Intensive care unit occupancy: Making room for more patients*

Monday, March 30, 1981 was the last day of my week on clinical call. It had been a busy weekend and all the intensive care unit (ICU) beds were full. Because three patients were ready for floor transfer and only two patients were scheduled for admission, one bed would be available later in the day. Monday's normal routine was suddenly interrupted by a TV news announcement—President Ronald Reagan had been shot at 2:30 PM. We soon heard that the President, his Press secretary, James Brady, and a Secret Service agent, Tim McCarthy, were in our emergency department.

Even with no clinical information, it never occurred to me that they would not be coming to the ICU. A discussion with the ICU nurse manager and Associate Director of Critical Care Nursing led to a list of potential ICU admissions and discharges. We also made arrangements for the care of patients who would be admitted, remain in ICU, or be discharged with special care needs. Under these circumstances, the efficiency of ICU discharge was unprecedented and our terrific staff ensured that nursing resources were practically unlimited.

Agent McCarthy was admitted to the ICU in stable condition after successful repair of a liver injury at 7:30 PM, but we heard nothing about the President. I called the recovery room and was told that the President had been there for an hour and had some disturbing blood gas results. I spent the night there providing him with respiratory care, while my colleague Bill Knaus cared for James Brady in the ICU, who had undergone a surgery for severe brain injury. The President's low Pa_{O_2} was due to blood in his airways and loss of lung volume, which quickly responded to suctioning and lung reexpansion. He was extubated at 2:30 AM, transferred to ICU at 6:15 AM, and was stable throughout his 12-hour ICU stay.

ICU clinicians know it is not unusual for a day to begin at full unit capacity and end with even higher occupancy. Beyond caring for the President, his Press secretary, and a Secret Service agent, what was unusual about the events described earlier was having practically unlimited nursing resources and an extremely efficient discharge process. In my 30 years in intensive care, I was more accustomed to begging nurses to work overtime, to perform a discharge process more difficult than "pulling teeth," and to stretching assignments to care for more patients. Sometimes we had to "board" patients in alternative locations, and occasionally requested that ambulances be rerouted or surgery cancelled because there were no more beds and nurses.

An increased patient load was a major cause of anxiety. Could we obtain sufficient resources to care for more patients? Will staff "burnout" be aggravated by the increased workload? Will admitting more patients compromise the quality of care? In this issue of *Critical Care Medicine*, Iwashyna et al (1) provide a reassuring answer to the latter question. In 108 ICUs at 46 hospitals, consistent patient mortality was maintained, despite an unusually high census on the day of admission. These ICUs were able to cope with a census that ranged from 65% to 147% of their mean daily census for a single day or as long as 2 weeks. They also found that census fluctuations had little impact on ICU stay and the rate of transfer to other hospitals.

It is comforting to know we are likely to maintain consistent outcomes when we "play musical beds" or "stretch the staff" or stated more politely, safely scale up operations to meet operating conditions. The scaling up of care capabilities in preparation for admitting President Regan, Press secretary Brady, and Agent McCarthy represents an extreme example, and I had never thought of this often painful process as the functioning of a "high-reliability organization." But I do feel that ICU physicians and nurses are often negatively impacted when workload is markedly increased and sustained. The literature on ICU burnout supports this opinion (2–4).

Iwashyna et al (1) state that their study "implies, but does not prove, the viability of regionalization strategies." The authors of the study have previously published convincing evidence about the potential value of regionalization and improved outcomes in association with concentrating patients in high-volume hospitals (5–7). I urge caution, however, in using this study to support regionalization.

There are several reasons why this study might not support regionalization: First, the study hospitals and ICUs are probably not representative of US ICUs. In addition, the study included nonteaching (34%) and small teaching hospitals (28%), institutions that are unlikely to be high-volume centers of excellence or referral hospitals. Second, the ability to successfully adjust to high occupancy for 1–14 days does not mean that caregivers could do this permanently. Third, the study did not address the ability to respond to the demands of regionalization. Additional ICU beds, professional staff, and financial resources might not be available to meet the demands of increased patient referral. Finally, the authors provide no data that identify the structural and managerial mechanisms used by these ICUs to meet these temporary increases in care demand.

All studies have limitations, but the take-home message of this one is pleasing. When faced with the need to scale up operations to meet increased patient demands, ICUs maintain consistent patient mortality and operate as high-reliability organizations. This conclusion is well supported and is good news.

Jack E. Zimmerman, MD, FCCM
Department of Anesthesia and Critical Care Medicine
The George Washington University
Washington, DC
Cerner Corporation
Vienna, VA

***See also p. 1545.**

Key Words: intensive care; patient outcome assessment; mortality; burnout; workload

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REFERENCES

1. Iwashyna TJ, Kramer AA, Kahn JM: Intensive care unit occupancy and patient outcomes. *Crit Care Med* 2009; 37:1545–1557
2. Embriaco N, Azoulay E, Barrau K, et al: High level of burnout in intensivists: Prevalence and associated factors. *Am J Respir Crit Care Med* 2007; 175:686–692
3. Poncet MC, Toullic P, Papazian L, et al: Burnout syndrome in critical care nursing staff. *Am J Respir Crit Care Med* 2007; 175:698–704
4. Stone PW, Larson EL, Mooney-Kane C, et al: Organizational climate and intensive care unit nurses' intention to leave. *Crit Care Med* 2006; 34:1907–1912
5. Kahn JM, Linde-Zwirble WT, Wunsch H, et al: Potential value of regionalized intensive care for mechanically ventilated medical patients. *Am J Respir Crit Care Med* 2008; 177:285–291
6. Kahn JM, Goss CH, Heagerty PJ, et al: Hospital volume and the outcomes of mechanical ventilation. *New Engl J Med* 2006; 355: 41–50
7. Barnato AE, Kahn JM, Rubenfeld GD, et al: Prioritizing the organization and management of intensive care services in the United States. The PrOMIS Conference. *Crit Care Med* 2007; 35:1003–1006

Profiling pediatric sepsis*

"There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we do not know. But there are also unknown unknowns. There are things we do not know we do not know." This quotation by Donald Rumsfeld (the former Secretary of Defense) is applicable not only to the subject Mr. Rumsfeld was discussing, but also to our understanding of the pathophysiology of the sepsis syndrome from systemic inflammatory response syndrome to septic shock. While we would like to think that we know much about the biology and pathophysiology of complex diseases, such as the sepsis syndrome, and that we know the areas where we need additional information to fill in the details, it seems as although there is still much that falls into the category of "unknown unknowns." Indeed, revealing those "unknown unknowns" is likely to generate new areas of research with potential for the development of novel therapies.

The sepsis syndrome is an exceedingly complex clinical syndrome. It exists as a continuum from minimal systemic inflammatory response syndrome manifested by fever and tachycardia to septic shock. Several complex molecular and cellular processes are involved that contribute to the clinical syndrome, including activation of the inflammatory and coagulation pathways, disruption of vascular integrity, and apoptosis. Many other processes and pathways are also activated and/or deactivated, some are known, others we have yet to imagine.

Over the past couple of decades, advances in molecular biology and biochemistry, as well as bioinformatics, have provided important tools to better understand complex human diseases. These tools have also allowed for the discovery of processes not previously thought to play important roles in disease. One such tool, genome-wide expression microarrays, has been used to examine the expression of all genes within the genome. In this issue of *Critical Care Medicine*, Wong et al (1) use this tool to examine genes that are up-regulated and down-regulated in children with varying degrees of the sepsis syndrome, from systemic inflammatory response syndrome to septic shock. The authors' aim was to determine whether there are expression signatures that are specific to septic shock. Their data demonstrate that septic shock seems to be uniquely characterized by a decreased expression both in genes involved in zinc-related biology and in genes involved in adaptive immunity-specific signaling pathways. There were also expression signatures common across the systemic inflammatory response syndrome to septic shock spectrum of the sepsis syndrome. Such signatures were primarily characterized by increased expression of genes involved in inflammation and innate immunity.

Before this and previous studies of Wong et al using an expression profiling, the possibility that proteins involved in zinc biology were associated with septic shock was not considered, it was one of the "unknown unknowns." However, now that these studies have pointed the field in this direction, it almost seems obvious that this group of proteins could be involved with septic shock. Zinc is considered to be an essential trace element for the immune system, and deficiencies in zinc can result in immune system dysfunction, most notable in acrodermatitis enteropathica, a zinc malabsorption syndrome (2). Zinc deficiency is also known to result in decreased antibody formation, natural killer cell killing activity, and lower levels of phagocytosis and intracellular killing by granulocytes, monocytes, and macrophages (3). In addition, zinc blunts the inflammatory cascade and protects against lipopolysaccharide-induced shock and liver injury in animal models (4, 5).

There are many genes involved in zinc-related biology that could be crucial players in septic shock, but the data on the degree of their involvement are largely lacking. Previous reports by Wong et al have demonstrated that in pediatric patients with septic shock two isoforms of metallothionein (intracellular metal-binding proteins that bind zinc) are up-regulated in nonsurvivors compared with survivors. Consistent with an increase in the expression of metallothionein, serum zinc levels are significantly lower in nonsurviving children of septic shock compared with survivors (6). In addition, in the mouse cecal ligation and puncture model of sepsis, metallothionein null mice have a significant survival advantage compared with wild-type mice (6). These studies suggest that zinc levels may impact survival in pediatric patients with septic shock.

In some instances, zinc is also an important trace element in bacterial pathogens (7). Zinc metalloproteases have been reported to be virulence factors for *Streptococcus pneumoniae* (8), *Pseudomonas aeruginosa*, *Legionella pneumophila* (9), and *Streptococcus suis* 2 (10), a strain noted for outbreaks of toxic shock syn-

***See also p. 1558.**

Key Words: sepsis; pediatrics; expression profiles; zinc

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drome in China in 1998 and 2005. Consequently, it will be of interest to determine whether the association of zinc levels in patients correlates with survival in sepsis with various bacterial etiologies.

In summary, the current study of Wong et al characterizes expression profiles in children with varying degrees of the sepsis syndrome and indicates that septic shock is characterized by decreased expression in genes involved in zinc-related biology and in adaptive immunity. The impact of this work relates not only to identifying novel pathways and genes involved in septic shock as a way to identify novel targets for therapeutics, but it may also help identify potential markers for disease severity in children with sepsis. Ultimately, this information will further our understanding of sepsis by converting the "unknown unknowns" into "known unknowns" and eventually "known knowns."

Mary K. Dahmer, PhD
Michael W. Quasney, MD, PhD
Division of Pediatric Critical Care
Department of Pediatrics
Medical College of Wisconsin and the Children's Research Institute
Children's Hospital of Wisconsin
Milwaukee, WI

REFERENCES

1. Wong HR, Cvijanovich N, Allen GL, et al: Genomic expression profiling across the pediatric systemic inflammatory response syndrome, sepsis, and septic shock spectrum. *Crit Care Med* 2009; 37:1558–1566
2. Kury S, Dreno B, Bezieau S, et al: Identification of SLC39A4, a gene involved in acrodermatitis enteropathica. *Nat Genet* 2002; 31:239–240
3. Rink L, Haase H: Zinc homeostasis and immunity. *Trends Immunol* 2007; 28:1–4
4. Snyder SL, Walker RI: Inhibition of lethality in endotoxin-challenged mice treated with zinc chloride. *Infect Immun* 1976; 13: 998–1000
5. Zhou Z, Wang L, Song Z, et al: Abrogation of nuclear factor-kappaB activation is involved in zinc inhibition of lipopolysaccharide-induced tumor necrosis factor-alpha production and liver injury. *Am J Pathol* 2004; 164: 1547–1556
6. Wong HR, Shanley TP, Sakthivel B, et al: Genome-level expression profiles in pediatric septic shock indicate a role for altered zinc homeostasis in poor outcome. *Physiol Genomics* 2007; 30:146–155
7. Chimienti F, Aouffen M, Favier A, et al: Zinc homeostasis-regulating proteins: New drug targets for triggering cell fate. *Curr Drug Targets* 2003; 4:323–338
8. Blue CE, Paterson GK, Kerr AR, et al: ZmpB, a novel virulence factor of *Streptococcus pneumoniae* that induces tumor necrosis factor alpha production in the respiratory tract. *Infect Immun* 2003; 71:4925–4935
9. Hase CC, Finkelstein RA: Bacterial extracellular zinc-containing metalloproteases. *Microbiol Rev* 1993; 57:823–837
10. Feng Y, Li M, Zhang H, et al: Functional definition and global regulation of Zur, a zinc uptake regulator in a *Streptococcus suis* serotype 2 strain causing streptococcal toxic shock syndrome. *J Bacteriol* 2008; 190: 7567–7578

Magic bullets and surrogate biomarkers circa 2009*

With the discovery almost 25 years ago that administration of tumor necrosis factor-α could produce shock and tissue injury similar to severe sepsis, the fundamental role for cytokines in experimental sepsis was established (1, 2) The dramatic improvement in survival, first seen in mice and then confirmed in primates with bacteremic shock, produced simply by inhibiting a single cytokine (3, 4), resulted in unbridled optimism that sepsis mortality in hospitalized patients could be dramatically reduced. This outlook pervaded the collective conscious for well over two decades, spawned a sundry of biological inhibitors, tested in a multitude of human clinical trials, all with the goal of recapitulating the survival benefit imparted by these "magic bullets" in preclinical animal models (5). Unfortunately, these efforts consumed an enormous amount of energy and financial resources, and demonstrated only minimal benefit to the treatment of human sepsis. Fortunately, the past decade has been spent in self-evaluation (some might also say self-denial), asking why such therapies have not yielded the clinic successes observed with preclinical models. Only now are we beginning to understand the complexity of human sepsis and the limits of our preclinical models (6).

In this issue of *Critical Care Medicine*, Osuchowski and co-workers (7) argue that although most antisepsis therapies, in general, and anticytokine therapies, in particular, have failed in severe sepsis clinical trials, the challenge has been to prospectively identify individuals who might benefit from such therapies (5). There is little disagreement that what we call "severe sepsis" is presently so poorly defined that our study populations are too broadly heterogenous to optimize drug efficacy. There is a strong precedent to suggest that anti-inflammatory therapies, in general, and anticytokine therapies, in particular, are most effective in the sickest individuals at the highest risk(s) of mortality. In a large meta-analysis including both preclinical and clinical studies, Eichacker et al (8) demonstrated a linear relationship between anti-inflammatory drug efficacy and overall mortality in the placebo groups. How then do we better identify prospectively those patients with severe sepsis who may benefit from such targeted therapies? Do surrogate biomarkers exist that can prospectively identify individuals who would benefit from such therapies?

Osuchowski et al has previously shown that even individual outbred mice subjected to a reproducible cecal ligation and puncture manifest a broad range of survival responses, but mortality could be predicted by their early circulating interleukin (IL)-6 concentration (9, 10). In this report, the investigators use the same stratification system to demonstrate that only mice predicted to die based on their IL-6 concentration responded favorably to goal-directed early

*See also p. 1567.

Key Words: biomarkers; sepsis; corticosteroids; IL-6; mortality

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supraphysiologic dexamethisone. In a 21st century landscape tainted by the history of earlier failed therapeutic interdiction (11), the authors should be applauded for their demonstration that early stratification based on circulating IL-6 levels can guide corticosteroid therapy to improve survival. Equally important, the authors demonstrate that the entire septic mouse cohort and the cohort of mice predicted to survive based on their plasma IL-6 concentrations gained no survival benefit from corticosteroid therapy. Thus, the authors have emphasized the challenges and shortcomings of past trials aimed at empirical treatment of poorly defined, heterogenous septic cohorts (5, 11).

Although the authors have provided convincing evidence that targeted therapies based on IL-6 concentrations can identify cohorts that might benefit from steroid therapies in a murine model of polymicrobial peritonitis, a number of perplexing questions remain. These studies were performed in a model of generalized peritonitis; however, different findings have been witnessed in a murine pneumonia model. Li et al (12) reported that corticosteroid therapies were broadly beneficial in a murine *Escherichia coli* model, regardless of the severity of the initial infection, and the steroids significantly lowered the plasma IL-6 concentrations across the board.

