate physical findings to hemodynamic abnormalities are difficult to

conduct and require precise, reproducible definitions of the findings, examiner blinding, and a homogeneous population in which a substantial proportion of the patients have the hemodynamic abnormalities being studied. Finally, all of this is irrelevant if PAC data cannot be related to some outcome, although not necessarily survival or death.

Richard Teplick

REFERENCES

1. Grissom CK, Morris AH, et al; for the NHLBI ARDS Network: Association of physical examination with pulmonary artery parameters in acute lung injury. *Crit Care Med* 2009; 37:2720–2726
2. Wheeler AP, Bernard GR, Thompson BT, et al: Pulmonary artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med* 2006; 354:2213–2224
3. Guyton AC, Lindsey AW, Abernathy JB, et al: Venous return at various right atrial pressures and the normal venous return curve. *Am J Physiol* 1957; 189:609–615
4. Suga H, Sagawa K, Demer L: Determinants of instantaneous pressure in canine left ventricles. *Circ Res* 1980; 46:256–263
5. Teplick R: Integrative view of cardiovascular function. *In: Foundations of Anesthesia Basic and Clinical Sciences*. First Edition. Hemmings H, Hopkins P (Eds). London, Harcourt, 2000, 391–418

Consequences of ventilator asynchrony: Why can't we all get along?*

Patient-ventilator asynchrony, a time mismatch between the patient's neural inspiration time and the ventilator's time for breath initiation, is commonly seen in critically ill patients (1). Ventilator breath triggering is most commonly based on the measurement of a change in pressure, flow, volume, or flow waveform (2). Pressure triggering requires the patient to generate a preset amount of negative pressure within the ventilator circuit to reach the threshold (sensitivity) and initiate a breath. In the case of flow and volume triggering, initiation of a breath occurs when the action of the respiratory muscles produces a set flow or volume (3). Flow triggering often utilizes a bias flow from which a change can be measured and is typically faster to respond than pressure triggering. Flow waveform breath triggering occurs when the patient's inspiratory flow causes 6 mL of volume to accumulate over baseline flow or when inspiratory effort distorts the expiratory flow waveform to a predetermined extent (4). The most common cause of asynchrony is ineffective triggering in which the inspiratory muscle effort fails to overcome the inherent trigger threshold within the ventilator circuit. Patients with chronic obstructive pulmonary disease, high levels of volume assistance, long inspiratory times, and blunted respiratory drives are at a higher risk of ineffective

triggering due to the innate dynamic hyperinflation that is present at the time of attempted triggering (5, 6).

In this issue of *Critical Care Medicine*, the article by Dr. de Wit et al (7) builds on the growing evidence that patient-ventilator asynchrony, specifically the rate of ineffective triggering, is associated with prolonged mechanical ventilation. A cohort of mechanically ventilated patients ($n = 60$) within a single intensive care unit were followed prospectively and had airway pressure-time and flow-time waveforms recorded for 10 mins within the first 24 hrs of mechanical ventilation. An ineffective trigger index—the number of ineffectively triggered breaths divided by the total number of breaths—of $\geq 10\%$ was used as a marker of higher asynchrony. Baseline characteristics between those with $\geq 10\%$ and $< 10\%$ ineffective trigger index were similar including measures of sedation, delirium, and rates of chronic obstructive pulmonary disease (12% and 11%, respectively). Patients with a higher rate of asynchrony were also found to have statistically higher rate of pressure-triggered breaths as well as a higher intrinsic respiratory rate. When pressure triggering rates were accounted for during multivariate analysis, those with a higher rate of asynchrony during the first day of mechanical ventilation were found to have a significantly longer duration of mechanical ventilation and a shorter ventilator-free survival. These findings proportionally lengthened the duration of intensive care unit stay as well as hospital length of stay.

This work is unique in that Dr. de Wit et al examined the pressure-time and flow-time waveforms early in the ventilation period. Thille et al and Chao et al also have demonstrated a relationship be-

tween asynchrony and duration of mechanical ventilation; however, the examination of patients' waveforms took place a median of 4.5 days and 27 days, respectively (5, 8). By examining the ventilator-patient relationship early in the intubation process, one may have more predictive power for future interventions. The population examined by Dr. de Wit et al also has fewer patients with the diagnosis of chronic obstructive pulmonary disease, as described by the previous groups (12% as compared with 26% and 44%, respectively). Both the lower rate of chronic obstructive pulmonary disease as well as the period in which patients were interrogated may have led to the described rate of 27% for ineffective trigger index $\geq 10\%$, which is higher than previous reports.

Although this new data add to our appreciation of the complexity of patient-ventilator interaction and asynchrony, there remain a host of unanswered questions. The authors studied patients early in the course of mechanical ventilation for consistency. However, early on, the patients' mean Richmond Agitation Sedation Scale score was -3 , suggesting heavy sedation. The effects of excessive sedation on the duration of mechanical ventilation and mortality are well known. It is possible that their finding of an increased rate of missed triggers was simply due to the sedation regimen. Interestingly, in this mixed medical intensive care unit, synchronized intermittent mandatory ventilation plus pressure support was the predominant mode of ventilation. Perhaps the inherent difficulties in synchrony associated with interspersing volume-targeted, time-cycled breaths with pressure-targeted, flow-cycled breaths contributed to their findings. Ad-

*See also p. 2740.

Key Words: mechanical ventilation; critical care; asynchrony; ineffective triggering intensive care unit

The authors have not disclosed any potential conflicts of interest.

Copyright © 2009 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/CCM.0b013e3181ad794d

ditionally, as the authors pointed out, it may be that a 10-min period of observation is insufficient.

Finally, there is the issue of plausibility. Although we can agree that a patient who is asynchronous may be uncomfortable, what is the mechanism by which asynchrony leads to mortality? The study could be markedly improved by matching observation of the patient to the waveforms. A patient uncomfortable and in distress with an increased ineffective trigger index seems to be quite different from a patient who is relatively quiet with asynchrony.

At the end of the day, the study confirms an association between asynchrony, duration of ventilation, and outcome, but not causality. At present, it seems more likely that severity of illness and excess sedation lead to missed triggers. Missed triggers

then become a marker of prolonged ventilation, not the cause. Future studies need to address these issues, evaluate new methods to improve patient-ventilator interaction and help us all to get along.

Bryce R. H. Robinson, MD

Richard D. Branson, MSc, RRT

University of Cincinnati

Cincinnati, OH

REFERENCES

1. Tobin MJ, Jubran A, Laghi F: Patient-ventilator interaction. *Am J Respir Crit Care Med* 2001; 163:1059–1063
2. Sassoon CS, Gruer SE: Characteristics of the ventilator pressure and flow triggering variables. *Intensive Care Med* 1995; 21:159–168
3. Georgopoulos G, Prinianakis G, Kondili E: Bedside waveforms interpretation as a tool to identify patient-ventilator asynchronies. *Intensive Care Med* 2006; 32:34–47. Epub 2005 Nov 9
4. Prinianakis G, Kondili E, Georgopoulos D: Effects of the flow waveform method of triggering and cycling on the patient-ventilator interaction during pressure support. *Intensive Care Med* 2003; 29:1950–1959
5. Thille AW, Rodriguez P, Cabello B, et al: Patient-ventilator asynchrony during assisted mechanical ventilation. *Intensive Care Med* 2006; 32:1515–1522
6. Leung P, Jubran A, Tobin MJ: Comparison of assisted ventilator modes on triggering, patient effort, and dyspnea. *Am J Respir Crit Care Med* 1997; 155:1940–1948
7. de Wit M, Miller K, Green D, et al: Ineffective triggering predicts increased duration of mechanical ventilation. *Crit Care Med* 2009; 37:2740–2745
8. Chao DC, Scheinhorn DJ, Stearn-Hassenpflug M: Patient-ventilator trigger asynchrony in prolonged mechanical ventilation. *Chest* 1997; 112:1592–1599

HLA-DR monitoring in the intensive care unit—More than a tool for the scientist in the laboratory?*

It is well known that the leukocyte function in septic patients undergoes dramatic changes entailing severe sequelae. For example, immune responses elicited by circulating antigen-presenting monocytes are reprogrammed to a status of reduced reactivity. This hyporeactive status of the immune system previously has been designated “immunoparalysis,” “immune incompetence,” or “leukocyte reprogramming” and is associated with a reduced capacity to mount proinflammatory cytokines in response to bacterial stimuli. One of the major reasons for the immunoparalysis during sepsis is the failure of monocytes to sufficiently present pathogenic peptides via the human leukocyte antigen (HLA) system to effector cells of the adaptive immune system. The HLA-DR molecule is encoded by the major histocompatibility complex on chromosome 16 as

the most prominent antigen-presenting surface molecule and, thus, is a central molecule to induce and maintain pathogen-directed immune responses.

Meanwhile, down-regulation of HLA-DR on the surface of circulating monocytes is generally accepted as a reliable marker for an immune dysfunction in septic patients. In the past, several investigators described a suppressed HLA-DR expression in monocytes in critically ill patients, especially in the very early phase of the disease. Furthermore, the prognostic value of low HLA-DR expression on monocytes has been elucidated and the severity of the sepsis and mortality has been correlated with low HLA-DR expression (1–3).

Changes in HLA-DR expression are not restricted to infectious diseases. “Immunoparalysis” in terms of decreased HLA-DR expression is described in almost all critically ill patients, e.g., after multiple trauma, burn injury, major surgery, or during pancreatitis. These patients are at high risk of infectious complications (4, 5). Therefore, low HLA-DR on monocytes may be more than a simple prognostic marker reflecting the severity of the disease. The degree of HLA-DR expression or the response of leukocytes to pathogenic stimuli in terms of proinflammatory

cytokine production may truly reflect the patients’ host response. Importantly, the “reprogramming” of leukocytes during sepsis or in other critically ill patients, e.g., after major trauma is reversible and can be counteracted by immunostimulating factors, such as interferon- γ or granulocyte-macrophage colony-stimulating factor (6–8). In these studies, monocytic HLA-DR expression was measured as a marker for the success of immunostimulating therapies.

In this issue of *Critical Care Medicine*, Lukaszewicz et al (9) present another study that correlates HLA-DR expression on monocytes with the outcome of intensive care unit (ICU) patients. Some aspects distinguish this study from the large number of formerly published studies dealing with HLA-DR in ICU patients. Most importantly, the patient number is extraordinarily high in comparison to former clinical evaluations of this marker. A total of 283 patients were monitored in terms of HLA-DR expression over a period of 3 wks. Reflecting the reality in many ICUs, Dr. Lukaszewicz et al did not focus on a certain subgroup of ICU patients, such as trauma or burn patients, but rather analyzed all patients admitted to the ICU exceeding a certain severity of illness reflected by Simplified

*See also p. 2746.

Key Words: HLA-DR; sepsis; trauma; immune monitoring; interferon gamma

The authors have not disclosed any potential conflicts of interest.

Copyright © 2009 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/CCM.0b013e3181ad7ac9

Acute Physiology Score II of >15. They found a correlation between clinical outcome and early HLA-DR expression on monocytes in the whole study population but not exclusively in septic patients. However, the low HLA-DR expression was not an independent outcome predictor because the correlation between outcome and early HLA-DR expression disappeared after adjustment to severity of illness by Sequential Organ Failure Assessment score or Simplified Acute Physiology Score II. So, the critical reader may ask whether the clinician in the ICU does really need another prognostic marker at the bedside without relevance for further therapeutic decisions.

The answer to this question is provided by the study of Dr. Lukaszewicz et al (9). These authors analyzed the HLA-DR kinetics and the development of secondary infections in ICU patients. A failure to clear an infection or prevent the development of a secondary infection has been used as the clinical correlate to immunoparalysis. The data of the study showed that slower recovery of the HLA-DR expression correlates with a high risk for developing a secondary infection. This observation inaugurates low HLA-DR expression from another more or less useful “prognostic marker” in ICU patients to a “true mediator” of immune dysfunction.

From a therapeutic standpoint, the data provide further evidence that HLA-DR expression is an important target for the “correction of immunoparalysis.” At least two potential immunostimulating substances (interferon- γ and granulocyte-macrophage colony-stimulating factor) are clinically approved and could be used in an “off label” fashion for enhancement of the immune response in critically ill patients. In the study of Dr. Grienay et al, two immunoparalyzed pa-

tients were included who received therapeutic support. In these patients, the authors could nicely show that recovery of HLA-DR expression as a marker, and/or as a mediator of immune function, paralleled the clearance of the persistent infection.

Currently, it is probably too early to claim HLA-DR measurement in conjunction with immunostimulation as standards in ICU protocol just as an arterial catheter and application of catecholamines. The few clinical trials with interferon- γ or granulocyte-macrophage colony-stimulating factor in ICU patients were of small sample size, partly uncontrolled, and therefore can only show the feasibility of immunostimulation, however, without demonstrating a beneficial clinical outcome (6, 8). In traumatology, several randomized studies with interferon- γ treatment exist, however, with overall disappointing results (10, 11). Unfortunately, these studies did not include the monitoring of the immune status, thus making it difficult to draw any conclusions on the efficacy of the applied immunostimulators.

Overall, the work of Dr. Grienay et al further stimulates the discussion to consider a controlled clinical trial with a clear immune monitoring to study the efficacy of immunostimulation in patients who fail to recover fast or early enough, with the aim of preventing secondary infections.

Sascha Flohé, MD

University Hospital Essen
Essen, Germany

Martin Scholz, PhD

University Hospital Duesseldorf
Duesseldorf, Germany

REFERENCES

1. Ditschkowsk M, Kreuzfelder E, Rebmann V, et al: HLA-DR expression and soluble

HLA-DR levels in septic patients after trauma. *Ann Surg* 1999; 229:246–254

2. Wakefield CH, Carey PD, Foulds S, et al: Changes in major histocompatibility complex class II expression in monocytes and T cells of patients developing infection after surgery. *Br J Surg* 1993; 80:205–209
3. Monneret G, Lepape A, Voirin N, et al: Persisting low monocyte human leukocyte antigen-DR expression predicts mortality in septic patients. *Intensive Care Med* 2006; 32: 1175–1183
4. Hershman MJ, Cheadle WG, Wellhausen SR, et al: Monocyte HLA-DR antigen expression characterizes clinical outcome in the trauma patient. *Br J Surg* 1990; 77:204–207
5. Venet F, Tissot S, Debard AL, et al: Decreased monocyte human leukocyte antigen-DR expression after severe burn injury: Correlation with severity and secondary septic shock. *Crit Care Med* 2007; 35:1910–1917
6. Doecke WD, Randow F, Syrbe U, et al: Monocyte deactivation in septic patients: Restoration by IFN-gamma treatment. *Nat Med* 1997; 3:678–681
7. Flohé S, Lendemans S, Selbach C, et al: Effect of granulocyte-macrophage colony-stimulating factor on the immune response of circulating monocytes after severe trauma. *Crit Care Med* 2003; 31:2462–2469
8. Nierhaus A, Montag B, Timmler N, et al: Reversal of immunoparalysis by recombinant human granulocyte-macrophage colony-stimulating factor in patients with severe sepsis. *Intensive Care Med* 2003; 29:646–651
9. Lukaszewicz A-C, Grienay M, Resche-Rigon M, et al: Monocytic HLA-DR expression in intensive care patients: Interest for prognosis and secondary infection prediction. *Crit Care Med* 2009; 37:2746–2752
10. Polk HC, Cheadle WG, Livingston DH, et al: A randomized prospective clinical trial to determine the efficacy of interferon-gamma in severely injured patients. *Am J Surg* 1992; 163:191–196
11. Dries DJ, Jurkovich GJ, Maier RV, et al: Effect of interferon gamma on infection-related death in patients with severe injuries. A randomized, double-blind, placebo-controlled trial. *Arch Surg* 1994; 129:1031–1041

Did we learn anything from Humpty Dumpty?*

Over the past three decades, significant efforts from practitioners, administrators, health policy advocates, academicians, and bureaucratic agencies have been made toward changing the healthcare system in the United States and elsewhere. The first efforts targeted excess capacity, which resulted in significant decreases in the number of acute care hospitals as well as overall acute care beds. In the face of these structural changes, we observed a substantial increase in intensive care unit (ICU) bed capacity, thereby reducing non-ICU bed capacity during this same period. Halpern et al (1) demonstrated that from 1985 to 2000, the number of hospitals providing critical care medicine (CCM) beds decreased 13.7%, while overall CCM bed capacity increased 71.8% and non-CCM bed capacity decreased 30.9%. The increase in ICU capacity has been seen as a positive structural change for certain aspects of acute care. McConnell et al (2) demonstrated that the increase in ICU capacity has decreased emergency department length of stay and ambulance diversion. Conversely, the changes in capacity resulted in increases in hospital occupancy and patient-to-staff ratios (on average), which have been identified as key determinants in methicillin-resistant *Staphylococcus aureus* transmission (3).