These latter findings are again different than those observed by Osuchowski and co-workers (6). In this report, the authors hypothesized that septic mice succumb to an early overwhelming systemic inflammatory response, which the authors believe may be ameliorated by strategic corticosteroid administration. Surprising was the fact that although early targeted corticosteroid therapy improved outcome, it had little impact on the circulating levels of IL-6, tumor necrosis factor-α, IL-1β, IL-2, macrophage inflammatory protein-1α, macrophage inflammatory protein-2, keratinocyte-derived cytokine, and monocyte chemoattractant protein-1, all bona fide inflammatory mediators, many with prognostic value in themselves. In addition, no significant reduction was observed on circulating numbers of neutrophils, platelets, or lymphocytes as is a common effect of corticosteroids and was observed earlier (13).

Although the authors present a rational, well-considered approach to use IL-6 as a prognosticator that highly predicts early mortality in their model, and a potential 29% survival benefit from corticosteroids, the fact remains that individual animal models are rather poor surrogates for human sepsis (5, 11, 14, 15). Even though the cecal ligation and puncture model was used to replicate human peritoneal sepsis (and to many represents the "gold standard"), there are numerous intangibles such as preexisting comorbidities, age, continuous fluid resuscitation, nutritional support, guided antibiotic therapy, and operative intervention that make human sepsis more complex, and routinely difficult to replicate in mice (16). Juxtaposed with the murine vs. human sepsis conundrum stands the mortality disparity between the cecal ligation and puncture model, which was 50% across the board and 90% in the group that showed benefit, compared with an overall mortality of approximately 25% in humans (14, 17, 18). It would be interesting to know whether a more modest (LD_{20}) model of murine sepsis (19) would yield as strong a sensitivity and specificity index for predicting 48-hour mortality, and whether the mice predicted to die would experience as great an improvement in survival from steroids. In a large clinical trial in severe sepsis with anti-tumor necrosis factor therapies using plasma IL-6 as an entry criterion, the study showed an 11% relative reduction in morbidity ($p = 0.041$) with anti-tumor necrosis factor antibodies in patients with elevated IL-6 concentrations (20). In patients with an elevated IL-6 level, placebo mortality was nearly 48%. It should be noted, however, that a smaller earlier study could not confirm these results (21).

Considering the current state-of-the-art medical care, and evidence-based protocol-driven practices employed in most tertiary referral centers, the dilemma experienced by practicing clinicians is not to improve 50% but to prevent 20% mortality. This translates into a higher cost in man hours and financial resources per percentage point of survival gained (5, 18). Indeed, the ability to predict, based on IL-6 responses or some other surrogate marker, which subjects will succumb early to sepsis would be invaluable; however, given the variable etiology of sepsis and the individuals experiencing the syndrome, early identification is unfortunately dependent on multiple circumstances that typically remain far from clinician control, and difficult to summarize with a single biological prognosticator (14).

Matthew J. Delano, MD, PhD
Lyle L. Moldawer, PhD
Department of Surgery
University of Florida
College of Medicine
Gainesville, FL

REFERENCES

1. Kawakami M, Cerami A: Studies of endotoxin-induced decrease in lipoprotein lipase activity. *J Exp Med* 1981; 154:631–639
2. Carswell EA, Old LJ, Kassel RL, et al: An endotoxin-induced serum factor that causes necrosis of tumors. *Proc Natl Acad Sci U S A* 1975; 72:3666–3670
3. Tracey KJ, Fong Y, Hesse DG, et al: Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. *Nature* 1987; 330:662–664
4. Beutler B, Milsark IW, Cerami AC: Passive immunization against cachectin/tumor necrosis factor protects mice from lethal effect of endotoxin. *Science* 1985; 229:869–871
5. Natanson C, Esposito CJ, Banks SM: The sirens' songs of confirmatory sepsis trials: Selection bias and sampling error. *Crit Care Med* 1998; 26:1927–1931
6. Riedemann NC, Guo RF, Ward PA: Novel strategies for the treatment of sepsis. *Nat Med* 2003; 9:517–524
7. Osuchowski MF, Connett J, Welch K, et al: Stratification is the key: Inflammatory biomarkers accurately direct immunomodulatory therapy in experimental sepsis. *Crit Care Med* 2009; 37:1567–1573
8. Eichacker PQ, Parent C, Kalil A, et al: Risk and the efficacy of antiinflammatory agents: Retrospective and confirmatory studies of sepsis. *Am J Respir Crit Care Med* 2002; 166:1197–1205
9. Remick DG, Bolgos GR, Siddiqui J, et al: Six at six: Interleukin-6 measured 6 h after the initiation of sepsis predicts mortality over 3 days. *Shock* 2002; 17:463–467
10. Osuchowski MF, Welch K, Yang H, et al: Chronic sepsis mortality characterized by an individualized inflammatory response. *J Immunol* 2007; 179:623–630
11. Deans KJ, Haley M, Natanson C, et al: Novel therapies for sepsis: A review. *J Trauma* 2005; 58:867–874
12. Li Y, Cui X, Li X, et al: Risk of death does not alter the efficacy of hydrocortisone therapy in a mouse E. coli pneumonia model: Risk and corticosteroids in sepsis. *Intensive Care Med* 2008; 34:568–577
13. Prigent H, Maxime V, Annane D: Clinical review: Corticotherapy in sepsis. *Crit Care* 2004; 8:122–129
14. Hotchkiss RS, Karl IE: The pathophysiology and treatment of sepsis. *N Engl J Med* 2003; 348:138–150
15. 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
16. Deitch EA: Animal models of sepsis and shock: A review and lessons learned. *Shock* 1998; 9:1–11
17. 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
18. Angus DC, Linde-Zwirble WT, Lidicker J, et al: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29:1303–1310
19. Delano MJ, Scumpia PO, Weinstein JS, et al: MyD88-dependent expansion of an immature GR-1+CD11b+ population induces T cell suppression and Th2 polarization in sepsis. *J Exp Med* 2007; 204:1463–1474
20. Reinhart K, Menges T, Gardlund B, et al: Randomized, placebo-controlled trial of the anti-tumor necrosis factor antibody fragment afelimomab in hyperinflammatory response during severe sepsis: The RAMSES Study. *Crit Care Med* 2001; 29: 765–769
21. Panacek EA, Marshall JC, Albertson TE, et al: Efficacy and safety of the monoclonal anti-tumor necrosis factor antibody F(ab')2 fragment afelimomab in patients with severe sepsis and elevated interleukin-6 levels. *Crit Care Med* 2004; 32:2173–2182

Acute respiratory distress syndrome and the *Art of War**

If you know the enemy and know yourself, you need not fear the result of a hundred battles.
If you know yourself but not your enemy, for every victory gained you will also suffer a defeat.
If you know neither the enemy nor yourself, you will succumb in every battle.
Sun Tzu, The Art of War, 6th century BC

Knowingly or unknowingly, in the fight against any disease, clinicians and researchers often apply age-old principles adapted from Sun Tzu's classic, the *Art of War*, the best-known of which reads, "*know the enemy and know yourself*" (1). The Acute Respiratory Distress Syndrome (ARDS) Network's 15-year battle is no exception, and the enemy—ARDS and acute lung injury (ALI)—cannot be underestimated. The defining article on ARDS by Ashbaugh et al (2) in 1967 introduced us to a highly lethal clinical entity; seven of their 12 patients died. There has since been some cause for optimism. Several observational studies documented a decrease in mortality from the 1980s to the mid-1990s, but their generalizability was limited given their single-center nature (3, 4). Enter the ARDS Network in 1994, and its multicenter randomized controlled trials (RCTs) documented mortality rates markedly lower than previous figures—in the 25% to 40% range (5–7). These observations led to hopeful assertions that mortality from ALI/ARDS has decreased over time (8). The all-important question, nevertheless, remains: do we have objective evidence of such a decrease, and if so, what are the contributory factors? In other words, are we winning the war, and if so, do we now know the enemy, or ourselves, or both?

In this issue of *Critical Care Medicine*, Erickson et al (9) present data that provide further insight into these questions. Mortality among 2,451 patients who were enrolled in three landmark ARDS Network trials was analyzed: the ARMA trial on delivered tidal volumes (5), the Assessment of Low tidal Volume and elevated End-expiratory volume to Obviate Lung Injury trial on positive and end-expiratory pressure (6), and the Fluid and Catheter Treatment Trial on fluid strategies and the pulmonary artery catheter (7). They found a significant trend for decreasing 60-day mortality over time from 1996 to 2005. This trend persisted on multivariable analysis, which adjusted for changes in case mix, disease severity, and receipt of low tidal volume ventilation. The authors concluded that "other advancements in critical care" apart from tidal volume limitation had contributed to the improvement in survival.

The study's findings are undeniably positive news for the critical care community. Are we finally winning the war on ALI/ARDS? Some caveats should be highlighted to allow a balanced interpretation of these results. First, although RCTs can lend themselves to many complex analyses because of the rich datasets available for each included patient, we must exercise caution when using them to make epidemiologic inferences because they generally represent only a highly selected subpopulation of all individuals affected with a disease or syndrome. Only consenting patients who met both the inclusion and exclusion criteria for these trials are included in the analysis. Indeed, these ARDS Network RCTs had at least 15 exclusion criteria each—many of which are associated with increased mortality—and excluded more than 90% of screened patients. Unfortunately, although these excluded patients had a higher mortality (10), information on their mortality trends is unavailable.

Second, the decline in mortality was predominantly restricted to the first 4 years (1996–1999) of the study period: 60-day crude mortality was 35%, 32%, 27%, 27%, and 26%, respectively, in the five 2-year time periods between 1996 and 2005. Changes in enrolment practices could have contributed to the dramatic 8% decrease in mortality between 1996 and 1999, although the temporal increase in Acute Physiology and Chronic Health Evaluation III scores argues against this. The bulk of the patients included during 1996–1999, when the large mortality reductions took place, were from the ARMA study, in which half of the population received higher tidal volumes of 12 mL/kg predicted body weight. However, in this specific case, the effects of high tidal volumes should have been accounted for in the multivariable analysis; it is known which pa-

***See also p. 1574.**

Key Words: acute respiratory distress syndrome; acute lung injury; randomized controlled trials; mortality

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tients were randomized to this group, and protocol adherence to lower tidal volume was good across all other groups. The authors hypothesized that "other advancements in critical care" led to the decrease in mortality, but the available data do not tell us just what these "other advancements" are. Tidal volume limitation remains the only intervention that has been convincingly shown to reduce mortality in ALI/ARDS (5), and even this is more a limitation of iatrogenic injury than a therapeutic intervention *per se*. Meanwhile, controversy surrounds other therapies for sepsis (a major cause of ALI/ARDS), including glucose control, human recombinant activated protein C, and corticosteroids (11).

What messages should we then take home from the findings of Erickson et al? The authors were rightly cautious to emphasize that their findings apply specifically to patients "treated at ARDS Network Centers." The improving trends suggest that patients with ALI/ARDS may benefit by being enrolled in an ARDS Network RCT. We can only speculate why this may be so. First, clinicians and researchers may have learnt more about the enemy over time, i.e., small tidal volumes can subdue the enemy. Second, clinicians and researchers may have learnt more about themselves over time, i.e., the ARDS Network centers may have steadily fine tuned their clinical and research infrastructure, thereby resulting in earlier case detection, better use of management bundles, such as early resuscitation, appropriate antibiotics, and sedation protocols (12), and/or they may have improved care simply through the experience of expert clinicians in centers with high volumes of patients with ALI.

The data of Erickson et al may be interpreted in light of two recent systematic reviews (including one from our group), which also dealt with mortality trends in ALI/ARDS (13, 14). While the first smaller review found a similar decline in mortality (13), when we evaluated 53 observational studies and 36 RCTs published between 1984 and 2006 (including the ARMA, Assessment of Low tidal Volume and elevated End-expiratory volume to Obviate Lung Injury, and Fluid and Catheter Treatment trials), we found a static mortality between 1994 and 2006, plus a significantly lower mortality in RCTs than observational studies.

Erickson et al must be applauded for shedding more light on this topic. They have clearly shown that outcomes among patients randomized in ARDS Network trials have improved over time. Yet, given the caveats we have highlighted, and in answer to our original question: no, we cannot say that we are winning the war on ALI/ARDS. We have come a long way in the last 40 years, however, we still do not know enough of this enemy that remains a mixed bag of heterogeneous disorders; and we do not yet know enough of our own armamentarium (8). The battle against this important clinical entity goes on.

Jason Phua, MBBS, MRCP(UK), EDIC
Division of Respiratory and Critical Care Medicine
Department of Medicine
National University Hospital
Singapore, Singapore
Joan R. Badia, MD, PhD
Hospital Clinic de Barcelona
IDIBAPS and CIBER de Enfermedades Respiratorias (CIBERES)
Barcelona, Spain
Niall D. Ferguson, MD, FRCPC, MSc
Interdepartmental Division of Critical Care and Department of Medicine
Division of Respirology
University Health Network and Mount Sinai Hospital
University of Toronto
Toronto, Canada

REFERENCES

1. Sun T: The Art of War. Translated by L. Giles. Special Edition. El Paso, El Paso Norte Press, 2007
2. Ashbaugh DG, Bigelow DB, Petty TL, et al: Acute respiratory distress in adults. *Lancet* 1967; 2:319–323
3. Milberg JA, Davis DR, Steinberg KP, et al: Improved survival of patients with acute respiratory distress syndrome (ARDS): 1983–1993. *JAMA* 1995; 273:306–309
4. Abel SJ, Finney SJ, Brett SJ, et al: Reduced mortality in association with the acute respiratory distress syndrome (ARDS). *Thorax* 1998; 53:292–294
5. The Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1301–1308
6. Brower RG, Lanken PN, MacIntyre N, et al; for the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004; 351: 327–336
7. National Heart Lung and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network: Comparison of two fluid-management strategies in acute lung injury. *N Eng J Med* 2006; 354:2564–2575
8. Wheeler AP, Bernard GR: Acute lung injury and the acute respiratory distress syndrome: A clinical review. *Lancet* 2007; 369:1553–1564
9. Erickson SE, Martin GS, Davis JL, et al: Recent trends in acute lung injury mortality: 1996–2005. *Crit Care Med* 2009; 37: 1574–1579
10. Suchyta MR, Morris AH, Thompson BT, et al: Attributes and outcomes of randomized vs excluded patients in ALI/ARDS clinical trials. *Am J Respir Crit Care Med* 2000; 161:A210
11. Ospina-Tascon GA, Buchele GL, Vincent JL: Multicenter, randomized, controlled trials evaluating mortality in intensive care: Doomed to fail? *Crit Care Med* 2008; 36: 1311–1322
12. 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
13. Zambon M, Vincent JL: Mortality rates for patients with acute lung injury/ARDS have decreased over time. *Chest* 2008; 133: 1120–1127
14. Phua J, Badia JR, Adhikari NK, et al: Has mortality from acute respiratory distress syndrome decreased over time? A systematic review. *Am J Respir Crit Care Med* 2009; 179: 220–227

Prolonged glucocorticoid treatment in acute respiratory distress syndrome: Evidence supporting effectiveness and safety*

In this issue of *Critical Care Medicine*, Tang et al (1) provide a systematic review and meta-analysis of nine controlled studies (n = 648) evaluating the effectiveness of prolonged glucocorticoid treatment (PGCT) in patients with acute lung injury and acute respiratory distress syndrome (ARDS) (2–10). These studies (Table 1) consistently report a significant improvement in Pa_{O_2}:Fi_{O_2} (2–10) and a significant reduction in markers of systemic inflammation (2–10), multiple organ dysfunction score (2, 5, 6, 8–10), duration of mechanical ventilation (2,4–6,10), and intensive care unit length of stay (2, 3, 5, 6, 10) (all with p values <0.05) without an increased rate of complications. The reduction in duration of mechanical ventilation is two- to three-fold greater than the reduction reported with low tidal volume ventilation or the conservative strategy of fluid management (11, 12). The more rapid resolution of lung injury and multiple organ dysfunction scores observed in these trials could positively affect long-term physical recovery (13) and survival (5). The relevance of these findings to public health and healthcare economics urges investment in clinical investigation of this inexpensive and highly effective anti-inflammatory therapy.

Because of differences in study design and patient characteristics and the limited size of the studies (1–4), the cumulative mortality summary should be interpreted with some caution. Nevertheless, all four studies (2–5) (n = 334) investigating treatment initiated within 3 days of meeting acute lung injury and ARDS criteria showed a significant reduction in mortality, with an overall 24% absolute reduction in mortality (risk ratio, 0.69; 95% confidence interval, 0.56–0.84). Two of the five studies (6, 9) investigating treatment initiated after 5–7 days of meeting ARDS criteria showed a significant reduction in mortality, whereas three studies (7, 8, 10) found no difference in mortality, with an overall 15% absolute reduction in mortality (risk ratio, 0.75; 95% confidence interval, 0.55–1.02) that increased to 19% for the larger subgroup of patients (n = 233) randomized before day 14 of ARDS (risk ratio, 0.65; 95% confidence interval, 0.45–0.94) (6, 8–10). In the three studies without a mortality benefit (7, 8, 10), treatment was associated with significant early physiologic improvement; however, rapid dosage reduction (8) or premature removal after extubation (as acknowledged by the authors) (10) might have affected final outcome. In the ARDS Network trial, the treated group had—before removal of treatment—a noteworthy 9.5 days' reduction in duration of mechanical ventilation ($p = 0.006$) (10). The ARDS Network trial reported a lower mortality for patients (n = 132) randomized before day 14 (27% vs. 36%; $p = 0.14$) and higher mortality for patients (n = 48) randomized after day 14 of ARDS (8% vs. 35%; $p = 0.01$) (10). The latter subgroup, however, had large imbalances in baseline characteristics and an uncharacteristically low mortality in the control group, and the mortality difference lost significance ($p = 0.57$) when adjusting for these imbalances (14, 15).

Treatment decisions involve a tradeoff between benefits on the one hand and risks, burdens, and, potentially, costs on the other (16). As an aggregate (n = 648), absolute and relative reduction in mortality is substantial for all patients (18% and 35%) and even greater when treatment is initiated before day 14 of ARDS (21% and 38%). While awaiting a larger confirmatory trial in early acute lung injury and ARDS, this meta-analysis provides evidence of a sizable reduction in duration of mechanical ventilation and intensive care unit stay and a considerable survival benefit with the potential saving of one life for every four treated patients (1). In the United States alone, this could translate to tens of thousands of lives saved per year and several billion dollars in reduced healthcare expenditures (17). Furthermore, the low cost of off-patent methylprednisolone—in the United States approximately $240 for 28 days of intravenous therapy (5)—makes this treatment globally and equitably available.

In their systematic review, Tang et al (1) report that PGCT at low-to-moderate doses was not associated with an increased rate of major complications, including infections and neuromyopathy. This counterintuitive finding deserves further elucidation and provides an opportunity to debunk common fallacies about glucocorticoid treatment-associated complications. Most misconceptions originate from the findings of sepsis and ARDS trials conducted in the 1980s that investigated a massive daily dose of glucocorticoids (methylprednisolone, up to 120 mg/kg/day) over a short time interval (24–48 hours). The experimental model supporting this treatment protocol relied on the intravenous administration of a lethal bolus of lipopolysaccharide that could be offset only by administering an equally massive dose of glucocorticoids before or within a brief experimentally generated inflammatory window (18–20). This experimental model did not replicate human sepsis or acute lung injury and was discredited in the early 1990s (18). Since then, longitudinal measurements of inflammatory cytokines in ARDS patients have clearly shown that significant systemic and pulmonary inflammation persists 28 days into the disease process (21–24) and that PGCT (14–21 days) followed by slow tapering is essential to achieve and sustain biological resolution of the disease process (21, 25).

In recent years, substantial evidence has accumulated showing that systemic inflammation, the central pathogenetic process in ARDS (21, 22, 24), is also implicated in the type of morbidity—

***See also p. 1594.**

Key Words: acute respiratory distress syndrome; complications; duration of mechanical ventilation; glucocorticoid treatment; infection; mortality

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Table 1. Prolonged glucocorticoid treatment in ALI-ARDS: Overall mortality, improvement in markers of systemic inflammation, gas exchange, duration of mechanical ventilation, and ICU stay

Study	Hospital Mortality[a]	Reduction in Inflammation	Improvement in PaO_2:FiO_2	Reduction in MV Duration	Reduction in ICU Stay
Early ALI-ARDS (n = 334)	38% vs. 62%	3 of 3	4 of 4	4 of 4	3 of 3
Confalonieri (2)	0.0% vs. 30%	Yes	Yes	Yes	Yes
Lee (3)	8% vs. 88%	NA	Yes	Yes	Yes
Annane (4)	64% vs. 73%	Yes	Yes	Yes	NA
Meduri (5)	24% vs. 43%	Yes	Yes	Yes	Yes
Late ARDS (n = 314)	28% vs. 43%	5 of 5	5 of 5	2 of 3	2 of 3
Meduri (6)[b]	12% vs. 62%	Yes	Yes	Yes	Yes
Keel (7)	38% vs. 67%	Yes	Yes	NA	NA
Varpula (8)	19% vs. 20% (30 d)	Yes	Yes	No	No
Huh (9)	43% vs. 74%	Yes	Yes	NA	NA
Steinberg (10)[b]	29% vs. 29% (60 d)	Yes	Yes	Yes	Yes
Early and Late ARDS	34% vs. 52%	8 of 8	9 of 9	6 of 7	5 of 6

Early ALI-ARDS, treatment initiated within 3 days of meeting acute lung injury-acute respiratory distress syndrome criteria; Late ARDS, treatment initiated after 5–7 days of meeting ARDS criteria; NA, not available or not applicable; d, days; MV, mechanical ventilation; ICU, intensive care unit.

[a]Mortality is reported as hospital mortality unless specified otherwise in parenthesis; [b]Two trials reported mortality in patients randomized before day 14 of ARDS: Meduri et al (6) (13% vs. 57%), and Steinberg et al (10) (27% vs. 36%). Comparisons are reported as glucocorticoid-treated vs. control.

hyperglycemia (26), neuromuscular weakness (27), increased risk for nosocomial infections (28), and delirium (27)—that is otherwise attributable to glucocorticoid treatment. Two sets of consequences follow. First, in uncontrolled studies, when the use of glucocorticoid treatment is limited to the "rescue" of the sickest patients, it is difficult to separate disease from treatment-related complications. Second, treatment-induced downregulation of systemic inflammation could theoretically prevent, or partly offset, development and progression of these complications. The findings reported by Tang et al (1) add credit to a new line of reasoning that views control of systemic inflammation as indispensable to decreased short- and long-term morbidity in ARDS and sepsis. We review evidence accumulated in the last decade that supports this paradigm shift in our traditional thinking. Because of space limitations, we will address only the topic of infection and neuromuscular weakness.

None of the reviewed trials reported an increased rate of nosocomial infection (1, 29), whereas two reported a significant reduction (5, 10). In the ARDS network trial (10), the infection rate for treated and control groups was 31% vs. 47% (relative risk 0.59, 95% confidence interval 0.40–0.88), respectively. A prospective ARDS study investigating the longitudinal relationship between inflammatory cytokine levels (plasma and bronchoalveolar lavage) and infections (28) showed that nosocomial infections are an epiphenomenon of dysregulated systemic inflammation (28, 30), a finding supported by recent experimental evidence (31). It is now appreciated that bacteria have receptors for cytokines tumor necrosis factor-α and interleukin (IL)-1β and that exposure of bacteria to inflammatory cytokines enhances their growth and virulence (reviewed in Ref. 30). Although a moderate degree of local inflammation is required to control infection, high levels of inflammatory cytokines favor bacterial proliferation and virulence following a U-shaped response. When fresh isolates of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Acinetobacter* sps. obtained from patients with ARDS were exposed *in vitro* to a lower concentration (10–250 pg) of tumor necrosis factor-α, IL-1β, or IL-6—similar to the plasma values detected in ARDS survivors—extracellular and intracellular bacterial growth was not promoted, and human monocytic cells were efficient in killing the ingested bacteria (32, 33). On the contrary, when bacteria were exposed to higher concentrations of proinflammatory cytokines—similar to the plasma values detected in ARDS nonsurvivors—intracellular and extracellular bacterial growth was enhanced in a dose-dependent manner (32, 33). In separate parallel experiments, impairment in intracellular bacterial killing by activated monocytes correlated with the increased monocyte expression of proinflammatory cytokines, whereas restoration of monocyte killing function upon exposure to methylprednisolone coincided with the downregulation of the expression of tumor necrosis factor-α and IL-1β (34). In experimental sepsis, the magnitude of induced systemic inflammation affects macrophage-associated host antibacterial innate immunity and susceptibility to infection (31).

Glucocorticoid treatment has been proven beneficial and safe for a wide variety of infections (35). In experimental pneumonia, animals randomized to glucocorticoid treatment had a significant reduction in bacterial burden (bronchoalveolar lavage and lung tissue) and histologic severity of pneumonia (36) and improved survival (37). Two randomized trials in patients with septic shock (most caused by pneumonia) reported that hydrocortisone infusion—while decreasing circulating IL-6 and IL-8 levels and neutrophil spontaneous release of hydrogen peroxide (H_2O_2)—was associated with *ex vivo* preserved or increased (in comparison to placebo) monocyte and neutrophil phagocytosis and preserved respiratory burst (38, 39). The cumulative evidence indicates that in ARDS and severe sepsis, glucocorticoid-induced downregulation of life-threatening systemic inflammation improves innate immunity (38, 39) and provides an environment less favorable to intracellular and extracellular bacterial growth (34, 36).

A number of reports, including muscle histopathologic studies (40), support an association between systemic inflammation and critical illness neuromuscular abnormality (CINMA) (27). In this regard, downregulation of systemic inflammation in ARDS could potentially prevent development and progression of CINMA. A recent systematic review of the literature found no clear association between glucocorticoid treatment and electro-

physiologically proven CINMA in patients on mechanical ventilation (41). Because CINMA is recognized as an independent predictor of prolonged weaning (42) and ARDS trials consistently report a sizable and significant reduction in duration of mechanical ventilation (2,4–6,10), clinically relevant CINMA caused by glucocorticoid or glucocorticoid-induced hyperglycemia is unlikely.

The ARDS network study (10) reported nine serious, unspecified (not defined in the text of the article) events associated with myopathy or neuropathy among treated patients ($p = 0.001$). Specific information about these patients, however, was not provided. Because greater than 40% of patients in the ARDS network trial were exposed to neuromuscular blocking agents (NMBA), it is difficult to factor how much the combination NMBA–glucocorticoid affected this finding. In ventilated patients with severe asthma on PGCT, the use of glucocorticoids in combination with an NMBA was associated with a much higher incidence of muscle weakness than was the use of glucocorticoids alone (20 of 69 vs. 0 of 38, $p < 0.001$) (43). In the single study that identified by multivariate analysis a positive relationship between glucocorticoid treatment and CINMA, most patients were exposed to NMBA for 3 days (44). For this reason, the use of NMBA is strongly discouraged in ARDS patients receiving glucocorticoid treatment (15).

It can be argued that, lacking a large confirmatory trial proving a definitive mortality benefit, caution is warranted in recommending PGCT in ARDS. Weighting in favor of this approach are concerns related to glucocorticoid-induced complications, a line of reasoning that is weakened by the findings of this meta-analysis. As reviewed by Tang et al, cumulative findings from multiple controlled ARDS studies have consistently demonstrated that PGCT is associated with a sizable and significant improvement in meaningful patient-centered outcome variables and a distinct survival benefit. Subgroup analysis should be interpreted with some caution. Although the analysis by Tang et al did not find the dosage strategy to affect outcome, we believe that corticosteroids should be initiated early at a dose not exceeding 1 mg/kg/day of methylprednisolone in patients meeting criteria for severe ARDS (Pao_2: Fio_2 $\geq$200 on positive end-expiratory pressure of 10 cm H_2O) and within 72 hours in patients without severe ARDS but failing to improve by day 3. In patients failing to improve lung injury score after days 5–7, present data are limited to the study investigating a dose of 2 mg/kg/day of methylprednisolone. In all cases, duration of treatment should be 14–21 days before final tapering. Most important, PGCT has a strong benefit/risk ratio in ARDS when it is applied in conjunction with measures demonstrated to reduce potential morbidity associated with glucocorticoids (5, 6). These measures include i) intensive infection surveillance, ii) avoidance of paralytic agents, and iii) avoidance of rebound inflammation with premature discontinuation of treatment that may lead to physiologic deterioration and reintubation (5).

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G. Umberto Meduri, MD
University of Tennessee Health Science Center
Memphis, TN
Memphis VA Medical Center
Memphis, TN
Paul E. Marik, MD
Division of Pulmonary and Critical Care Medicine
Thomas Jefferson University
Philadelphia, PA
Djillali Annane, MD, PhD
Critical Care Department
Université de Versailles SQY (UniverSud Paris)
Garches, France

REFERENCES

1. Tang BMP, Craig JC, Eslick GD, et al: Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: A systematic review and meta-analysis. *Crit Care Med* 2009; 37:1594–1603
2. Confalonieri M, Urbino R, Potena A, et al: Hydrocortisone infusion for severe community-acquired pneumonia: A preliminary randomized study. *Am J Respir Crit Care Med* 2005; 171:242–248
3. Lee HS, Lee JM, Kim MS, et al: Low-dose steroid therapy at an early phase of postoperative acute respiratory distress syndrome. *Ann Thorac Surg* 2005; 79:405–410
4. Annane D, Sebille V, Bellissant E: Effect of low doses of corticosteroids in septic shock patients with or without early acute respiratory distress syndrome. *Crit Care Med* 2006; 34:22–30
5. Meduri GU, Golden E, Freire AX, et al: Methylprednisolone infusion in early severe ARDS: Results of a randomized controlled trial. *Chest* 2007; 131:954–963
6. Meduri GU, Headley S, Golden E, et al: Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome. A randomized controlled trial. *JAMA* 1998; 280:159–165
7. Keel JB, Hauser M, Stocker R, et al: Established acute respiratory distress syndrome: Benefit of corticosteroid rescue therapy. *Respiration* 1998; 65:258–264
8. Varpula T, Pettila V, Rintala E, et al: Late steroid therapy in primary acute lung injury. *Intensive Care Med* 2000; 26:526–531
9. Huh J, Lim C, Jegal Y, et al: The effect of steroid therapy in patients with late ARDS. *Tuberculosis Respir Dis* 2002; 52:376–384
10. Steinberg KP, Hudson LD, Goodman RB, et al: Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006; 354:1671–1684
11. Bower G, Matthay M: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342:1301–1308
12. Wiedemann HP, Wheeler AP, Bernard GR, et al: Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354:2564–2575
13. Herridge MS, Cheung AM, Tansey CM, et al: One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med* 2003; 348:683–693
14. Thompson BT, Ancukiewicz M, Hudson LD, et al: Steroid treatment for persistent ARDS: A word of caution. *Crit Care* 2007; 11:425
15. Meduri GU, Marik PE, Chrousos GP, et al: Steroid treatment in ARDS: A critical appraisal of the ARDS network trial and the recent literature. *Intensive Care Med* 2008; 34:61–69
16. Guyatt G, Gutterman D, Baumann MH, et al: Grading strength of recommendations and quality of evidence in clinical guidelines: Report from an American college of chest physicians task force. *Chest* 2006; 129:174–181
17. Umberger R, Headley AS, Waters T, et al: Cost-effectiveness of methylprednisolone treatent (MPT) in unreolving ARDS (U-ARDS) (abstract). *Am J Respir Crit Care Med* 2002; 165:A22
18. Meduri GU: An historical review of glucocorticoid treatment in Sepsis. Disease pathophysiology and the design of treatment investigation. *Sepsis* 1999; 3:21–38
19. Michie HR, Manogue KR, Spriggs DR, et al: Detection of circulating tumor necrosis factor after endotoxin administration. *N Engl J Med* 1988; 318:1481–1486
20. Zanetti G, Heumann D, Gerain J, et al: Cytokine production after intravenous or peritoneal gram-negative bacterial challenge in mice. Comparative protective efficacy of antibodies to tumor necrosis factor-alpha and to lipopolysaccharide. *J Immunol* 1992; 148: 1890–1897