More recently, those interested in healthcare reform have invested in exploring our clinical practices with the intent to identify “best-practice” models for adoption across large sectors of our healthcare system. To understand potential improvements, we have taken a fractionated approach to process changes, focusing on specific interventions or process while paying little or no attention to overall system performance. This focus

on investigation has been most prominent in ICU practice models. Brook et al (4) published results of their findings related to nursing-implemented sedation protocol and their impact on duration of mechanical ventilation. In 2002, Pronovost and colleagues (5) published their results that examined the impact of physician staffing patterns on clinical outcomes. Numerous citations can be found in the literature that examine many aspects of critical care medicine, but few of these studies examined the overall impact that these practice changes may have on hospital outcome.

In 1966, Donabedian (6) published his landmark study that drew our attention to the concept that outcome is a function of both structure and process. To fully understand the outcome, one must be cognizant of how changes in structure, process, or both can affect the quality of health care provided and the outcome that patients will experience. In this issue of *Critical Care Medicine*, Chrusch and colleagues (7) presented two primary focuses that I believe are salient to this discussion.

First, this study provides information on key determinants of ICU readmission. In this study, Chrusch and colleagues (7) raise the issue that ICU occupancy may affect decision making regarding discharge of patients as intensivists are forced to triage the acuity of patients when resources are restricted. When ICU discharges occurred during periods of no vacancy, there was a significant increase in risk of death or ICU readmissions compared with periods associated with ICU vacancy. Dr. Chrusch and colleagues’ work suggests that attention to key non-ICU drivers of readmission, such as changes in the patient’s respiratory status, may influence the need for readmission if interventions or supportive non-ICU therapy were enacted sooner, although in-depth examination of this issue was beyond the scope of this study.

Second, Chrusch and colleagues’ (7) work draws our attention back to the original efforts of Dr. Donabedian, who called for a more global understanding of how changes in structure and process can affect ultimate outcome of our patients.

Like Humpty Dumpty, health care today sits atop a wall being assailed by many factors that threaten to topple our current system. Our ability to understand and appreciate how our current efforts to change either structures or processes in health care affect our outcomes will allow us, unlike all the king’s men, to put our Humpty Dumpty (health care) back together again.

The primary weakness of this study is that it was performed at a single center, so that our ability to generalize the findings is limited. Second, the study examines average ICU occupancy, so we cannot determine the impact that day-to-day or within-day variable in occupancy has on outcome (ICU readmission or death). In addition, we have no insight into the decision-making process used to triage individual patients at the time of discharge, nor do we have an assessment of patient acuity at the time of discharge. The investigators have acknowledged these weaknesses in their discussion and indicate that further research is warranted in these areas. However, the current study supports our efforts to understand and appreciate the impact that our healthcare processes have on patient outcomes. This study highlights the need for awareness in all areas of support, including those patients being discharged from an ICU. As demands on healthcare services, processes, and structures increase, allocation of healthcare resources to address issues associated with high-occupancy discharges and readmissions will be difficult. Only through additional research, review, and reporting will we be able to promote ongoing quality and improved outcomes in this area.

Ronald E. Dechert, RRT, DPH,
MS, FAARC

Critical Care Support Services,
University of Michigan Health
System

Ann Arbor, MI

REFERENCES

1. Halpern NA, Pastores SM, Thaler HT, et al: Changes in critical care beds and occupancy in

*See also p. 2753.

Key Words: intensive care; readmission; occupancy; mortality; outcome; transfer; vacancy

The author has not disclosed any potential conflicts of interest.

Copyright © 2009 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/CCM.0b013e3181b39f6f

- the United States 1985–2000: Differences attributable to hospital size. *Crit Care Med* 2006; 34:2105–2112
2. McConnell KJ, Daya M, Bernell SL, et al: Effect of increased ICU capacity on emergency department length of stay and ambulance diversion. *Ann Emerg Med* 2005; 45:471–478
 3. Clements A, Graves N, Pettit A, et al: Overcrowding and understaffing in modern health-care systems: Key determinants in methicillin-resistant *Staphylococcus aureus* transmission. *Lancet Infect Dis* 2008; 8:427–434
 4. Brook AD, Ahrens TS, Schaiff R, et al: Effect of nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med* 1999; 27:2609–2615
 5. Pronovost PPJ, Angus DC, Dorman T, et al: Physician staffing patterns and clinical outcomes in critically ill patients: A systematic review. *JAMA* 2002; 288:2151–2162
 6. Donabedian A. Evaluating the quality of medical care. *Milbank Mem Fund Q* 1966; 44 (3, part 2):166–203
 7. Chrusch CA, Olafson KP, McMillan PM, et al: High occupancy increases the risk of early death or readmission after transfer from intensive care. *Crit Care Med* 2009; 39:2753–2758

Is it time for intensivists to learn genomics?*

Intensivists routinely care for patients with the sepsis syndrome. This complex syndrome, characterized by a dysregulated host response to an infection, is increasing in prevalence, and carries an unacceptably high case fatality rate (1). Despite an improved understanding of the pathophysiology of sepsis, treatment of patients with sepsis is primarily centered around early identification of patients, early treatment with antibiotics, volume resuscitation, and avoidance of nosocomial complications (2) (3).

It is not uncommon to see a septic patient do poorly despite adequate therapy, or unexpectedly do better than the treating team might have initially predicted. It is therefore tempting to speculate that these discordant patient responses to sepsis might be causally related to genetic variation. Initial studies to evaluate this possibility examined whether the presence of a mutation in a single nucleotide base pair or single nucleotide polymorphism (SNP) is associated with the development of sepsis, or sepsis outcomes (4, 5). The SNPs chosen for evaluation in these early studies involved genes implicated in the pathophysiology of sepsis by prior human or animal research—a so-called candidate gene approach. Although this is a reasonable approach, many studies were hampered by small sample sizes and inconsistent association with sepsis and sepsis outcomes (6).

In this issue of *Critical Care Medicine*, Flores et al (7) report a well-designed prospective case control genetic association study of 175 septic patients and 357 population-based controls to evaluate the association between lipopolysaccharide-binding protein (LBP) haplotypes and severe sepsis. Several previous reports have implicated LBP, an acute-phase reactant involved with the processing of endotoxin, with the development of septic shock (8) and the severity of sepsis (9). In the study by Dr. Flores and colleagues, a common haplotype in the LBP gene, present in 41% of controls and 53% of the patients, was associated with the development of severe sepsis (7). After adjustment for multiple comparisons, none of the individual LBP SNPs were associated with sepsis. Serum LBP levels, adjusted for demographic and clinical exposures, were also higher in patients with this risk haplotype, suggesting a potential mechanism for the association. Strengths of the study include a sample size and power calculation, blinded genotyping, a conservative analytic technique to correct for multiple tests, and the use of haplotypes, in addition to SNPs to test association with severe sepsis.

Despite the careful study design and analysis of Dr. Flores and colleagues, it is important to note some trial design issues that may limit the external validity of these findings. First, the patients enrolled were from a European patient population, and the association of this LBP risk haplotype with severe sepsis may not be present in patients with different ethnicities. Second, the patients enrolled had abdominal and gastrointestinal sepsis as the most frequent site of infection; most studies of patients with sepsis in Europe and elsewhere have shown the lung as the most common site of infection, also raising concerns about the gen-

eralizability of the findings (10, 11). In addition, more than half of the patients did not have positive blood cultures, and no data are presented regarding which organisms caused sepsis in those patients with positive cultures. Because LBP is involved with endotoxin processing, classically seen with Gram-negative infections, it is unclear whether the association of this LBP haplotype with sepsis will be found in patients with Gram-positive or fungal infections that activate patients' host defense system through other pathways.