21. Meduri GU, Headley S, Tolley E, et al: Plasma and BAL cytokine response to corticosteroid rescue treatment in late ARDS. *Chest* 1995; 108:1315–1325
22. Meduri GU, Kohler G, Headley S, et al: Inflammatory cytokines in the BAL of patients with ARDS. Persistent elevation over time predicts poor outcome. *Chest* 1995; 108: 1303–1314
23. Meduri GU, Headley S, Kohler G, et al: Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS. Plasma IL-1 beta and IL-6 levels are consistent and efficient predictors of outcome over time. *Chest* 1995; 107:1062–1073
24. Meduri GU, Muthiah MP, Carratu P, et al: Nuclear factor-kappaB- and glucocorticoid receptor alpha- mediated mechanisms in the regulation of systemic and pulmonary inflammation during sepsis and acute respiratory distress syndrome. Evidence for inflammation-induced target tissue resistance to glucocorticoids. *Neuroimmunomodulation* 2005; 12:321–338
25. Meduri GU, Tolley EA, Chrousos GP, et al: Prolonged methylprednisolone treatment suppresses systemic inflammation in patients with unresolving acute respiratory distress syndrome. Evidence for inadequate endogenous glucocorticoid secretion and inflammation-induced immune cell resistance to glucocorticoids. *Am J Respir Crit Care Med* 2002; 165:983–991
26. Raghavan M, Marik PE: Stress hyperglycemia and adrenal insufficiency in the critically ill. *Semin Respir Crit Care Med* 2006; 27: 274–285
27. Pustavoitau A, Stevens RD: Mechanisms of neurologic failure in critical illness. *Crit Care Clin* 2008; 24:1–24, vii
28. Headley AS, Tolley E, Meduri GU: Infections and the inflammatory response in acute respiratory distress syndrome. *Chest* 1997; 111:1306–1321
29. Peter JV, John P, Graham PL, et al: Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: Meta-analysis. *BMJ* 2008; 336: 1006–1009
30. Meduri GU: Clinical review: A paradigm shift: The bidirectional effect of inflammation on bacterial growth. Clinical implications for patients with acute respiratory distress syndrome. *Crit Care* 2002; 6:24–29
31. Takahashi H, Tsuda Y, Takeuchi D, et al: Influence of systemic inflammatory response syndrome on host resistance against bacterial infections. *Crit Care Med* 2004; 32:1879–1885
32. Meduri GU, Kanangat S, Stefan J, et al: Cytokines IL-1beta, IL-6, and TNF-alpha enhance in vitro growth of bacteria. *Am J Respir Crit Care Med* 1999; 160:961–967
33. Kanangat S, Meduri GU, Tolley EA, et al: Effects of cytokines and endotoxin on the intracellular growth of bacteria. *Infect Immun* 1999; 67:2834–2840
34. Meduri GU, Kanangat S, Bronze MS, et al: Effects of methylprednisolone on intracellular bacterial growth. *Clin Diagn Lab Immunol* 2001; 8:1156–1163
35. McGee S, Hirschmann J: Use of corticosteroids in treating infectious diseases. *Arch Intern Med* 2008; 168:1034–1046
36. Sibila O, Luna C, Agustí C, et al: Effects of corticosteroids an animal model of ventilator-associated pneumonia. *Proc Am Thorac Soc* 2006; 3:A 21
37. Li Y, Cui X, Li X, et al: Risk of death does not alter the efficacy of hydrocortisone therapy in a mouse *E. coli* pneumonia model: Risk and corticosteroids in sepsis. *Intensive Care Med* 2008;34:568–577
38. Keh DBT, Weber-Cartens S, Schulz C, et al: Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: A double-blind, randomized, placebo-controlled, crossover study. *Am J Respir Crit Care Med* 2003; 167:512–520
39. Kaufmann I, Briegel J, Schliephake F, et al: Stress doses of hydrocortisone in septic shock: Beneficial effects on opsonization-dependent neutrophil functions. *Intensive Care Med* 2008; 34:344–349
40. De Letter MA, van Doorn PA, Savelkoul HF, et al: Critical illness polyneuropathy and myopathy (CIPNM): Evidence for local immune activation by cytokine-expression in the muscle tissue. *J Neuroimmunol* 2000; 106: 206–213
41. Stevens RD, Dowdy DW, Michaels RK, et al: Neuromuscular dysfunction acquired in critical illness: A systematic review. *Intensive Care Med* 2007; 33:1876–1891
42. De Jonghe B, Bastuji-Garin S, Sharshar T, et al: Does ICU-acquired paresis lengthen weaning from mechanical ventilation? *Intensive Care Med* 2004; 30:1117–1121
43. Leatherman JW, Fluegel WL, David WS, et al: Muscle weakness in mechanically ventilated patients with severe asthma. *Am J Respir Crit Care Med* 1996; 153:1686–1690
44. De Jonghe B, Sharshar T, Lefaucheur JP, et al: Paresis acquired in the intensive care unit: A prospective multicenter study. *JAMA* 2002; 288:2859–2867

How can severity scoring methods maintain clinical and temporal relevance with advances in critical care practice? Here's one way*

One dilemma facing users of risk-adjusted severity scoring as a surrogate for quality in the intensive care unit (ICU) is the difficulty in ensuring that predictive modeling accurately reflects advancements in clinical care, admission criteria, or other practice changes. Earlier in this decade, Glance et al (1), using the standardized mortality ratio (ratio of mortality predicted by a severity score to actual mortality) as a measure of ICU quality, hypothesized that existing individual scoring systems should consistently and reproducibly demonstrate high-quality or low-quality ICU outliers. While establishing that there was only a fair to moderate agreement among Acute Physiology and Chronic Health Evaluation II (2), Simplified Acute Physiology Score II (3), and Mortality Probability Admission Model (MPM_0-II) (4) in determining ICU quality outliers using the Project IMPACT (5) database, they also demonstrated an interesting, unintended finding: that most of the ICUs were, with apologies to Garrison Keillor and the Lake Wobegon effect (6), "above average" (i.e., of high quality).

Because the severity scoring methods used in the aforementioned study (1) were published 10–15 years prior, most clinicians would argue that skewing of the bell-shaped curve toward inflation of ICU quality is indicative of the prediction models losing their relevance as care practices change over time. Unfortunately, the only way to refine an exist-

*See also p. 1619.

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ing predictive model is by subjecting it to a new, contemporary dataset of ICUs or patients—a process that is typically expensive and time consuming. Recognizing that periodic updating of prediction models is necessary, Acute Physiology and Chronic Health Evaluation (7), Simplified Acute Physiology Score (8), and MPM (9) have all recently been recalibrated to align with evolving clinical practices.

However, the time between published updates of these scoring systems, typically a decade or more, may be undesirably long for clinicians to accept that a particular model remains temporally relevant. In this issue of *Critical Care Medicine*, Higgins et al (10) performed a prospective revalidation of MPM_0-III using a new patient population acquired from Project IMPACT 15 months after the original population, with the goal of demonstrating ongoing robustness of the model. The researchers analyzed more than 55,000 admissions from 77 hospitals and 103 ICUs; nearly a quarter of the included ICUs were not part of the initial MPM_0-III development or internal validation dataset. They assessed discrimination using the receiver operating characteristic, and calibration using graphic, Hosmer-Lemeshow goodness of fit, and Brier score statistical methodologies (10). Despite limitations inherent in using a closed database like Project IMPACT (such as its retrospective nature, underrepresentation of ICU types, and exclusion of patient subsets), the authors conclude that the MPM_0-III calibrates and discriminates well using a new, more contemporary patient population (10). In addition, their results remain stable even though the more recent study group had statistically significant reductions in the number of low-risk patients and increases in those receiving active treatment and mechanical ventilation when compared with the original validating population (10). These significant differences occurring only 15 months apart suggest that even relatively brief time lapses may lead to substantial clinical practice changes.

The critical care medicine community has been at the forefront of developing risk-adjusted clinical scoring systems, such as Acute Physiology and Chronic Health Evaluation, Simplified Acute Physiology Score, and MPM, that could arguably be considered surrogates for helping to define quality of care. Yet, clinical mortality-based measures of outcome (e.g., the standardized mortality ratio) have not become ubiquitous in ICUs, despite being available in one form or another for a quarter century. Reasons for this lack of embracement include the distaste for the high costs associated with what has evolved into a proprietary, for-profit enterprise; the additionally expensive but required labor-intensive data collection process; concerns that a scoring system would not accurately reflect a particular patient population; or, perhaps the lack of transparency in knowing whether a particular severity score may underpredict or overpredict outcomes during those lengthy intervals between published updates. The study by Higgins et al (10) addresses this latter concern by demonstrating that their scoring system remained robust with a different, more contemporary patient population. It may be, then, that one way to alleviate concerns about the relevance of a particular scoring system would be insistence by the critical care community that studies like the one by Higgins et al (10), transparent and subjected to peer review, are published more frequently and continually in the medical literature. Such studies may be necessary to convert skeptical clinicians that outcome predictions and surrogates for ICU quality (such as the standardized mortality ratio) retain reliability sufficient to accept into their practices.

Obviously, there are economic issues at stake regarding future completion of labor-intensive clinical revalidation studies. A major limitation of the current study by Higgins et al (10) is that all of the authors have some financial ties to, and most are direct employees of, the company that owns the rights to MPM_0-III. That the study was completed at all is illustrative of the integration of science and industry necessary for maintaining validity of their severity scoring model. To ensure frequent, future revalidation studies, it may be time to consider assembling interested investigators, perhaps funded by a novel governmental, third-party payer and for-profit enterprise consortium, with the (admittedly lofty) goal of producing frequent, independent, high-quality, transparent, peer-reviewed literature demonstrating reliability of (or recalibrating as necessary) the available risk-adjusted scoring systems. The study by Higgins et al (10) might be seen as an initial step by the critical care community in accepting that risk-adjusted severity scores and outcome measurements (like the standardized mortality ratio) have resiliently withstood the test of time and focusing investigative efforts on how to scientifically and transparently ensure their ongoing clinical and temporal relevance.

Marc J. Popovich, MD, FCCM
Department of General
Anesthesiology/Critical Care
Cleveland Clinic
Cleveland, OH

REFERENCES

1. Glance LG, Osler TM, Dick A: Rating the quality of intensive care units: Is it a function of the intensive care unit scoring system? *Crit Care Med* 2002; 30:1976–1982
2. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13:818–829
3. Le Gall J, Lemeshow S, Saulnier F: A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA* 1993; 270:2957–2963
4. Lemeshow S, Teres D, Klar J, et al: Mortality Prediction Models (MPM II) based on an international cohort of intensive care unit patients. *JAMA* 1993; 270:2478–2486
5. Project IMPACT. Available at: www.cerner.com/piccm. Accessed December 1, 2008
6. Behal R: The Lake Wobegon effect: When all the patients are sicker. *Am J Med Qual* 2006; 21:365–366
7. Zimmerman JE, Kramer AA, McNair DS, et al: Acute Physiology and Chronic Health Evaluation (APACHE) IV: Hospital mortality assessment for today's critically ill patients. *Crit Care Med* 2006; 34:1297–1310
8. Metnitz PG, Moreno RP, Almeida E, et al: SAPS 3—From evaluation of the patient to evaluation of the intensive care unit. Part 1: Objectives, methods and cohort description. *Intensive Care Med* 2005; 31:1336–1344
9. Higgins TL, Teres D, Copes WS, et al: Assessing contemporary intensive care unit outcome: An updated Mortality Probability Admission Model (MPM_0-III). *Crit Care Med* 2007; 35:827–835
10. Higgins TL, Kramer AA, Nathanson BH, et al: Prospective validation of the intensive care unit admission Mortality Probability Model (MPM_0-III). *Crit Care Med* 2009; 37:1619–1623

Nosocomial bacteremia a continuing challenge—A challenge we can meet*

Hospitals, and more explicitly intensive care units (ICUs), are healthcare delivery sites where activities aimed at improving patient outcomes are coupled with risks that may lead to increased patient morbidity and mortality. This harm is a byproduct of the intrinsic characteristics of the critically ill patients who we care for; however, our care delivery systems also have a prominent role.

The topic of nosocomial infections has been extensively reviewed (1, 2), with urinary tract, lower respiratory tract, surgical site, and primary bloodstream infections being the most frequent sources. The epidemiology and outcomes of nosocomial infections have been described, and the results indicate an increasing toll on our patients.

In this issue of *Critical Care Medicine*, Blot et al (3) focus on nosocomial bacteremia, one of the most frequent and lethal nosocomial infections in ICU patients (1). They provide us data on the trends and outcomes over a 15-year timeframe of nosocomial bacteremia in critically ill patients from their clinical database. Their study, a single institution's retrospective cohort study, examines 984 ICU patients (cardiosurgical ICU 55.1%, medical ICU 37.8%, and burn unit 7.1%) with 1228 episodes of microbiologically confirmed nosocomial bacteremia. The source of nosocomial bacteremia was primary (31.8%), catheter related (18.5%), lung (14.5%), intra-abdominal (11.9%), wound (7.9%), urinary tract (7.9%), and either another site or multiple sites (7.5%). A total of 48.7% episodes were caused by Gram-positive organisms, 41.3% by Gram-negative organisms (70% *Enterobacteriaceae* and 30% nonfermenting Gram-negative bacteria), 2.2% by anaerobic bacteria, 7.8% by *Candida* species, and 15.3% by polymicrobial bloodstream infections. The article provides some new insights and some thoughts on what needs to be done to improve performance.

The authors categorized patients into middle aged (patients 45–64 years), old (65–74 years), and very old (≥75 years). They assessed a number of parameters, with the most important being the age distribution of patients in the ICU, the age distribution of those with nosocomial bacteremia, and the prevalence of nosocomial bacteremia and in-hospital mortality in ICU patients with nosocomial bacteremia as it relates to age.

They observed that from study onset to the end, despite a 10% decrease in overall ICU admissions, the number of patients in the very old group increased by 33%. The prevalence of nosocomial bacteremia increased significantly over the 1992–2006 timeframe from 21.3 of 1000 admissions in 1992 to 33.6 of 1000 admissions in 2006 in the old age group ($p < 0.001$) and from 9.7 of 1000 admissions to 21.3 of 1000 admissions in the very old group ($p < 0.002$).

In-hospital mortality increased significantly with age: 42.9%, 49.1%, and 56.0% for middle aged, old, and very old patients, respectively. Observed mortality (56.0%) significantly exceeded expected mortality (based on Acute Physiology and Chronic Health Evaluation II scores) in the very old group and fell outside the 95% confidence intervals of the expected mortality (35.6% to 45.5%).

The proportion of elderly patients in our population continues to grow and the proportion of elderly patients admitted to intensive care is increasing and will continue to increase (4, 5). Although the authors' results bear out the changing demographic of our ICUs (6, 7), their article reinforces the mandate that age is an important factor to be considered in our care processes.