A final limitation to this study is related to the complexity of the sepsis syndrome. It is likely that more than a single gene or pathway is responsible for the development of sepsis, or sepsis outcomes. Of note, attempts to modulate bacterial products, such as endotoxin in patients with sepsis, were not successful at improving outcomes for patients with sepsis (12). Future studies of sepsis susceptibility may examine the interaction of several genes involved with the host-pathogen response or the interaction of genes with different treatments.

Knowledge of genomics may be important for clinicians caring for patients with cystic fibrosis, where variation in the cystic fibrosis transmembrane conductance regulator gene as well as modifier genes may affect patient's symptoms and survival (13). Knowledge of genomics may also be important for clinicians caring for patients requiring warfarin therapy, where genotype has been associated with response to therapy (14). For clinicians caring for patients with sepsis, knowledge of genomics is less useful at this time. When additional studies confirm the presence of high-risk haplotypes or SNPs for septic patients and we are able to rapidly identify such patients, it may be possible to target individual therapies to those patients.

*See also p. 2759.

Key Words: sepsis; severe sepsis; haplotype; single nucleotide polymorphism

The author has not disclosed any potential conflicts of interest.

Copyright © 2009 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/CCM.0b013e3181ad78ea

This report by Dr. Flores and colleagues is an important addition to the literature and suggests the importance of LBP, and possibly LBP gene variants, in the development of sepsis in a European patient population. Although readers of this journal will likely continue to see genetic association studies on a regular basis, limitations of this and other published genetic association studies in patients with sepsis make the results of these studies, for now, of more interest to researchers than to patients and clinicians.

Jonathan Sevransky, MD, MHS
 Johns Hopkins University
 School of Medicine
 Baltimore, MD

REFERENCES

1. Martin GS, Mannino DM, Eaton S, et al: The epidemiology of sepsis in the united states from 1979 through 2000. *N Engl J Med* 2003; 348:1546–1554
2. Dellinger RP, Levy MM, Carlet JM, et al: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2008; 36: 296–327
3. Kumar A, Roberts D, Wood KE, et al: Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; 34:1589–1596
4. Mira JP, Cariou A, Grall F, et al: Association of TNF2, a TNF-alpha promoter polymorphism, with septic shock susceptibility and mortality: A multicenter study. *JAMA* 1999; 282:561–568
5. Stuber F, Petersen M, Bokelmann F, et al: A genomic polymorphism within the tumor necrosis factor locus influences plasma tumor necrosis factor-alpha concentrations and outcome of patients with severe sepsis. *Crit Care Med* 1996; 24:381–384
6. Clark MF, Baudouin SV: A systematic review of the quality of genetic association studies in human sepsis. *Intensive Care Med* 2006; 32:1706–1712
7. Flores C, Pérez-Méndez L, Maca-Meyer N, et al: A common haplotype of the *LBP* gene predisposes to severe sepsis. *Crit Care Med* 2009; 37:2759–2766
8. Prucha M, Herold I, Zazula R, et al: Significance of lipopolysaccharide-binding protein (an acute phase protein) in monitoring critically ill patients. *Crit Care* 2003; 7: R154–R159
9. Opal SM, Scannon PJ, Vincent JL, et al: Relationship between plasma levels of lipopolysaccharide (LPS) and LPS-binding protein in patients with severe sepsis and septic shock. *J Infect Dis* 1999; 180:1584–1589
10. Vincent JL, Sakr Y, Sprung CL, et al: Sepsis in european intensive care units: Results of the SOAP study. *Crit Care Med* 2006; 34: 344–353
11. Silva E, Pedro Mde A, Sogayar AC, et al: Brazilian sepsis epidemiological study (BASES study). *Crit Care* 2004; 8:R251–R260
12. Natanson C, Hoffman WD, Suffredini AF, et al: Selected treatment strategies for septic shock based on proposed mechanisms of pathogenesis. *Ann Intern Med* 1994; 120: 771–783
13. Buranawuti K, Boyle MP, Cheng S, et al: Variants in mannose-binding lectin and tumor necrosis factor alpha affect survival in cystic fibrosis. *J Med Genet* 2007; 44: 209–214
14. International Warfarin Pharmacogenetics Consortium, Klein TE, Altman RB, et al: Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med* 2009; 360:753–764

No brain, no pain: Does the injured brain stack up opioids?*

Providing adequate analgesia and sedation to critically ill patients with acute brain injury is beyond argument even though there is to date no clear evidence that analgesia itself serves to control intractable intracranial hypertension and improves neurologic outcome (1). Few randomized controlled trials comparing different analgesic regimens in patients with acute brain injury have been conducted that aim at the neurologic outcome as one of the study's end points.

As for opioids, a randomized controlled trial with 42 moderately or severely head-injured patients revealed a significantly improved neurologic out-

come after 6 mos for sedation with high dose (≥ 100 mg/kg body weight) but not for low-dose propofol (< 100 mg/kg body weight) as compared with low-dose morphine administration at a rate of 1 to 3 mg/hr (2).

In addition, determining the adequate level of analgesia and sedation is even more challenging in critically ill patients with structural brain damage and neurologic dysfunction than in neurologically unimpaired patients. In this respect, it is worth mentioning that there is increasing evidence for brain injury—let it be traumatic, infectious, ischemic, cancerous, or neurodegenerative—to alter the permeability of the blood-brain-barrier (BBB) for a variety of substrates, among those opioids commonly administered for analgesia in intensive care units (3, 4). The precise mechanisms underlying these alterations are not yet fully understood, especially in patients.

As for morphine, acting on central and peripheral opioid receptors, *in vitro* and *in vivo* models suggest that penetration of the BBB is modulated by P-glycopro-

tein (P-gp) (5), a member of the adenosine triphosphate (ATP)-binding cassette family of drug efflux transporters that is expressed at various tissues throughout the body, notably the BBB (6). However, the case is not that clear for its active metabolites morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). For M6G, animal studies in rodents have revealed a P-gp-independent active transport at the BBB that might involve the glucose transporter GLUT-1 and a digoxin-sensitive transporter, probably the organic anion transporting polypeptide oap2 (7). Under physiologic conditions, these efflux mechanisms are supposed to prevent the brain from accumulation of potentially neurotoxic substrates. Under pathologic conditions, such as structural brain damage, however, various mechanisms have been identified by which BBB permeability is increased, among those a cascade of proinflammatory cytokines, such as interleukin- β , interleukin-6, and tumor necrosis factor- α that are secreted by central nervous system macrophages,

*See also p. 2767.

Key Words: acute brain injury; interleukin-6; morphine; morphine-3/6-glucuronide; blood-brain-barrier; drug transport mechanisms; analgesia

The authors have not disclosed any potential conflicts of interest.

Copyright © 2009 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/CCM.0b013e3181ad7b33

microglia, astrocytes, and cerebral endothelial cells (4). However, data on the disruption of BBB by proinflammatory cytokines are mainly derived from animal studies.

In this issue of *Critical Care Medicine*, the single-center observational pharmacokinetic study by Roberts et al (8) demonstrates elegantly that increased interleukin-6 levels in the cerebrospinal fluid of 16 critically ill patients with acute brain injury of different origin (subarachnoid hemorrhage, intracerebral/intraventricular hemorrhage, closed head injury) comes along with an intrathecal accumulation of the morphine metabolites M3G and M6G, but not morphine itself. At the same time, the cerebrospinal fluid/plasma ratio of albumin remains unaltered, indicating a physically intact BBB. This observation leads the authors to the conclusion that central nervous system inflammation may selectively inhibit the activity of specific drug transport mechanisms other than the morphine-associated ATP-binding cassette efflux transporter P-gp.

However, the study design is purely descriptive and lacks a control group; any discussion on the BBB drug transport mechanisms is speculative and findings should not be overstretched. Further limitations include a small and heterogeneous patient sample and correlation of cerebrospinal fluid levels of morphine and its metabolites to only one of the many proinflammatory cytokines presumably involved in BBB disruption. Additionally, animal studies have already demonstrated the existence of a strong interindividual variability not only of cytokine levels but also of P-gp expression and ATPase activity levels, resulting in a negative relationship between morphine analgesia and P-gp expression levels in the rodent brain (9), making it even more difficult to draw conclusions from a relatively small study sample. Finally, the timing of presumed inflammatory pro-

cesses in relation to the different brain pathologies is nonuniform and any follow-up study should attempt to capture proinflammatory cytokines for a longer time span. Nevertheless, this work adds indirect but valuable evidence to the assumption that, not only in animal models but also in patients, a central nervous system proinflammatory state is associated with penetration of drug efflux transporter substrates that are under physiologic conditions excluded from passing the BBB.

One can speculate about the implications of facilitated passage of opioids through the BBB in brain tissues at risk. From an experimental point of view, the opioidergic system has been shown to exert neuroprotective effects in cerebral ischemia (10, 11), an observation that is not yet supported by the few outcome studies performed for analgesedative drugs in critically ill patients. From a clinical standpoint, it might help to protect the injured brain from nociceptive thus stressful stimuli. Whether the modulation of transport mechanisms for morphine and its metabolites mediated by a brain injury-associated functional BBB disruption is a piece in the puzzle of developing opioid tolerance remains one of the questions to answer. Neurointensivists trying to achieve adequate analgesia and sedation in brain-injured intensive care unit patients should be aware that this might differ considerably from neurologically intact critically ill patients, be it a matter of opioid tolerance or accumulation.

Christine Dictus, MD

Oliver W. Sakowitz, MD

Department of Neurosurgery

University Hospital Heidelberg
Heidelberg, Germany

REFERENCES

1. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of

Neurological Surgeons, et al: Guidelines for the management of severe traumatic brain injury. XI. Anesthetics, analgesics, and sedatives. *J Neurotrauma* 2007; 24(Suppl 1): S71–S76

2. Kelly DF, Goodale DB, Williams J, et al: Propofol in the treatment of moderate and severe head injury: A randomized, prospective double-blinded pilot trial. *J Neurosurg* 1999; 90:1042–1052
3. Ohtsuki S, Terasaki T: Contribution of carrier-mediated transport systems to the blood-brain barrier as a supporting and protecting interface for the brain; importance for CNS drug discovery and development. *Pharm Res* 2007; 24:1745–1758. Epub 2007 July 10
4. De Vries HE, Kuiper J, De Boer AG, et al: The blood-brain barrier in neuroinflammatory diseases. *Pharmacol Rev* 1997; 49: 143–155
5. Letrent SP, Polli JW, Humphreys JE, et al: P-glycoprotein-mediated transport of morphine in brain capillary endothelial cells. *Biochem Pharmacol* 1999; 58:951–957
6. Hennessy M, Spiers JP: A primer on the mechanics of P-glycoprotein the multidrug transporter. *Pharmacol Res* 2007; 55:1–15
7. Bourasset F, Cisternino S, Tamsamani J, et al: Evidence for an active transport of morphine-6-beta-d-glucuronide but not P-glycoprotein-mediated at the blood-brain barrier. *J Neurochem* 2003; 86:1564–1567
8. Roberts D, Goralski K, Renton K, et al: Effect of acute inflammatory brain injury on accumulation of morphine and morphine 3- and 6-glucuronide in the human brain. *Crit Care Med* 2009; 37:2767–2774
9. Hamabe W, Maeda T, Kiguchi N, et al: Negative relationship between morphine analgesia and P-glycoprotein expression levels in the brain. *J Pharmacol Sci* 2007; 105: 353–360
10. Zhao P, Huang Y, Zuo Z: Opioid preconditioning induces opioid receptor-dependent delayed neuroprotection against ischemia in rats. *J Neuropathol Exp Neurol* 2006; 65: 945–952
11. Kao TK, Ou YC, Liao SL, et al: Opioids modulate post-ischemic progression in a rat model of stroke. *Neurochem Int* 2008; 52: 1256–1265

Aminoglycosides—Engineering important patient-centered outcomes with antibiotics*

Aminoglycosides, such as gentamicin and tobramycin, are old but effective broad-spectrum antibiotics that have seen much less increase in microbial resistance over the years when compared with β lactam antibiotics. Once-daily administration of these agents may have increased their efficacy and utility, particularly in fluid-resuscitated patients with increased volume of distribution who populate our intensive care units (1). However, the Achilles heels of aminoglycosides remains ototoxicity and nephrotoxicity.

Nephrotoxicity is of particular concern as in other patient populations; biochemical renal dysfunction not requiring renal replacement therapy is associated with increased risk of death (2). Acute renal failure in the intensive care unit requiring renal replacement therapy is also an independent risk factor for death (3, 4). Classically, aminoglycoside nephrotoxicity is characterized as being of gradual onset over a period of days and reversible. Nevertheless, this risk of acute kidney injury and its possible consequences may temper enthusiasm for their use by some critical care practitioners. On the other hand, inappropriate choice of antibiotic, one which is not effective against the invading pathogen, is also associated with increased mortality (5, 6). Use of combination therapy with an aminoglycoside may be seen as reducing the risks of inappropriate cover and thus reducing mortality risk. Recent evidence, which confirmed that late administration of antibiotic is also associated with increased mortality risk as well as acute kidney injury, underscored the importance of appropriate choices and early administration of antibiotic (7, 8).

*See also p. 2782.

Key Words: aminoglycosides; antibiotics; gentamicin; tobramycin; nephrotoxicity

The author has not disclosed any potential conflicts of interest.

Copyright © 2009 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/CCM.0b013e3181b00457

In this issue of *Critical Care Medicine*, Lipcsey et al (9), with the aid of a porcine model of endotoxin-induced sepsis, try to shed light on whether a single dose of tobramycin, 7 mg/kg, has deleterious effects on renal function. Their carefully conducted study of 24 healthy pigs failed to demonstrate any important effect of a single dose of tobramycin on a number of biochemical indices of renal function or on renal ultrastructure. If the results of this study could be extrapolated to human populations, clinical practitioners might feel reassured that the benefits of a single dose of tobramycin with potentially better microbial coverage would outweigh any risks as identification of the pathogen was awaited to better guide subsequent therapy (9).

However, this conclusion may be premature. The authors only studied the animals for 6 hrs after a single dose of tobramycin, which only attained modest peak concentrations, and their small study may have been insufficiently powered for all outcomes presented. Also, as indicated by the authors, other workers using different models have produced different results. Using very large doses of gentamicin in rodents, Zager found that the drug in combination with other risk factors, such as hypovolemia, fever, and endotoxemia, did result in renal injury (10). Importantly, old animals seem more susceptible to these toxic effects (11). Thus, results from healthy pigs may not be applicable to an elderly human population with multiple comorbidities and receiving other nephrotoxic drugs. Further, practitioners should be cautious about extrapolating these results of single-dose tobramycin to other aminoglycosides, as there is some controversy as to whether nephrotoxic potential differs among aminoglycosides (12, 13).

Neither should these results be extrapolated to more protracted combination therapy with an aminoglycoside, as two large systematic reviews demonstrated no overall survival advantage of combination therapy but the forest plots clearly dem-

onstrate a substantially higher risk of nephrotoxicity, however defined in the original papers (14, 15). Similar findings have been documented for initial low-dose aminoglycosides in *Staphylococcus aureus* endocarditis (16).

Nevertheless, the work of Dr. Lipcsey and colleagues could lay the foundation to conduct clinical trials to ascertain whether initial high-dose tobramycin combined with β lactams can further improve important patient-centered outcomes. This might be achieved by ensuring better spectrum of antimicrobial cover as well as allowing time for the coadministered β lactam to reach its pharmacokinetic goal of achieving maximum time above minimum inhibitory concentration (1).

Early appropriate antibiotic cover for serious infection in the intensive care unit is a key issue for engineering important patient-centered outcomes in intensive care. The research must go on.