Blot et al reported that the number of very old increased by 33% during the study timeframe, whereas the prevalence of nosocomial bacteremia with its associated elevated mortality in this population increased disproportionately to more than 240%. This trend is indeed sobering. One unfortunate issue that the authors highlight is that nosocomial bacteremia in the critically ill may be following the path of sepsis in the general population; with a significant overrepresentation of the elderly, this prevalence may be growing at a more rapid rate and with poorer outcomes (8).

The study has a number of limitations, which include the following: nutritional and functional status, comorbidities central components for outcomes for the elderly were not assessed. The authors did not explore whether limitations of care initiated by physicians or patients contributed to mortality. Transfusion history, which is associated with an increased rate of nosocomial bacteremia, was not part of the database (9). The types of ICUs in the authors' institution may not reflect the makeup of many of our facilities. The classic age categories used in a number of studies on nosocomial bacteremia differ from those used in the current study.

The elderly are an ever-present and ever-increasing populace in our ICUs, and they have age-associated factors added to comorbidities that lead to increased rates of nosocomial bacteremias. The roles played by impaired host defenses, altered immune function, anatomical or physiologic derangements, or comorbidities are unclear and warrant further investigation.

Despite our lack of understanding of the cause of nosocomial bacteremias, a number of risk factors for nosocomial bacteremias, such as central venous catheterization, urinary catheterization, ICU-acquired pneumonia, neurologic impairment, increased length of ICU stay, mechanical ventilation, diagnosis of trauma, certain chronic disease processes, and high intensity of care, have been identified (1).

Many of these factors can be mitigated and that is where our focus should be

*See also p. 1634.

Key Words: nosocomial; bacteremia; elderly; mortality; catheter; prevention

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directed. An excellent example is the prevention of catheter-related bloodstream infections by incorporating into ICU practice five evidence-based procedures that have the greatest effect on the rate of catheter-related bloodstream infections and the lowest barriers to implementation (10). Additional measures to be considered include the Surgical Infection Prevention Process Measures, prevention of ventilator-associated pneumonia with a ventilator-associated bundle, and the use of policies and practices to prevent catheter-related urinary tract infections (11).

Edward Arsura, MD
Clinical Medicine
New York Medical College
Richmond University
Medical Center
Staten Island, NY

REFERENCES

1. Vincent JL, Bihari DJ, Suter PM, et al: The prevalence of nosocomial infection in intensive care units in Europe. *JAMA* 1995; 274:639–644
2. Richards MJ, Edwards JR, Culver DH, et al: Nosocomial infections in medical intensive care units in the United States. *Crit Care Med* 1999; 27:887–892
3. Blot S, Cankurtaran M, Petrovic M, et al: Epidemiology and outcome of nosocomial bloodstream infections in elderly critically ill patients: A comparison between middle-aged, old, and very old patients. *Crit Care Med* 2009; 37:1634–1641
4. Arsura EL: Care of the critically ill elderly: Time to move to the next generation of care delivery. *Crit Care Med* 2006; 34: 2246–2247
5. Paz HL, Martin A: Sepsis in an aging population. *Crit Care Med* 2006; 34:234–235
6. Kaarlola A, Tallgren MI, Pettila V: Long-term survival, quality of life, and quality-adjusted life-years among critically ill elderly patients. *Crit Care Med* 2006; 34: 2120–2126
7. Hennessy D, Juzwishin K, Yergens D, et al: Outcomes of elderly survivors of intensive care: A review of the literature. *Chest* 2005; 127:1764–1774
8. Martin GS, Mannino DM, Moss M: The effect of age on the development and outcome of adult sepsis. *Crit Care Med* 2006; 34:15–21
9. Schorr AF, Jackson WL, Kelly Kathleen KM, et al: Transfusion practice and blood stream infections in critically ill patients. *Chest* 2005; 127:1722–1728
10. Pronovost P, Needham D, Berenholtz S, et al: An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med* 2006; 355:2725–2732
11. Levy M. MD, Vincent JL, Jaeschke R: Surviving Sepsis Campaign: Guideline clarification. *Crit Care Med* 2008; 36:2490–2491

A marker for posttraumatic-sepsis: Searching for the Holy Grail around intensive care units*

In the Western world, trauma continues to be one of the major causes of mortality in people younger than 50 years. Patients with trauma die either as a direct consequence of their injuries or from the development of secondary complications such as sepsis and sepsis-related multiple organ failure (the leading cause of death in intensive care units). Risk assessments and prompt diagnosis have become major tools to prevent sepsis in posttraumatic patients. An early diagnosis is extremely important due to a lack of proven treatments for improving the final outcome in septic patients. The host injury level is evaluated by scoring systems that combine clinical signs and measurements of proinflammatory parameters (1). The most relevant sepsis markers currently used are C-reactive protein (CRP), procalcitonin (PCT), proinflammatory cytokine production (such as IL-6, IL-8, and IL-18), and polymorphonuclear leukocyte (PMNL) count (2). Unfortunately, these parameters are also increased in a variety of other conditions, creating uncertainty at the time of diagnosis and prognosis of sepsis. Thus, searching for new biochemical or immunologic marker(s) has been a major goal for researchers during the past decades. In this issue of *Critical Care Medicine*, Keel et al (3) present data supporting the role of plasma PSP/reg (pancreatic stone protein or reg) levels as a prognosis maker for posttraumatic complications such as sepsis. PSP/reg is a secreted tryptic fragment found in pancreatic juice as well as in pancreatic stones (4, 5). PSP/reg is also produced in the small intestine (6) and stomach (7) and has been involved in cellular regeneration and healing (8, 9). Plasma levels of PSP/reg dramatically increased in patients with acute and chronic pancreatitis (10). In their study, Keel et al used a small group of severely injured young patients (average age of 38 years) who were divided into three groups, patients without infection (n = 18), patients with local infection (n = 32), and septic patients (n = 33), and these groups were compared with a group of healthy volunteers. Their data showed that on the day of admission, all the four groups had similar levels of plasma PSP/reg. However, within a couple of days, a significant increase in PSP/reg levels was observed in patients with local infection and in those with sepsis. These two groups had different kinetics of increase, which were unrelated to pancreatic damage (measured as lipase and amylase activity). As expected, sepsis markers, CRP, leukocyte count, IL-6, and PCT showed an early peak (around day 7) in septic patients, and their values were significantly different from those observed in patients with local or no infection. In an attempt to elucidate whether this increase in PSP/reg level has a biological function, the authors decided to evaluate the effect of this protein on PMNL function. They found that incubation of control PMNL with recombinant PSP/reg (at levels similar to those found in plasma) resulted in cell surface reduction of CD62L (by shedding or internalization?) and an increase of CD11b. This profile strongly suggests that PMNL exposed to PSP/reg develop a firm adherence phenotype, which may facilitate their infiltration and, therefore, their activation. These authors ruled out potential endotoxin contamination by boiling PSP/reg samples before incuba-

*See also p. 1642.

Key Words: PSP/reg; neutrophils; inflammation; multiple organ failure; immune response

Dr. Vega has been employed with UCSD.

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tion with PMNL. Additionally, direct binding of PSP/reg to PMNL derived from healthy volunteers was observed. Incubation of PMNL isolated from septic patients with PSP/reg did not show an effect over CD62L or CD11b cell surface levels. These data may suggest tolerance-like phenomena, although further investigations are required. One of the questions that remained unanswered in this work is what is the binding capacity of PSP/reg by sepsis-derived PMNL? In addition, it will be important to know if this unresponsiveness to PSP/reg or altered binding capacity are parameters that may be used as prognosis indexes. To assess the real relevance of PSP/reg as a sepsis marker will require further investigations. Furthermore, PSP/reg will be competing with new sepsis marker candidates such as peripheral endothelial progenitor cells (11), plasma Treg cells, CD25 levels (12), and B-type natriuretic peptide (13) to be crowned as the definitive sepsis marker.

Thus, finding the "perfect" sepsis marker has been one of the most elusive dreams in modern medicine. The list of potential sepsis markers increases day by day, and we still do not have a parameter or a group of them that can accurately and rapidly diagnose sepsis. Most of the current markers (clinical signs and laboratory measurements) are the product of the proinflammatory stage and therefore are nonspecific. Thus, if we can make a wish for the ideal sepsis marker, what would we ask for? Probably an important characteristic would be a parameter that is altered in all types of sepsis, independently of the agent causing the infection. This characteristic would eliminate "subpopulation of septic patients" and all the nightmares associated with conflicting data at the moment of evaluating a potential sepsis marker. Thus, it would be desirable to have a substance that reports early changes and can be detected in an easy and rapid way. Prognosis potential is also a characteristic that should be added to this wish list. PSP/reg seems to have a certain potential as a predictor of sepsis, although only time will tell if this protein fulfills the minimum requirements to be called a true sepsis marker.

Virginia L. Vega, PhD
Department of Surgery
University of California San Diego
La Jolla, CA

REFERENCES

1. Pape HC, Remmers D, Rice J, et al: Appraisal of early evaluation of blunt chest trauma: Development of a standardized scoring system for initial clinical decision making. *J Trauma* 2000; 49:496–504
2. Ventetuolo CE, Levy MM: Biomarkers: Diagnosis and risk assessment in sepsis. *Clin Chest Med* 2008; 29:591–603
3. Keel M, Härter L, Reding T, et al: Pancreatic stone proteins is highly increased during posttraumatic sepsis and activates neutrophil granulocytes. *Crit Care Med* 2009; 37: 1642–1648
4. De Caro A, Lohse J, Sarles H: Characterization of a protein isolated from pancreatic calculi of men suffering from chronic calcifying pancreatitis. *Biochem Biophys Res Commun* 1979; 87:1176–1182
5. Watanabe T, Yonekura H, Terazono K, et al: Complete nucleotide sequence of human reg gene and its expression in normal and tumoral tissues. The reg protein, pancreatic stone protein, and pancreatic thread protein are one and the same product of the gene. *J Biol Chem* 1990; 265:7432–7439
6. Zenilman ME, Kim S, Levine BA, et al: Ectopic expression of reg protein: A marker of colorectal mucosa at risk for neoplasia. *J Gastrointest Surg* 1997; 1:194–201
7. Fukui H, Kinoshita Y, Maekawa T, et al: Regenerating gene protein may mediate gastric mucosal proliferation induced by hypergastrinemia in rats. *Gastroenterology* 1998; 115:1483–1493
8. Livesey FJ, O'Brien JA, Li M, et al: A Schwann cell mitogen accompanying regeneration of motor neurons. *Nature* 1997; 390:614–618
9. Kazumori H, Ishihara S, Hoshino E, et al: Neutrophil chemoattractant 2 beta regulates expression of the Reg gene in injured gastric mucosa in rats. *Gastroenterology* 2000; 119: 1610–1622
10. Schmiegel W, Burchert M, Kalthoff H, et al: Immunochemical characterization and quantitative distribution of pancreatic stone protein in sera and pancreatic secretions in pancreatic disorders. *Gastroenterology* 1990; 99:1421–1430
11. Becchi C, Pillozzi S, Fabbri LP, et al: The increase of endothelial progenitor cells in the peripheral blood: A new parameter for detecting onset and severity of sepsis. *Int J Immunopathol Pharmacol* 2008; 21:697–705
12. Saito K, Wagatsuma T, Toyama H, et al: Sepsis is characterized by the increases in percentages of circulating CD4+CD25+ regulatory T cells and plasma levels of soluble CD25. *Tohoku J Exp Med* 2008; 216:61–68
13. Post F, Weilemann LS, Messow CM, et al: B-type natriuretic peptide as a marker for sepsis-induced myocardial depression in intensive care patients. *Crit Care Med* 2008; 36:3030–3037

Predictive models: The angel is in the details*

Models for measuring severity of illness and predicting hospital mortality for patients in intensive care units (ICUs) are now in their third and fourth generation (1–3), and newer models have appeared recently (4, 5). This has come about as a result of the desire to assess ICU performance by comparing observed and predicted mortality (6, 7) and, at least in part, to the ability to capture data electronically. Large data sets containing numerous measurements on all patients have enabled the development of sophisticated predictive models. Simplicity, however, is not a hallmark of these systems. The leanest critical care hospital mortality model, Mortality Probability Model (MPM_0-III), still requires the collection of 17 data elements (3).

Statistical modeling in other acute care settings has lagged behind that in critical care. Recent attempts have been made to introduce predictive models outside of the ICU, most particularly in the area of rapid response teams/medical emergency teams (8). One example is the Modified Early Warning System (9), which was developed on 206 patients in a postoperative ward. This scoring system assigns "weights" to six physiologic measurements. The weights are summed and

*See also p. 1649.

Key Words: intensive care; patient outcome assessment; Sequential Organ Failure Assessment Score; emergency department; mortality

Dr. Kramer is employed with Cerner Corporation.

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a cut-point >4 is used as an early warning signal. What is common among decision algorithms in rapid response teams/medical emergency teams is that they use triggers ("antecedents") and/or uncomplicated scoring algorithms to indicate possible patient deterioration. Here, simplicity is desirable, until such time as electronic data capture mechanisms permit the assimilation and multivariate analysis of high-dimensional data.

In this issue of *Critical Care Medicine*, Jones et al (10) examine how the Sequential Organ Failure Assessment (SOFA) score (11) measured while the patient is in the emergency department (ED), can predict hospital mortality for patients subsequently admitted to an ICU. The authors also gathered data for the SOFA score collected 72 hours postadmission as well as the difference between this value and the value recorded in the ED. These additional measurements may be useful variables for stratification in *post hoc* analyses, but as they are based on information collected after admission to the ICU, they cannot be used as a predictor for patients in the ED.

In addition to the SOFA score, the authors collected information on other physiologic measures while patients were in the ED: vital signs, oxygen saturation, Glasgow Coma Score, white blood cell count, and lactate concentration. These were all recorded prospectively on standardized forms. The patient population is narrowly focused in terms of case mix: 248 patients with severe sepsis who had resuscitation procedures initiated in the ED. This strategy is a wise one, given the difficulty of developing a model using what would be an otherwise heterogeneous population. Limiting the study to a single institution, however, means that the results reported by Jones et al must be considered exploratory.

The primary statistic chosen for determining the ability to predict hospital mortality was the area under the receiver operating characteristics curve (AU-ROC) (12). This is a measure of "discrimination," i.e., the ability to distinguish between patients who die vs. those who survive. The AU-ROC ranges from 0.50, which indicates that the prediction is no better than flipping a coin, to 1.00, which is a perfect predictor. All of the ICU predictive models cited above have AU-ROC values >0.80. Values lower than that are considered mediocre. Unfortunately, the AU-ROC to predict mortality using the SOFA score taken in the ED was only 0.75.

The authors compare this value with the AU-ROC generated by other variables they had collected, and found that none had higher AU-ROC values than the SOFA score. Given the additional physiologic variables that Jones et al collected, they might have considered a more sophisticated approach. They certainly could have constructed a pseudo–Modified Early Warning System instrument, which most likely would have increased their AU-ROC beyond 0.80.

The authors should be commended for assessing the value of the relatively simple SOFA score in the ED as a predictor of subsequent in-hospital mortality. But in their attempt to maintain simplicity, they gave away the opportunity to look at a metric that had high discrimination with little additional data capture burden. I agree with the authors that using ICU predictive models in the ED is at present not feasible. But, although simplicity can be alluring, it should not trump a comprehensive inclusion of enough variables to generate a precise yet timely prediction. When it comes to predicting outcomes, the angel is in the details.

Andrew A. Kramer, PhD
Cerner Corporation
Vienna, VA

REFERENCES

1. Zimmerman JE, Kramer AA, McNair DS, et al: Acute Physiology and Chronic Health Evaluation (APACHE) IV: Hospital mortality assessment for today's critically ill patients. *Crit Care Med* 2006; 34:1297–1310
2. Metnitz PGH, Moreno RP, Almeida E, et al: SAPS 3—From evaluation of the patient to evaluation of the intensive care unit. Part I: Objectives, methods and cohort description. *Intensive Care Med* 2005; 31:1336–1344
3. Higgins TL, Teres D, Copes WS, et al: Assessing contemporary intensive care unit outcome: An updated Mortality Probability Admission Model (MPM0-III). *Crit Care Med* 2007; 35:827–835
4. Harrison DA, Parry GJ, Carpenter JR, et al: A new risk prediction model for critical care: The Intensive Care National Audit & Research Centre (ICNARC) model. *Crit Care Med* 2007; 35:1091–1098
5. Render ML, Kim M, Deddens J, et al: Variation in outcomes in Veterans Affairs intensive care units with a computerized severity measure. *Crit Care Med* 2005; 33:930–939
6. Bakhshi-Raiez F, Peek N, Bosman RJ, et al: The impact of different prognostic models and their customization on institutional comparison of intensive care units. *Crit Care Med* 2007; 35:2553–2560
7. Zimmerman JE, Kramer AA: Outcome prediction in critical care: The Acute Physiology and Chronic Health Evaluation models. *Curr Opin Crit Care* 2008; 14:491–497
8. DeVita MA, Bellomo R, Hillman K, et al: Findings of the First Consensus Conference on Medical Emergency Teams. *Crit Care Med* 2006; 34:2463–2478
9. Stenhouse C, Coates S, Tivey M, et al: Prospective evaluation of a modified Early Warning Score to aid earlier detection of patients developing critical illness on a general surgical ward. *Br J Anaesth* 1999; 84:663
10. Jones AE, Trzeciak S, Kline JA: The Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation. *Crit Care Med* 2009; 37:1649–1654
11. Vincent JL, Moreno R, Takala J, et al: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med* 1996; 22:707–710
12. Hanley JA, McNeil BJ: The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982; 143:29–36

Old friends: Pneumonia and interleukin-6*

Pneumonia has been termed "The old man's friend" because it may ease suffering at the end of life (1). Previously, investigators have reported that pneumonia has a worse prognosis in elderly men compared with women (2). In this issue of *Critical Care Medicine*, Reade et al (3) provides insights into why older men with pneumonia have a worse prognosis. They specifically measured circulating biomarkers and demonstrated that at admission to the emergency department, men had higher levels of tumor necrosis factor, interleukin-6 (IL-6), IL-10, and lower coagulation factors, including antithrombin-III and factor IX. Men had lower survival compared with women at 30, 90, and 365 days.

The study design strengthens the results reported by this group. First, the study evaluated a large number of patients, 2183, in multiple clinical settings. This increases the likelihood that the results may be generalized to other patients. Second, only community-acquired pneumonia was evaluated rather than multiple different severe, lethal infectious diseases. With this design, the authors increased patient heterogeneity by examining a large number of patients and also increased homogeneity by restricting the study to community-acquired pneumonia. Third, the sophisticated statistical analysis of large, complex data sets with multiple adjustments for confounding factors increases enthusiasm for the work.

Several aspects of this study were anticipated, although there is still value in having a recent publication provide rigorous data documenting widely held beliefs. These beliefs include the observation that men are more likely than women to die of pneumonia. Additionally, men were more likely than women to receive antibiotics within 8 hours of diagnosis further contributing to the literature demonstrating better health care delivered to men compared with women, although it must be acknowledged that there was no difference in the percent of patients receiving antibiotics for 4 hours.

IL-6 is another old friend and it has been widely reported as a biomarker of inflammatory diseases. Other investigators determined that plasma levels of IL-6 are elevated in patients with community-acquired pneumonia (4–6). A small study by Monton et al (7) evaluated cytokine concentrations both within the serum and the bronchoalveolar lavage of patients with pneumonia. Patients with pneumonia had higher levels of IL-6 than controls, and there was a trend toward higher serum levels of IL-6 in patients who died, and also generally higher IL-6 in the lavage fluid compared with serum. Another report by the GenIMS investigators (the same group reporting the findings in this article) showed that plasma levels of IL-6 at discharge also predict mortality over a 1-year period (8).

Numerous previous reports documented that in another lethal infectious disease, sepsis, high circulating levels of IL-6 correlate with mortality (reviewed in Ref. 9). It is probably safe to say that most investigators agree that biomarkers have utility to diagnose disease and predict outcome. It is also probably safe to say that most investigators strongly disagree about the best biomarker for predicting outcome. Another contentious area is whether the biomarkers merely predict clinical trajectory or if they actually cause the disease. In the cecal ligation and puncture model of murine sepsis, plasma levels of IL-6 strongly predict outcome (10), but probably do not actually induce mortality (11). Certainly, the low levels of plasma IL-6 observed in these patients with community-acquired pneumonia did not induce lung injury or mortality (3), even though the data clearly demonstrate that higher levels are associated with worse outcome.

IL-6 has also been reported to be elevated in patients with cardiac disease who are at increased risk of dying or myocardial infarction (12). In the current study, significantly more men had cardiac disease (32%) compared with women (20%). This raises the possibility that the men with their preexisting cardiac disease may have had higher baseline levels of IL-6 that was further elevated by pneumonia.

IL-6 is classically considered a proinflammatory cytokine, whereas IL-10 is an anti-inflammatory cytokine, yet both were elevated in patients who would die. This creates a bit of a quandary for the classic paradigm that deaths caused by bacterial infections are secondary to an overwhelming proinflammatory response that injures cells, tissues, and organs. However, an alternative viewpoint would be that a proinflammatory response manifests itself by the host's ability to produce something, anything, be it a proinflammatory cytokine or an anti-inflammatory cytokine (13). In other words, the capacity to synthesize new proteins not present in the circulation of normal individuals reflects the inflammatory status. Producing either IL-6 or IL-10 shows the capacity to respond. However, additional data in this article would argue against this viewpoint because coagulation proteins were found in patients more likely to die.

The important concept provided by this article is that older men dying of pneumonia have higher levels of the biomarkers tumor necrosis factor, IL-6, and IL-10. A cautious clinical implication of these findings is that men may be a more appropriate target for initial directed anti-inflammatory therapies compared with women.

Daniel G. Remick, MD
Department of Pathology and Laboratory Medicine
Boston University School of Medicine
Boston, MA

REFERENCES

1. Hensel WA: The old man's friend. *JAMA* 2000; 283:1793–1794
2. Myles PR, McKeever TM, Pogson Z, et al: The incidence of pneumonia using data from a

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computerized general practice database. *Epidemiol Infect* 2008:1–8
3. Reade MC, Yende S, D'Angelo G, et al: Differences in immune response may explain lower survival among older men with pneumonia. *Crit Care Med* 2009; 37:1655–1662
4. Calbo E, Alsina M, Rodriguez-Carballeira M, et al: Systemic expression of cytokine production in patients with severe pneumococcal pneumonia: Effects of treatment with a beta-lactam versus a fluoroquinolone. *Antimicrob Agents Chemother* 2008; 52:2395–2402
5. Puren AJ, Feldman C, Savage N, et al: Patterns of cytokine expression in community-acquired pneumonia. *Chest* 1995; 107:1342–1349
6. Thomsen RW, Riis A, Norgaard M, et al: Rising incidence and persistently high mortality of hospitalized pneumonia: A 10-year population-based study in Denmark. *J Intern Med* 2006; 259:410–417
7. Monton C, Torres A, El-Ebiary M, et al: Cytokine expression in severe pneumonia: A bronchoalveolar lavage study. *Crit Care Med* 1999; 27:1745–1753
8. Yende S, D'Angelo G, Kellum JA, et al: Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis. *Am J Respir Crit Care Med* 2008; 177:1242–1247
9. Remick DG: Cytokine therapeutics for the treatment of sepsis: Why has nothing worked? *Curr Pharm Des* 2003; 9:75–82
10. Remick DG, Bolgos GR, Siddiqui J, et al: Six at six: Interleukin-6 measured 6 h after the initiation of sepsis predicts mortality over 3 days. *Shock* 2002; 17:463–467
11. Remick DG, Bolgos G, Copeland S, et al: Role of interleukin-6 in mortality from and physiologic response to sepsis. *Infect Immun* 2005; 73:2751–2757
12. Fisman EZ, Benderly M, Esper RJ, et al: Interleukin-6 and the risk of future cardiovascular events in patients with angina pectoris and/or healed myocardial infarction. *Am J Cardiol* 2006; 98:14–18
13. Osuchowski MF, Welch K, Siddiqui J, et al: Circulating cytokine/inhibitor profiles reshape the understanding of the SIRS/CARS continuum in sepsis and predict mortality. *J Immunol* 2006; 177:1967–1974

High-frequency percussive ventilation: An old mode with a great future*

Hypoxemia and atelectasis are well-known and serious complications of one-lung ventilation (1). Intubation using a double-lumen tube facilitates independent lung ventilation, which alleviates hypoxemia, increases lung volume, and overcomes atelectasis in one-lung ventilation. However, the double-lumen tube does not function optimally in high-resistance airways and hinders access for suctioning secretions (2, 3).

High-frequency ventilation is characterized by breathing frequencies higher than 1 Hz where tidal volumes of 1–3 mL/kg are less than the dead space (4). High-frequency percussive ventilation (HFPV) is a mode of high-frequency ventilation that delivers small bursts of gas at 300–600 cycles per minute and relies on chest wall elastic recoil pressure for passive exhalation. HFPV is designed to be used in conjunction with mechanical ventilation or as a stand-alone treatment. The amplitude of pressure oscillations depends on the pulsatile flow amplitude and on the impedance of the respiratory system. Therefore, flow oscillations can be delivered on top of mechanical breaths or on top of spontaneous breathing (5, 6). Nowadays, high-frequency ventilation modes are a late option to sustain adequate gas exchange in adult patients with acute respiratory distress syndrome (4), and HFPV has led to improved oxygenation in cohort studies of patients with acute brain injury (7), acute respiratory distress syndrome (8), or acute smoke inhalation (9). In parallel, HFPV has been used to facilitate high-frequency–assisted airway clearance by vibrating the cilia layer. However, there is not enough data to consider HFPV superior to other techniques of high-frequency–assisted airway clearance like chest wall compression or chest wall oscillation (10, 11).

In this issue of *Critical Care Medicine*, Lucangelo et al (12) report the results of a randomized study on a novel use of HFPV in patients undergoing elective partial lung resection. After patients were placed in lateral decubitus and dependent lung ventilation was instituted, the nondependent lung was randomized to receive either humidified continuous positive airway pressure at 5 cm H_2O or HFPV at a percussion rate of 500 cycles per minute and a mean pulsatile pressure of 5 cm H_2O. After the surgical procedure was completed, patients had the same standard of care until hospital discharge. Interestingly, patients in the HFPV group had significantly better oxygenation and airway clearance of secretions, as well as a higher probability of being discharged earlier to the ward.

The study by Lucangelo et al (12) is important because it demonstrates that HFPV is efficacious not only in increasing Pao_2 during one-lung ventilation, but also in improving clearance of secretions, thus, enabling better outcome. These results from the well-controlled perioperative period might also have importance in the more general critical care arena. HFPV helps mobilize secretions from the periphery of the lung to larger airways; however, eliminating secretions depends on the patient's ability to cough them up or, in intubated patients, on the healthcare team's ability to aspirate them. This is clear in the article by Lucangelo et al (12), where although the final amount of secretions was the same in both groups, it was eliminated 1 day earlier in the HFPV group. In critically ill patients, secretion removal is crucial. We can speculate that in patients with effective cough, early-assisted airway clearance might increase the number of ventilator-free days, decreasing episodes of nosocomial lung infections and extubation failures. In fact, Clini et al (13) recently reported that the addition of percussive ventilation to the usual chest physiotherapy routine in tracheostomized patients

***See also p. 1663.**

Key Words: one-lung ventilation; hypoxemia; lung resection; high-frequency percussive ventilation; lung secretions; mechanical ventilation

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improved gas exchange and expiratory muscle performance and reduced the incidence of pneumonia. However, these potential benefits might be totally lost in patients who are unable to expectorate, like patients with neuromuscular diseases or intensive care unit–acquired weakness, where secretions, although present in the airways, are extremely difficult to be mechanically suctioned.

Several points must be considered before the broad application of HFPV in mechanically ventilated critically ill patients. First, adding HFPV to conventional ventilation reduces humidity and a heated humidifier on the inspiratory line would be necessary to provide adequate humidification (14). Second, mechanical loads, such as those caused by alterations in resistance and compliance, affect flow, volume, airway pressure, and their waveforms (6, 14). Third, in conjunction with a driving ventilator, intrapulmonary percussive ventilation may add pressure and volume to tidal ventilation and generate intrinsic positive end-expiratory pressure (14). Fourth, before HFPV can be considered suitable for standard intensive care practice, evidence needs to be accumulated to demonstrate better patient–ventilator interaction with HFPV and the absence of significant adverse effects. Finally, when HFPV is added to current ventilators it could adversely affect the ventilator's ability to monitor pressures and volumes and may cause the ventilator alarm to go off incessantly.

In conclusion, HFPV is an old but very attractive technique. In short-term use, HFPV helps earlier secretion mobilization with some clinical benefits and no adverse effects. However, before broadly applying HFPV in intensive care patients, it is necessary to determine which subgroups of patients might benefit most from HFPV, and further technological developments are necessary to ensure that the technique does not alter ventilator function.

Luis Blanch, MD, PhD
CIBER de Enfermedades Respiratorias
Instituto de Salud Carlos III
Madrid, Spain
Critical Care Center
Corporació Parc Tauli
Sabadell, Barcelona, Spain
Jesús Villar, MD, PhD
CIBER de Enfermedades Respiratorias
Instituto de Salud Carlos III
Madrid, Spain
Research Unit
Hospital Universitario Dr. Negrin
Las Palmas, Spain
J. López Aguilar, PhD
CIBER de Enfermedades Respiratorias
Instituto de Salud Carlos III
Madrid, Spain
Critical Care Center
Corporació Parc Tauli
Sabadell, Barcelona, Spain

REFERENCES

1. Sentürk M: New concepts of the management of one-lung ventilation. *Curr Opin Anaesthesiol* 2006; 19:1–4
2. Tuxen DW: Independent lung ventilation. *In*: Principles and Practice of Mechanical Ventilation. Second Edition. Tobin MJ (Ed). New York, McGraw Hill 2006, pp 573–593
3. Blanch L, Van der Kloot TE, Youngblood AM, et al: Application of tracheal gas insufflation to acute unilateral lung injury in an experimental model. *Am J Respir Crit Care Med* 2001; 164:642–647
4. Fessler HE, Derdak S, Ferguson ND, et al: A protocol for high-frequency oscillatory ventilation in adults: Results from a roundtable discussion. *Crit Care Med* 2007; 35:1649–1654
5. Gallagher TJ, Boysen PG, Davidson DD, et al: High-frequency percussive ventilation compared with conventional mechanical ventilation. *Crit Care Med* 1989; 17:364–366
6. Lucangelo U, Antonaglia V, Zin WA, et al: Effects of mechanical load on flow, volume and pressure delivered by high-frequency percussive ventilation. *Respir Physiol Neurobiol* 2004; 142:81–91
7. Salim A, Miller K, Dangleben D, et al: High-frequency percussive ventilation: An alternative mode of ventilation for head-injured patients with adult respiratory distress syndrome. *J Trauma* 2004; 57:542–546
8. Velmahos GC, Chan LS, Tatevossian R, et al: High-frequency percussive ventilation improves oxygenation in patients with ARDS. *Chest* 1999; 116:440–446
9. Reper P, Wibaux O, Van Laeke P, et al: High frequency percussive ventilation and conventional ventilation after smoke inhalation: A randomised study. *Burns* 2002; 28:503–508
10. Chatburn RL: High-frequency assisted airway clearance. *Respir Care* 2007; 52:1224–1235
11. Hass CF, Loik PS, Gay SE: Airway clearance applications in the elderly and in patients with neurologic and neuromuscular compromise. *Respir Care* 2007; 52:1362–1381
12. Lucangelo U, Antonaglia V, Zin WA, et al: High-frequency percussive ventilation improves perioperatively clinical evolution in pulmonary resection. *Crit Care Med* 2009; 37:1663–1669
13. Clini EM, Antoni FD, Vitacca M, et al: Intrapulmonary percussive ventilation in tracheostomized patients: A randomized controlled trial. *Intensive Care Med* 2006; 32:1994–2001
14. Dellamonica J, Louis B, Lyazidi A, et al: Intrapulmonary percussive ventilation superimposed on conventional ventilation: Bench study of humidity and ventilator behaviour. *Intensive Care Med* 2008; 34:2035–2043

Is lactate the "Holy Grail" of biomarkers for sepsis prognosis?*

When oxygen delivery falls below a critical delivery or anaerobic threshold, the amount of oxygen available for consumption is not able to meet the needs of an organism. These delivery and consumption inadequacies result in cellular hypoxia. Under hypoxic conditions, mitochondrial oxidative phosphorylation fails and energy metabolism becomes dependent on anaerobic glycolysis (1). Anaerobic glycolysis sharply increases the production of cellular lactate that diffuses into the blood during prolonged cell ischemia. Elevated circulating lactate concentration thus indicates widespread inadequate tissue oxygenation due to inadequate oxygen delivery and/or consumption (2).