David W. Noble

Aberdeen Royal Infirmary
Aberdeen, Scotland

REFERENCES

1. Roberts JA, Lipman J: Pharmacokinetic issues for antibiotics in the critically ill patient. *Crit Care Med* 2009; 37:840–851
2. Turner JH: Acute renal failure—A dangerous condition. *JAMA* 1996; 275:1516–1517
3. Metnitz PGH, Krenn CG, Stelzer H, et al: Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. *Crit Care Med* 2002; 30:2051–2058
4. Barrantes F, Tian J, Vazquez R, et al: Acute kidney injury criteria predict outcomes of critically ill patients. *Crit Care Med* 2008; 36:1397–1403
5. Valles J, Rello J, Ochagavia A, et al: Community-acquired bloodstream infection in critically ill adult patients. Impact of shock and inappropriate antibiotic therapy on survival. *Chest* 2003; 123:1615–1624
6. Luna CM, Aruj P, Garzon J, et al: Appropriateness and delay to initiate therapy in ventilator-associated pneumonia. *Eur Respir J* 2006; 27:159–164
7. Kumar A, Roberts D, Wood KE, et al: Dura-

tion of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; 34:1589–96

8. Bagshaw SM, Lapinsky S, Dial S, et al: Acute kidney injury in septic shock: clinical outcomes and impact of duration of hypotension prior to initiation of antimicrobial therapy. *Intensive Care Med* 2009; 35:871–881
9. Lipcsey M, Carlsson M, Larsson A, et al: Effect of a single dose of tobramycin on systemic inflammatory response-induced acute kidney injury in a 6-hour porcine model. *Critical Care Medicine* 2009; 37: 2782–2790
10. Zager RA: Endotoxemia, renal hypoperfusion, and fever: Interactive risk factors for aminoglycoside and sepsis-associated acute renal failure. *Am J Kidney Dis* 1992; 20: 223–230
11. Peters-Volleberg GW, Dortant PM, Speijers GJ: Comparison of tobramycin nephrotoxicity in young adult and aged female rats. *Pharmacol Toxicol* 1999; 84:147–153
12. Schentag JJ, Plaut ME, Cerra FB: Comparative nephrotoxicity of gentamicin and tobramycin: Pharmacokinetic and clinical studies in 201 patients. *Antimicrob Agents Chemother* 1981; 19:859–866
13. Smyth A, Lewis S, Bertenshaw C, et al: Case-control study of acute renal failure in patients with cystic fibrosis in the UK. *Thorax* 2008; 63:532–535
14. Paul M, Soares-Weiser K, Leibovici L: β lactam monotherapy versus β lactam aminoglycoside combination therapy for fever with neutropenia: A systematic review and meta-analysis of randomised trials. *BMJ* 2003; 326: 1111
15. Paul M, Benuri-Sibiger I, Soares-Weiser K, et al: β lactam monotherapy versus β lactam combination therapy in immunocompetent patients: A systematic review and meta-analysis of randomised trials. *BMJ* 2004; 328: 668
16. Cosgrove SE, Vigianni GA, Fowler VG Jr, et al. Initial low-dose gentamicin for *Staphylococcus aureus* bacteremia and endocarditis is nephrotoxic. *Clin Infect Dis* 2009; 48: 713–721

Could insulin sensitization be used as an alternative to intensive insulin therapy to improve the survival of intensive care unit patients with stress-induced hyperglycemia?*

The efficacy and safety of tight glucose control achieved by intensive insulin therapy (IIT) in critically ill patients have been issues of intense investigation and controversy for a decade. Hyperglycemia is associated with poor prognosis in critically ill patients. In a landmark study published in 2001, Van den Berghe and colleagues (1) demonstrated that strict glucose control by IIT halved the mortality of adult patients in the surgical intensive care unit (ICU) compared with the conventional glucose control regimen. Thereafter, many ICUs worldwide updated protocols to intensify glycemic control in critically ill patients. Subsequent large-scale, prospective, randomized, controlled clinical trials and meta-analyses, however, failed to find the benefit of IIT while showing increased risk for hypoglycemic episodes (2–5). A clinical trial was prematurely terminated because of a lack of evidence of efficacy and an unacceptably high rate of hypoglycemia (2).

This controversy raises several pressing questions (4–7). Is IIT beneficial only in a select subpopulation of patients (e.g., surgical patients)? Is accurate blood glucose monitoring required to achieve the beneficial effects of IIT (given that peripheral blood samples do not always reflect systemic glycemic status, particularly in ICU patients with impaired circulation)? Is glycemic variability (i.e., a within-patient fluctuation in blood glucose levels) a more sensitive predictor of prognosis and mortality than mean blood glucose levels (8–10)? Is the beneficial effect of IIT in the ICU specific to patients receiving parenteral, but not enteral, nutrition? Of note, recent studies (2, 3) have reported a lower blood glucose level in controls compared with the preceding landmark study (1). Therefore, the improved glycemic control in the control groups of recent trials may be a significant contributor to the lack of demonstrated benefit of IIT. Furthermore, hyperglycemia in the ICU can be stratified into two categories: diabetes-induced hyperglycemia and stress-induced hyperglycemia (SIH) without preexisting diabetes. Hyperglycemia, glycemic variability, and tight glucose control seem to have a greater impact on nondiabetic SIH patients than diabetic ICU patients. These new questions and conflicting data leave critical care clinicians in a quandary.

Although most of these issues await further investigations, one of the questions demands immediate attention. In the findings of the multinational Normoglycemia in the Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study involving 6,104 patients, mortality was significantly increased in the IIT group (death at 90 days, 27.5% vs. 24.9% with conventional control; odds ratio, 1.14; $p = .02$) (3). Not surprisingly, the incidence of severe hypoglycemic (blood glucose <40 mg/dL) was greater in the IIT group than in the control group (6.8% vs. 0.5%, $p < .001$). Hypoglycemia is a major adverse event that hampers the successful implementation of IIT. However, it is unclear whether this difference in the hypoglycemic incidence can fully account for the differences in mortality between IIT and control groups (6). Another possibility is that exogenous insulin elicits deleterious effects, independent of glucose lowering, that increase mortality rate in the IIT group. Insulin has a number of glucose-independent actions, including stimulation of potassium transport into the cells, sympathetic activation, sodium retention, anti-inflammatory effects, and anti-apoptotic, anabolic, and mitogenic actions. These pleiotropic actions can be either protective or detrimental, dependent presumably on insulin levels and

*See also p. 2791.

Key Words: intensive insulin therapy; insulin sensitization; stress-induced hyperglycemia

The authors have not disclosed any potential conflicts of interest.

Copyright © 2009 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/CCM.0b013e3181aff7bb

cellular context. The deleterious effects of hyperinsulinemia have been documented in disease states other than critical illness and IIT. Hyperinsulinemia is an independent risk factor for the development of atherosclerosis and ischemic heart disease. It is reasonable to speculate, therefore, that the hyperinsulinemia caused by IIT might exert deleterious effects in ICU patients, contributing to their reduced survival. The impact of hyperinsulinemia (or insulin dosage) on outcome of IIT warrants further investigation. Collectively, the accumulating evidence suggests that both hypoglycemia and the deleterious effects of hyperinsulinemia may be involved in the increased mortality observed with IIT. Therefore, one of the highest priorities in managing strict glucose control in the ICU should be to determine how to avoid severe hypoglycemia and the adverse effects of hyperinsulinemia.