Numerous previous studies have documented the utility of lactate as a prognostic indicator in shock states (2, 3). The use of lactate measurements is gaining recognition in acute care medicine as a useful indicator of tissue hypoperfusion. In fact, several recent reports document the value of considering lactate levels for inclusion in aggressive resuscitation protocols for septic shock and in monitoring the response of septic patients to resuscitation (4–6). Furthermore, lactate screening as a method of risk stratification and prognosis has been shown to be beneficial in hemodynamically stable patients with suspected infection (7). Underscoring the importance of these data is the fact that point-of-care testing performed at the patient's bedside is becoming more common (8, 9).

In this issue of *Critical Care Medicine*, Mikkelsen et al (10) present a retrospective cohort study of emergency department patients with severe sepsis to investigate the association between initial serum lactate, organ dysfunction, and shock. These investigators asked a particularly important question: are elevated lactate levels usually seen in subjects with clinically apparent organ dysfunction and shock? Said another way, does the value of a lactate level in septic patients remain, even in the absence of obvious clinical markers of illness severity (organ dysfunction and shock)?

The authors of this report present a methodologically sound study with meticulous detail in assuring the internal validity of the study by using standard definitions and recommended methods for retrospective chart reviews. The study was fairly large, with 830 subjects included. As has been previously reported (11), nonsurvivors had significantly higher initial levels than did survivors in subjects both with and without shock. The authors also found that when lactate levels are grouped (low <2, intermediate 2–3.9, and high >3.9 mmol/L), both intermediate and high levels are associated with significantly higher mortality compared with low levels, as has been previously reported (7). However, one interesting finding in this report (depicted in Fig. 2) was that the prognostic value reached a plateau in the nonshock group around 8 mmol/L, but that same plateau was not reached in the shock group until 18 mmol/L. This suggests that high lactate levels need to be interpreted in context of the clinical scenario and that simply thinking of lactate levels in compartments or groups (low, intermediate, and high) may marginalize the value of this test.

The most important finding in this report was that the association between lactate level and mortality was independent of clinically apparent organ dysfunction and shock. This finding substantially enhances our understanding of the prognostic value of an initial lactate level performed at the time of recognition of sepsis. These data indicate that the clinician should carefully consider the significance of an elevated lactate level in a patient who has no other clinically apparent signs of high acuity.

Many studies have shown that escalation of care in patients with severe sepsis and hypoperfusion (manifested as persistent hypotension after fluids or a lactate ≥ 4 mmol/L) is associated with benefit (5, 4, 12–14). The study by Mikkelsen et al and others (11) have found even intermediate (2–3.9 mmol/L) lactate levels to be associated with higher mortality. What we do not presently know, and the question that this study does not answer, is what should we do with patients who have severe sepsis, are not in shock, and have an intermediate level (the group that makes up the largest lactate stratum in the study by Mikkelsen et al)?

In the end, Mikkelsen et al have presented a study that enhances our knowledge about the value of lactate in patients with sepsis. Namely, lactate measurements in patients with sepsis without clinically apparent organ dysfunction have important prognostic value. Given the cumulative data known about lactate to date, it makes one wonder if lactate is the "Holy Grail" of biomarkers for sepsis.

Alan E. Jones, MD
Michael A. Puskarich, MD
Department of Emergency Medicine
Carolinas Medical Center
Charlotte, NC

REFERENCES

1. Watts JA, Kline JA: Bench to bedside: The role of mitochondrial medicine in the pathogenesis and treatment of cellular injury. *Acad Emerg Med* 2003; 10:985–997
2. Weil MH, Afifi AA: Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). *Circulation* 1970; 41:989–1001
3. Huckabee WE: Abnormal resting blood lactate. *Am J Med* 1961; 30:833–839
4. Jones AE, Focht A, Horton JM, et al: Prospective external validation of the clinical effectiveness of an emergency department-based early goal-directed therapy protocol for severe sepsis and septic shock. *Chest* 2007; 132:425–432
5. Trzeciak S, Dellinger RP, Abata NL, et al: Translating research to clinical practice: A 1-year experience with implementing early goal-directed therapy for septic shock in the emergency department. *Chest* 2006; 129: 225–235
6. Nguyen HB, Rivers EP, Knoblich BP, et al:

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Key Words: lactate; sepsis; shock; organ dysfunction

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Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med* 2004; 32:1637–1642
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. Jones AE, Kline JA: Use of goal-directed therapy for severe sepsis and septic shock in academic emergency departments. *Crit Care Med* 2005; 33:1888–1889
9. Sivayoham N: Management of severe sepsis and septic shock in the emergency department: A survey of current practice in emergency departments in England. *Emerg Med J* 2007; 24:422
10. Mikkelsen ME, Miltiades AN, Gaieski DF, et al: Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. *Crit Care Med* 2009; 37:1670–1677
11. Howell MD, Donnino M, Clardy P, et al: Occult hypoperfusion and mortality in patients with suspected infection. *Intensive Care Med* 2007; 33:1892–1899
12. Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377
13. Micek ST, Roubinian N, Heuring T, et al: Before-after study of a standardized hospital order set for the management of septic shock. *Crit Care Med* 2006; 34:2707–2713
14. Shapiro NI, Howell MD, Talmor D, et al: Implementation and outcomes of the Multiple Urgent Sepsis Therapies (MUST) protocol. *Crit Care Med* 2006; 34:1025–1032

Keratinocyte growth factor in acute lung injury—A work in progress*

In experimental and clinical studies of lung injury, improvement in alveolar epithelial function is associated with a reduction in pulmonary edema (1–3), indicating that a strategy to accelerate epithelial repair in acute lung injury (ALI) may be beneficial. Keratinocyte growth factor (KGF) modulates a variety of mechanisms recognized to be important in alveolar repair and resolution in ALI. Effects of KGF on alveolar epithelial cells *in vitro* include increased proliferation, increased surfactant protein production, and altered matrix metalloproteinase release. KGF also down-regulates proinflammatory cytokines and enhances endothelial cell resistance to injury (4). In animal models of ALI, KGF treatment reduces alveolar capillary permeability and pulmonary edema, and improves survival (5). Two clinical studies have reported KGF levels in patients with ALI. KGF was higher in nonsurvivors with more severe lung injury. This may indicate that the reparative activity associated with increased KGF in the setting of severe alveolar damage is insufficient, providing a rationale for augmentation of KGF levels as a therapy to restore alveolar function during injury (6, 7).

In this issue of *Critical Care Medicine*, Chandel et al (8) report the potentially interesting finding that bronchoalveolar lavage (BAL) fluid from a small cohort of patients with ALI decreases KGF messenger RNA (mRNA) expression and that this effect is mediated in part by transforming growth factor (TGF)-β1. However, shortcomings in the experimental design and data available limit the interpretation of the data.

In relation to the BAL procedure in this study, several important issues are worth highlighting. The authors report instilling 60 mL aliquots up to three times in keeping with published recommendations (9); however, it is unclear how the reported instilled volumes of 90 ± 32 mL for the patients with ALI, 72 ± 26 mL for the patients with cardiogenic edema, and 60 mL for the control subjects were achieved. Furthermore, although the authors acknowledge this as a limitation in the discussion, there was a 50% variation in the volume of BAL instilled in the patients with ALI compared with the control subjects. The authors argue that a larger volume instilled with the attendant greater dilutional effects on alveolar mediators might be expected to attenuate the ALI BAL fluid–induced fall in KGF mRNA expression. This does not hold good if a mediator that promotes KGF mRNA expression, such as interleukin-1β, tumor necrosis factor-α, or prostaglandin E2 (5), is diluted to a greater extent. The variable dilutional effects of using different BAL volumes is clearly a major weakness in this article. Another consideration is that the control subjects were not strictly healthy subjects with normal lung parenchyma; it would have been reassuring to have data that the subjects had no underlying pathology. Finally, given that nonbronchoscopic lavage may not sample the alveolar space and does not provide similar results in the assessment of alveolar inflammation in patients with ALI compared with bronchoscopic lavage (10), the use of both bronchoscopic and nonbronchoscopic lavage is inappropriate in the same study. These limitations emphasize the need for standardization on the use of BAL in research in ALI in keeping with published recommendations (9) to allow data to be interpreted with confidence.

In this study, BAL fluid from patients with ALI decreased KGF at the gene level. However, a fundamental question remains as to how much translates to the protein level. In this study, although KGF levels in BAL from patients with ALI are reported, KGF levels from the patients with cardiogenic pulmonary edema and control subjects are not presented and, therefore, it is not possible to determine the effects on protein secretion. Furthermore, although discussed, the absence of a correlation between ALI BAL fluid KGF protein levels and KGF mRNA suppressing activity is not adequately explained. These data contrast with a recent study that comprehensively examined the effect of BAL fluid from a larger well-characterized cohort of patients with ALI, ventilated controls, and control subjects (defined as normal bronchoscopy, chest computed tomography, and microbiologic examination) on both KGF protein secretion and mRNA expression (11). In this study, Quesnel et al found the oppo-

***See also p. 1678.**

Key Words: ALI; keratinocyte growth factor; bronchoalveolar lavage

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site effect, with up-regulation of KGF from fibroblasts by BAL from patients with ALI. A possible reason, which is discussed, for this difference relates to the differing time points of BAL sampling in the two studies (within 48 hours after intubation in this study compared with a mean of 4 days). However, clearly more data on temporal mRNA expression and protein levels would add to our understanding of the role of KGF during the course of ALI. This may have implications on the timing of pharmacologic treatment of ALI with exogenous KGF.

That the effect of KGF down-regulation is mediated by TGF-β1 is interesting but unconfirmed. TGF-β1 can be activated by many mechanisms and BAL fluid processing can lead to TGF-β1 activation and, therefore, may not accurately reflect *in vivo* activity (12). With the above caveat in relation to accuracy of TGF-β1 bioactivity measurement in BAL fluid *ex vivo*, TGF-β1 activity in BAL fluid was not measured in this study. The authors report historical data that transcriptionally active TGF-β1 is detected at concentrations up to 5 ng/mL in early ALI BAL fluid. Considering the effects of BAL dilution, this would approximate to 250–500 ng/mL in epithelial lining fluid. Therefore, it would have been more useful to use TGF-β1 levels in the *in vitro* experiments, which reflect the pathophysiologically relevant levels seen in patients with ALI.

KGF is available as a recombinant human protein and is approved for human administration in the treatment of oral mucositis associated with radiotherapy and chemotherapy and may represent a novel pharmacologic therapy in ALI. Although this study is interesting, further translational research is required to understand the role of KGF in the pathogenesis and resolution of ALI. These data, if confirmed, support the concept that exogenous KGF may be a therapeutic option, particularly early in the course of ALI, to augment epithelial repair and overcome the inhibitory effect of the inflammatory milieu in the alveolar space in ALI on endogenous KGF production.

Cecilia M. O'Kane, PhD
Respiratory Medicine Research Programme
Centre for Infection and Immunity, School of Medicine
Dentistry and Biomedical Sciences, Queen's University of Belfast
Belfast, UK
David R. Thickett, DM
Lung Injury and Fibrosis Treatment Programme
Department of Medical Sciences, Medical School
University of Birmingham
Birmingham, UK
Danny F. McAuley, MD
Respiratory Medicine Research Programme
Centre for Infection and Immunity, School of Medicine
Dentistry and Biomedical Sciences, Queen's University of Belfast
Belfast, UK

REFERENCES

1. McAuley DF, Frank JA, Fang X, et al: Clinically relevant concentrations of beta2-adrenergic agonists stimulate maximal cyclic adenosine monophosphate-dependent airspace fluid clearance and decrease pulmonary edema in experimental acid-induced lung injury. *Crit Care Med* 2004; 32: 1470–1476
2. Perkins GD, McAuley DF, Thickett DR, et al: The beta agonist lung injury trial (BALTI): A randomised placebo controlled clinical trial. *Am J Respir Crit Care Med* 2006; 173: 281–287
3. Perkins GD, Gao F, Thickett DR: In vivo and in vitro effects of salbutamol on alveolar epithelial repair in acute lung injury. *Thorax* 2008; 63:215–220
4. Gillis P, Savla U, Volpert OV, et al: Keratinocyte growth factor induces angiogenesis and protects endothelial barrier function. *J Cell Sci* 1999; 112:2049–2057
5. Ware LB, Matthay MA: Keratinocyte and hepatocyte growth factors in the lung: Roles in lung development, inflammation, and repair. *Am J Physiol Lung Cell Mol Physiol* 2002; 282:L924–L940
6. Verghese GM, McCormick-Shannon K, Mason RJ, et al: Hepatocyte growth factor and keratinocyte growth factor in the pulmonary edema fluid of patients with acute lung injury. Biologic and clinical significance. *Am J Respir Crit Care Med* 1998; 158: 386–394
7. Stern JB, Fierobe L, Paugam C, et al: Keratinocyte growth factor and hepatocyte growth factor in bronchoalveolar lavage fluid in acute respiratory distress syndrome patients. *Crit Care Med* 2000; 28:2326–2333
8. Chandel NS, Budinger GRS, Mutlu GM, et al: Keratinocyte growth factor expression is suppressed in early acute lung injury/acute respiratory distress syndrome by smad and c-Abl pathways. *Crit Care Med* 2009; 37: 1678–1684
9. Haslam PL, Baughman RP: Report of ERS task force: Guidelines for measurement of acellular components and standardization of BAL. *Eur Respir J* 1999; 14:245–248
10. Perkins GD, Chatterjee S, McAuley DF, et al: Non-bronchoscopic bronchoalveolar lavage cannot replace bronchoscopic bronchoalveolar lavage in the assessment of alveolar inflammation in ARDS. *Crit Care Med* 2005; 34:57–64
11. Quesnel C, Marchand-Adam S, Fabre A, et al: Regulation of hepatocyte growth factor secretion by fibroblasts in patients with acute lung injury. *Am J Physiol Lung Cell Mol Physiol* 2008; 294:L334–L343
12. Munger JS, Huang X, Kawakatsu H, et al: The integrin alpha v beta 6 binds and activates latent TGF beta 1: A mechanism for regulating pulmonary inflammation and fibrosis. *Cell* 1999; 96:319–328

Steroids in cardiac surgery: Right time, right dose, right patient group*

Cardiac surgery involving cardiopulmonary bypass (CPB) evokes a predictable systemic inflammatory insult. Despite modification of surgical techniques, improvement in biocompatibility of the bypass circuit, and advances in postoperative intensive care, cardiac surgery remains associated with significant postoperative morbidity—capillary leak, decline in cardiac function, disordered hemostasis, and multiorgan dysfunction. Corticosteroids have been used intermittently for their anti-inflammatory effects in sepsis and trauma, and perioperatively in cardiac surgery. Although administration of perioperative steroids (both immunosuppressive and physiologic doses) have consistently been associated with a reduction of circulating biomarkers following cardiac surgery, clear evidence of clinical benefit remains obscured by conflicting single-center study results (1–4).