The binding of insulin to its cognate receptor results in activation of multiple intracellular signaling pathways. Among others, the phosphatidylinositol 3-kinase (PI3K)-Akt/protein kinase B pathway plays a central role in insulin's actions on glucose metabolism. Insulin sensitivity is determined by hypoglycemic response to insulin, which is mainly mediated by activation of the PI3K-Akt pathway. Previous studies indicate that the PI3K-Akt pathway is specifically impaired where the insulin-resistant state is induced by obesity and trauma in rodents (11, 12), while other signaling cascades, such as the mitogen-activated protein kinase (MAPK) pathway, are spared. Compensatory hyperinsulinemia secondary to insulin resistance promotes atherogenesis even in the absence of hyperglycemia, presumably by hyperactivation of the signaling cascades (e.g., MAPK) parallel to the PI3K-Akt pathway. In contrast, activity of the PI3K-Akt pathway is not elevated by secondary hyperinsulinemia. It is tempting to speculate, therefore, that essentially the same mechanism, hyperactivation of glucose metabolism-unrelated insulin signaling pathways, may underlie the putative detrimental effects of hyperinsulinemia in critically ill patients. Insulin resistance (impaired hypoglycemic response to insulin) plays a crucial role in SIH in critical illness, including sepsis, trauma, and major surgery. Insulin-sensitization reduces the insulin requirement to maintain euglycemia and hence helps achieve normal glucose levels with no insulin treatment or with lower dosages of insulin. In aggregate, a

logical proposition is that insulin sensitization is a potential solution of the current two major issues in glycemic control in SIH: hypoglycemia and hyperinsulinemia. To date, however, this possibility has not been explored, partly because the two clinically approved insulin sensitizers, thiazolidinediones and metformin, are contraindicated in many critically ill patients owing to the adverse side effects (e.g., edema and heart failure for thiazolidinediones, lactic acidosis for metformin).

In this issue of *Critical Care Medicine*, Dr. Matsuda and colleagues (13) present the beneficial effects of an insulin sensitizer in a mouse model of sepsis. The authors show that inhibition of nuclear factor (NF)- κ B reverses glucose intolerance and ameliorates insulin resistance and hyperinsulinemia in septic mice. Importantly, the insulin sensitization was accompanied by improved survival of the animals. Sepsis-associated hyperglycemia is a common finding in the ICU. NF- κ B is a key transcription factor that regulates the expression of genes that play important roles in inflammation, including proinflammatory cytokines (e.g., tumor necrosis factor- α) and inducible nitric oxide synthase. In this study, after sepsis was induced by cecal ligation and puncture (CLP), the mice were treated with the NF- κ B decoy oligodeoxynucleotide, which blocks the binding of NF- κ B to the promoter region of the downstream genes and thereby NF- κ B-mediated transcription. The improved insulin sensitivity and glucose tolerance by NF- κ B inhibition paralleled the reversal of attenuated insulin signaling, in particular the activities of the PI3K-Akt pathway in septic mice. The important role of NF- κ B activation in rodent models of obesity-induced insulin resistance has been established. Chronic low-grade inflammation plays an important role in obesity-induced insulin resistance (14). Gene disruption of NF- κ B protects mice from obesity-induced diabetes. Furthermore, a clinical trial is underway to evaluate the efficacy and safety of an NF- κ B inhibitor for the treatment of type 2 diabetes. The present study clearly indicates that NF- κ B plays a critical role in sepsis-induced insulin resistance in mice as well. Collectively, the present findings warrant further preclinical studies to investigate the effects of insulin-sensitization on mortality in animal models of SIH, including sepsis, trauma, and major surgery.

Dr. Matsuda and colleagues' study (13) also forewarns of some potential pitfalls

that should be considered in designing future studies. First, the septic mice did not exhibit overt hyperglycemia, although the animals were substantially insulin resistant and glucose intolerant. Unlike humans and rats, mice are resistant to stress-induced hyperglycemia. Thus, rats rather than mice may be a more appropriate rodent model of SIH. Other insights can be gleaned about the protective effects of the insulin sensitizer. For example, possibilities exist that not only hyperglycemic but also euglycemic ICU patients could benefit from insulin sensitization and that the blood glucose level-independent beneficial actions of insulin, which were attributed to the insulin sensitizer, might be operative in septic mice. Of note, a recent study showed that the severity of insulin resistance is associated with the severity of critical illness, although no significant association was found between insulin resistance and basal blood glucose levels (15). Second, the impact of NF- κ B inhibition on survival was modest, although it was statistically significant. This could in part be explained by the absence of overt hyperglycemia and/or modest insulin sensitization in the mice, as reflected by mild amelioration of hyperinsulinemia. Alternatively, this result might be attributable to the choice of NF- κ B inhibitor used in this study. Anti-inflammatory strategies, such as using antagonists of tumor necrosis factor- α , failed to show the efficacy in septic patients in clinical trials, conceivably because inflammatory responses are necessary to combat pathogenic microorganisms in critically ill patients despite the toxic effects of hyperinflammation. Furthermore, NF- κ B functions as a major antiapoptotic mechanism in cells. Recent studies indicate that apoptosis of immune cells or in other tissues confers increased susceptibility to infection and exacerbates organ dysfunction, which in turn lead to increased mortality in sepsis. Taken together, these findings suggest that anti-inflammatory and proapoptotic actions of NF- κ B inhibition might hamper the prosurvival effects of insulin sensitization in septic mice. It is worth testing the effects of insulin sensitizers other than NF- κ B inhibitors in rodent models of SIH. For example, Sirt1, the mammalian homolog of the yeast longevity gene, may be a potential target for improving survival in patients with SIH in the ICU. Activation of Sirt1 reverses insulin resistance in mouse models of obesity and type 2 diabetes (16) and confers stress

resistance in a number of pathologic states, including neurodegeneration and heart failure (17). A clinical trial has just been started that will test the efficacy and safety of resveratrol, a Sirt1 activator, for the treatment of patients with type 2 diabetes. Regardless of the potential pitfalls and limitations, the present study by Dr. Matsuda and colleagues (13) opens a new avenue of investigation for determining whether insulin sensitization, which targets the root problem of SIH, insulin resistance, and helps avoid severe hypoglycemia and hyperinsulinemia, is a viable alternative strategy to the current IIT for reducing mortality in ICU patients with SIH. Key questions that need to be addressed in future preclinical studies include these: What type of insulin sensitizer is more effective in promoting survival in animal models of SIH? What factors can we find that will serve as surrogate markers of the glucose-independent beneficial and adverse actions of insulin? Which conditions are the best targets of insulin sensitization: sepsis, trauma, or major surgery? Investigations of the relation between insulin dosage (and plasma insulin concentrations) and outcome of IIT in future clinical studies and *post hoc* analysis of previous studies should provide important and useful information on future development of glycemic care in the ICU.

Masao Kaneki, MD, PhD
Shohei Shinozaki, PhD

Department of Anesthesia and
Critical Care
Massachusetts General
Hospital
Harvard Medical School
Charlestown, Massachusetts

Kyungho Chang, MD, PhD
Department of Anesthesia and
Pain Relief Center
Graduate School of Medicine
University of Tokyo
Tokyo, Japan
Nobuyuki Shimizu, MD, PhD
Department of Gastrointestinal
Surgery
Graduate School of Medicine
University of Tokyo
Tokyo, Japan

REFERENCES

- van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001; 345:1359–1367
- 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
- Finfer S, Chittock DR, Su SY, et al: Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; 360:1283–1297
- Griesdale DE, de Souza RJ, van Dam RM, et al: Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ* 2009; 180:821–827; discussion 799–800
- Wiener RS, Wiener DC, Larson RJ: Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA* 2008; 300:933–944
- Inzucchi SE, Siegel MD: Glucose control in the ICU: how tight is too tight? *N Engl J Med* 2009; 360:1346–1349
- Balasubramanyam A: Intensive glycemic control in the intensive care unit: promises and pitfalls. *J Clin Endocrinol Metab* 2009; 94:416–417
- Kaneki M, Sakai M, Shimizu N, et al: Is normalized mean blood glucose level good enough for the intensive care unit?—glycemic variability as a new independent predictor of mortality. *Crit Care Med* 2008; 36:3104–3106
- Krinsley JS: Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med* 2008; 36:3008–3013
- Egi M, Bellomo R, Stachowski E, et al: Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology* 2006; 105:244–252
- Jiang ZY, Lin YW, Clemont A, et al: Characterization of selective resistance to insulin signaling in the vasculature of obese Zucker (fa/fa) rats. *J Clin Invest* 1999; 104:447–457
- Sugita H, Kaneki M, Sugita M, et al: Burn injury impairs insulin-stimulated Akt/PKB activation in skeletal muscle. *Am J Physiol Endocrinol Metab* 2005; 288:E585–E591
- Matsuda N, Yamamoto S, Yokoo H, et al: Nuclear factor-kappaB decoy oligodeoxynucleotides ameliorate impaired glucose tolerance and insulin resistance in mice with cecal ligation and puncture-induced sepsis. *Crit Care Med* 2009; 37:2791–2799
- Martyn JA, Kaneki M, Yasuhara S: Obesity-induced insulin resistance and hyperglycemia: etiologic factors and molecular mechanisms. *Anesthesiology* 2008; 109:137–148
- Zauner A, Nimmerrichter P, Anderwald C, et al: Severity of insulin resistance in critically ill medical patients. *Metabolism* 2007; 56:1–5
- Milne JC, Lambert PD, Schenk S, et al: Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes. *Nature* 2007; 450:712–716
- Hsu CP, Odewale I, Alcendor RR, et al: Sirt1 protects the heart from aging and stress. *Biol Chem* 2008; 389:221–231

Lactate: Finally ready for prime time?*

Lactate has been around for a while. To put that comment in perspective—by the end of the Battle of Stalingrad in World War II, we had been measuring lactate in

human sepsis for 100 yrs (1). Why, then, should we pay attention to the study by Dr. Jansen and colleagues (2) in the current issue of *Critical Care Medicine*, in which they report on a Health Technology Assessment of lactate monitoring in the critically ill? If the only contribution were its focused, succinct, and accessible discussion of the sometimes intimidating quantity of literature about nonhypoperfusion-related causes of lactic acidosis (alkalemia, issues with pyruvate dehydrogenase, liver dysfunction, medications, and even beriberi, among others), it

would be worth reading. However, the article's real contribution is something substantially more.

What Is Health Technology Assessment?

Health Technology Assessment may well be unfamiliar to many intensive care unit practitioners, particularly in the United States. What is it? There are many definitions, but the National Information Center on Health Services Research and Health Care Technology offers this defi-

*See also p. 2827.

Key Words: lactate; lactic acid; health technology assessment; sepsis; occult hypoperfusion

The author has not disclosed any potential conflicts of interest.

Copyright © 2009 by the Society of Critical Care Medicine and Lippincott Williams & Wilkins

DOI: 10.1097/CCM.0b013e3181ad79ca

nition: “the systematic evaluation of properties, effects, and/or impacts of health care technology. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policy-making in health care” (3).

Health Technology Assessment is often used by national health systems to help guide decisions on wide-ranging policy issues (4–6). The best known such system that frequently uses this kind of assessment may well be the United Kingdom’s National Institute for Health and Clinical Excellence (NICE) (4). The study by Dr. Jansen et al does not provide guidance for this kind of national policy decision-making, but it does begin to provide the framework for future efforts. Furthermore, it is clear that there are many approaches to performing Health Technology Assessments (5) and that local-level policy decisions are appropriate uses of this type of analysis (6).

Why Now?

The study by Dr. Jansen and colleagues comes at a particularly opportune time for three reasons. First, although lactate has been used for many years, until recently studies were often of fairly small size. The past 5 yrs, however, have seen dramatically larger sample sizes in studies of the prognostic utility of lactate; they have also enrolled a broader range of patients (7–13). This provides markedly greater confidence in the authors’ conclusions that lactate provides important risk stratification and prognostic information than could have been attained as recently as 2005. Second, lactate is now commonly used to guide entry into sepsis therapy protocols and is even monitored as a quality indicator for sepsis care (14). Third, as part of an approach to national healthcare reform, the new U.S. Presidential administration has clearly laid out comparative effectiveness research, an important component of Health Technology Assessment as a major national priority (15).

What Did We Learn?

Dr. Jansen et al provide a synthesis of >150 lactate-related studies gathered using an explicit and transparent search strategy. Their conclusions are remarkably concise: 1) lactate measurement is technically reliable (even though it has complex metabolism that can cloud interpretation);

2) it should be directly measured, not calculated from other laboratory values; 3) lactate provides key diagnostic and prognostic information; 4) it can alter provider behavior; and 5) it is likely to be applicable to many critically ill patients in many settings.

What’s Next?

Equally important, Dr. Jansen et al point out what we do not know. First, no studies address lactate’s cost-effectiveness. More importantly, however, is the question of whether lactate can be used to guide resuscitation. Although it is clear that lactate is an important risk stratifier, there are only observational data supporting lactate as a resuscitation end point outside of the cardiac surgical setting. It is hard to overstate the importance of this: We do not yet know if therapies that can cause lactate to decrease will be associated with improved outcomes. There are outstanding reasons to think that a lactate-guided resuscitation protocol might work as well as—or better than—current resuscitative strategies. But, given all that we have learned with surrogate end points in other aspects of critical care (suppressing premature ventricular contractions with lidocaine, generalizing tight glycemic control to septic patients, transfusing to a hemoglobin of >10 mg/dL, ventilating patients with acute respiratory distress syndrome with a goal of keeping the blood gas normal, etc.), we need to wait for more definitive data before assuming that it is correct just because it makes sense.

Fortunately, at least two randomized controlled trials are underway that address this issue (clinicaltrials.gov #NCT00270673 and #NCT00372502) (available at <http://clinicaltrials.gov/ct2/show/NCT00270673> and <http://clinicaltrials.gov/ct2/show/NCT00372502>). One trial focuses on a range of intensive care unit patients; the other trial focuses on patients with severe sepsis and septic shock. These will provide the first evidence of the safety and efficacy of lactate-guided resuscitation in a broad array of critically ill patients, and—like Dr. Jansen and colleagues—I eagerly await the answer.

Michael D. Howell, MD, MPH
Silverman Institute for
Healthcare Quality and
Safety
Beth Israel Deaconess
Medical Center
Harvard Medical School
Boston, MA

REFERENCES

1. Kompanje EJ, Jansen TC, van der Hoven B, et al: The first demonstration of lactic acid in human blood in shock by Johann Joseph Scherer (1814–1869) in January 1843. *Intensive Care Med* 2007; 33:1967–1971
2. Jansen TC, Bommel Jv, Bakker J: Blood lactate monitoring in critically ill patients: A systematic Health Technology Assessment. *Crit Care Med* 2009; 37:2827–2838
3. National Information Center on Health Services Research and Health Care Technology. HTA 101: Glossary. 08 September 2008. Available at <http://www.nlm.nih.gov/nichsr/hta101/ta101014.html>. Accessed 20 March 2009
4. Hawkes N: Health Technology Assessment. NICE goes global. *BMJ* 2009; 338:b103. doi: 10.1136/bmj.b103.
5. Teerawattananon Y, Chaikledkaew U: Thai health technology assessment guideline development. *J Med Assoc Thai* 2008; 91(Suppl 2):S11–S15
6. Goodman CS: HTA 101: Introduction to Health Technology Assessment: National Information Center on Health Services Research and Health Care Technology 2004. Available at <http://www.nlm.nih.gov/nichsr/hta101/hta101.pdf>. Accessed 20 March 2009
7. Shapiro NI, Howell MD, Talmor D, et al: Serum lactate as a predictor of mortality in emergency department patients with infection. *Ann Emerg Med* 2005; 45:524–528
8. Pal JD, Victorino GP, Twomey P, et al: Admission serum lactate levels do not predict mortality in the acutely injured patient. *J Trauma* 2006; 60: 583–587; discussion 587–589
9. Paladino L, Sinert R, Wallace D, et al: The utility of base deficit and arterial lactate in differentiating major from minor injury in trauma patients with normal vital signs. *Resuscitation* 2008; 77:363–368
10. Howell MD, Donnino M, Clardy P, et al: Occult hypoperfusion and mortality in patients with suspected infection. *Intensive Care Med* 2007; 33:1892–1899
11. Trzeciak S, Dellinger RP, Chansky ME, et al: Serum lactate as a predictor of mortality in patients with infection. *Intensive Care Med* 2007; 33:970–977
12. Dunne JR, Tracy JK, Scalea TM, et al: Lactate and base deficit in trauma: does alcohol or drug use impair their predictive accuracy? *J Trauma* 2005; 58:959–966
13. Martin MJ, FitzSullivan E, Salim A, et al: Discordance between lactate and base deficit in the surgical intensive care unit: Which one do you trust? *Am J Surg* 2006; 191: 625–630
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
15. Pear R: U.S. to compare medical treatments. *New York Times* [16 February 2009. Available at <http://www.nytimes.com/2009/02/16/health/policy/16health.html>.