In this issue of *Critical Care Medicine*, Weis et al (5) have added to the evidence suggesting that where selectively administered, perioperative continuous dosing with hydrocortisone may improve clinical outcome in adult patients undergoing CPB. In this prospective study, 36 high-risk adults undergoing cardiac surgery were randomized to receive placebo or 100 mg of hydrocortisone intravenously before induction of anesthesia, followed by 24 hours of continuous infusion of 10 mg/hr, with reducing dose during the following 3 days. Reflecting the advantage of single-center studies, anesthesia, CPB, and postoperative intensive care were standardized, and all patients received the anti-inflammatory agent aprotinin. In keeping with the primary end point, this study showed a significant reduction in circulating interleukin-6 levels at 4 and 24 hours in those patients receiving hydrocortisone, with higher levels of circulating interleukin-10 at the slightly earlier time points of 1 and 4 hours postoperatively.

Although the study was powered to detect a difference in postoperative circulating cytokine levels (interleukin-6/interleukin-10 ratio), the group of patients receiving stress dose hydrocortisone (n = 19) had a trend toward increased postoperative indices of oxygenation, with a significant reduction in the incidence of atrial fibrillation, duration of catecholamine support, and intensive care unit stay. Of note, however, the improved oxygenation did not translate into shorter duration of ventilation. Therefore, the reader may conclude that the reduced intensive care unit stay was secondary to improved postoperative hemodynamic stability and, consequently, a decreased requirement for catecholamine support. Interestingly, the overall length of hospitalization was not significantly different in the two groups.

Mortality (although easy to define) is no longer an appropriate end point in clinical studies of cardiac surgery. Although morbidity is felt largely to be secondary to the patients' inflammatory response to surgery and CPB, acceptable and measurable end points are contentious. Acute measures of cardiac function and end organ perfusion are desirable, but despite a market flooded with technology to measure cardiac output (pulmonary artery catheter, NICO, PiCCO, LiDCO, CardioQ), we have failed to even show a correlation between cardiac output and outcome in critical care. Perhaps for the patient duration of ventilation, length of hospital stay and quality of life on discharge are what truly matter. However, many factors contribute to delay a patient's discharge and there is still no agreed measure for quality of life.

As a result, many studies rely on modified biomarker levels as evidence of effect and use correlations between biomarkers and outcome measures to suggest efficacy. Weis et al have added to the existing data to suggest stress dose steroids given to patients at risk of significant postoperative systemic inflammatory response syndrome and organ dysfunction will attenuate the inflammatory response observed in adult patients undergoing CPB. However, a large study showing definitive association with clinical benefit is lacking. As raised by the authors in the discussion, conflicting results from previously published studies may reflect inappropriate selection of target population, type, dose, and dosing regimen of the steroid used. Thirty years of heterogeneous use of perioperative steroids in cardiac surgery has failed to consistently demonstrate benefit and allay concerns about harm. As in septic shock, the time has come for an adequately powered multicentered randomized control trial to scientifically test if perioperative corticosteroids are of clinical benefit to patients undergoing cardiac surgery, to identify those patients most likely to benefit and the most effective dosing regimen to use, and to dispel concerns of potential harm (6).

Meredith L. Allen, FRACP, PhD
Nazima Pathan, MRCPCH, PhD
Imperial College/Royal
Brompton Hospital
London, UK

REFERENCES

1. Whitlock RP, Chan S, Devereaux PJ, et al: Clinical benefit of steroid use in patients undergoing cardiopulmonary bypass: A meta-analysis of randomized trials. *Eur Heart J* 2008; 29:2592–2600
2. Whitlock RP, Rubens FD, Young E, et al: Pro: Steroids should be used for cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 2005; 19: 250–254
3. Sulzer CF, Mackensen GB, Grocott HP: Con: Methylprednisolone is not indicated for patients during cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 2005; 19:255–258
4. Chaney MA: Corticosteroids and cardiopulmonary bypass: A review of clinical investigations. *Chest* 2002; 121:921–931
5. Weis F, Beiras-Fernandez A, Schelling G, et al: Stress doses of hydrocortisone in high-risk patients undergoing cardiac surgery: Effects on interleukin-6 to interleukin-10 ratio and early outcome. *Crit Care Med* 2009; 37: 1685–1690
6. Sprung CL, Annane D, Keh D, et al: Hydrocortisone therapy for patients with septic shock. *N Engl J Med* 2008; 358:111–124

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The cycles of heart, lungs, and science*

In 1988, Lemaire et al (1) published a landmark investigation into the cardiovascular effects of weaning. By using an array of invasive physiologic and nuclear radiographic measurements, they showed that some patients failed weaning because they developed left ventricular dysfunction and elevated pulmonary artery occlusion pressure (PAOP) on switching from positive pressure to spontaneous breathing. Fast forward to 2009, Dr. Teboul, who was then a junior author of that article, is now the senior author of a follow-up study by Lamia et al (2) published in this issue of *Critical Care Medicine*.

Lamia et al update the invasive diagnostics of 1988 by showing that certain echocardiographic findings during a spontaneous breathing trial correspond to a PAOP >18 mm Hg. This may have substantial clinical utility. On the basis of the work done by Lemaire et al, I suspect left ventricular dysfunction as a cause of weaning failure in patients whose respiratory mechanics would otherwise predict success. However, resting echocardiography may be normal, and I do not routinely insert a pulmonary artery catheter in such patients. Echocardiography during the stress of a spontaneous breathing trial might confirm weaning-induced cardiac dysfunction, and thereby guide therapy. In a letter to the editor, Teboul and Richard (3) had decried the lack of echocardiographic data allowing noninvasive evaluation of the left ventricular response to weaning. I applaud their effort to fill that void. This is not, however, the data from this study that I find most curious.

I was a fellow in training when Lemaire et al (1) published their seminal article. My mentor, Sol Permutt, reviewed it and wrote an editorial (4). I impetuously questioned the reasoning in his editorial, prompting two decades of periodic friendly and stimulating argument. It is now I who has been given the opportunity to review and editorialize this follow-up article, and I am struck by some of the same findings that intrigued Dr. Permutt.

Patients who seemed ready to wean but had failed two spontaneous breathing trials were studied during a third trial. For this, they were changed from positive pressure ventilation with 5–7 mm Hg positive end-expiratory pressure (PEEP) to a T-piece. When changing from positive pressure with PEEP to spontaneous breathing without PEEP, pleural pressure should fall both during inspiration, due to patient effort, and during expiration, due to the loss of PEEP. One would also expect right atrial pressure (RAP) to fall, because pleural pressure surrounds the right atrium. In the study by Lemaire et al, the patients who manifested left ventricular dysfunction during weaning paradoxically *increased*, rather than *decreased*, RAP when they began breathing spontaneously. Although venous return will rise when pleural pressure falls, this could not cause RAP to rise above its baseline value, because it is the fall in RAP that augments venous return in the first place. Dr. Permutt reasoned that RAP was rising above its starting value because the diaphragm was now contracting around an engorged splanchnic and hepatic vasculature. This directed more blood back toward the heart than would lower pleural pressure alone.

In the current study, patients were divided into those whose PAOP either rose or failed to rise above 18 mm Hg by the end of their trial of spontaneous breathing. Among the latter, there was no change in RAP. However, once again, in the patients whose PAOP rose from a mean of 12 to 26 mm Hg, RAP rose from 5 to 12 mm Hg (both $p < 0.05$; Table 1 in Ref. 2). If one conservatively estimates that pleural pressure fell by 2 mm Hg because of the loss of PEEP, the transmural filling pressure of the right ventricle seems to have risen by 9 mm Hg at end expiration. What factors may have caused this?

First, contraction of the diaphragm seems, at best, a minor cause. Although Dr. Permutt may be rising to rebut as he reads this, the RAP is reported at end expiration when the diaphragm is relaxed. One might speculate that the inspiratory increase in venous return has not yet fully left the right side of the heart by end expiration, despite the passage of at least three heartbeats. However, this end-expiratory remnant of an enormous inspiratory increase in right ventricular preload should have induced a proportionally large increase in cardiac output. Yet, the stroke volume index in these patients fell slightly from 39 to 37 mL/m^2 (not significant; Table 1 in Ref. 2). Therefore, an increase in preload is an unsatisfying unitary explanation for the RAP elevation. Another potential explanation is that the observed increase in pulmonary artery pressure precipitated acute cor pulmonale. This is not supported by such a stable mean stroke volume, but the combined increase in right ventricular preload and afterload from all of the above mechanisms may certainly have combined to increase RAP.

A final explanation for the increase in RAP is that pleural pressure rose, rather than fell, during spontaneous breathing trials in these patients. Dynamic hyperinflation and expiratory muscle recruitment have been shown to increase both esophageal and PAOP when patients with chronic obstructive pulmonary disease exercise or hyperventilate (5, 6). Dyspneic subjects recruit expiratory muscles and can elevate PAOP even in the absence of air flow obstruction (7–9). In the current article, the same group of patients whose PAOP and RAP rose during spontaneous breathing also increased their pulmonary artery pressure (see Ref. 2, Table 1). A potential unifying explanation for this is that pleural pressure was the tide lifting all of these intrathoracic boats.

Regardless of whether RAP rose because of preload, left heart dysfunction, pleural pressure elevation, or a combination of factors, it might serve as another

***See also p. 1696.**

Key Words: heart–lung interactions; weaning; mechanical ventilation; hemodynamic monitoring

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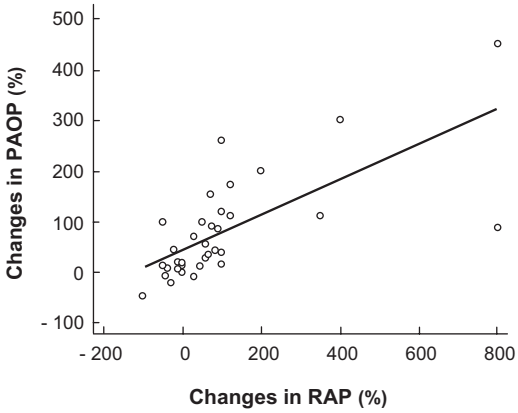

Figure 1. Relationship between percent changes in right atrial pressure (*RAP*) and pulmonary artery occlusion pressure (*PAOP*) induced by the trial of spontaneous breathing in the subjects in Ref. 2. Changes in the two variables correlated with each other ($Y = 0.34x + 44$; $r^2 = .47$, $p < 0.05$).

marker of PAOP elevation. The authors kindly shared Figure 1, which shows that the increases in PAOP and RAP correlated with each other (Fig. 1). Although less accurate than the echocardiographic indices, they calculated that a >60% increase in RAP predicted a PAOP >18 mm Hg with sensitivity and specificity of 85% and 76%, respectively. In patients with central venous catheters or in hospitals lacking the echocardiographic expertise, observation of the weaning-induced change in RAP may also identify patients who could benefit from diuresis.

Lamia et al provide a beautiful illustration of the many cycles of heart–lung interactions. To the respiratory cycle and the cardiac cycle, we can add the cycle of scientists. I hope that now one of my impetuous fellows will read these articles and challenge *my* reasoning.

Henry E. Fessler, MD
Division of Pulmonary and Critical Care Medicine
Johns Hopkins University
Baltimore, MD

REFERENCES

1. Lemaire F, Teboul JL, Cinotti L, et al: Acute left ventricular dysfunction during unsuccessful weaning from mechanical ventilation. *Anesthesiology* 1988; 69:171–179
2. Lamia B, Maizel J, Ochagavia A, et al: Echocardiographic diagnosis of pulmonary artery occlusion pressure elevation during weaning from mechanical ventilation. *Crit Care Med* 2009; 37:1696–1701
3. Teboul JL, Richard C: How to diagnose weaning-induced pulmonary edema? *Intensive Care Med* 2006; 32:938
4. Permutt S: Circulatory effects of weaning from mechanical ventilation: The importance of transdiaphragmatic pressure. *Anesthesiology* 1988; 69:157–160
5. Butler J, Schrijen F, Henriquez A, et al: Cause of the raised wedge pressure on exercise in chronic obstructive pulmonary-disease. *Am Rev Respir Dis* 1988; 138: 350–354
6. Potter WA, Olafsson S, Hyatt RE: Ventilatory mechanics and expiratory flow limitation during exercise in patients with obstructive lung disease. *J Clin Invest* 1971; 50:910–919
7. Chandra A, Coggeshall JW, Ravenscraft SA, et al: Hyperpnea limits the volume recruited by positive end-expiratory pressure. *Am J Respir Crit Care Med* 1994; 150:911–917
8. Lessard MR, Lofaso F, Brochard L: Expiratory muscle-activity increases intrinsic positive end-expiratory pressure independently of dynamic hyperinflation in mechanically ventilated patients. *Am J Respir Crit Care Med* 1995; 151:562–569
9. Hoyt JD, Leatherman JW: Interpretation of the pulmonary artery occlusion pressure in mechanically ventilated patients with large respiratory excursions in intrathoracic pressure. *Intensive Care Med* 1997; 23: 1125–1131

Surviving critical illness is not without its perils: A perspective on depression in acute lung injury survivors*

The experience of surviving an acute life-threatening illness or sustaining a severe physical injury necessitating treatment in an intensive care unit (ICU) is inherently stressful and frightening. There has been a growing body of literature demonstrating that surviving critical illness carries with it a substantial psychological burden, including depression. Recent systematic reviews of depression in general ICU and acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) survivors found that 28% of patients had substantial depressive symptoms up to 2 years following hospital discharge (1, 2).

Several logical questions are stimulated by these investigations. What is the etiology of depressive symptoms in critical illness survivors? Are endogenous patient-related factors to blame? Are ICU service-delivery characteristics the primary culprit? Emerging studies are producing clues to this enigma. A pre-ICU history of depression predicted depressive symptoms at 2 and 6 months post-ICU in one study of patients who survived acute respiratory failure (3). In the ALI/ARDS survivor population, longer ICU lengths of stay, durations of mechanical ventilation, and durations of sedation predicted later depressive symptoms (4, 5), a finding not duplicated in general ICU survivors (1). Also, ICU hypoglycemia predicted substantial depressive symptoms in ALI/ARDS survivors 3 months after hospital discharge in one recent study (6).

In this issue of *Critical Care Medicine*, Dowdy et al (7) provide further insights into the answers to these questions by reporting on the prevalence of, as well as

***See also p. 1702.**

Key Words: intensive care units; critical care; depression; respiratory distress syndrome; adult; outcome assessment (health care)

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potential risk factors for, substantial depressive symptoms in the largest cohort of ALI/ARDS survivors assembled 6 months post-ICU. This study prospectively assessed depressive symptoms in 160 patients using the Hospital Anxiety and Depression scale. The point prevalence of symptoms suggestive of major depression in this sample was 26%, similar to prior studies on ALI/ARDS survivors (2). Also, Dowdy et al found that pre-ICU depressive and/or anxiety symptoms, admission to a surgical ICU, a maximum Sequential Organ Failure score of >10, and a single ICU service-delivery characteristic, a mean daily benzodiazepine dose of ≥75 mg of midazolam equivalent, all predicted a greater post-ICU depressive symptom burden. Studies on general ICU survivors have found that ICU benzodiazepine receipt may increase the risk of subsequent posttraumatic stress disorder symptoms (8). Dowdy et al are the first to find this association with post-ICU depressive symptoms.

It is important to note that this study does have limitations. First, a screening questionnaire, the Hospital Anxiety and Depression scale, was used to ascertain depressive symptoms. Although a screening questionnaire can assess the burden of symptoms, a diagnosis of major depression cannot be made without a structured or semistructured diagnostic interview. In addition, pre-ICU depressive and anxiety symptoms were assessed retrospectively, creating the possibility of recall bias because of current symptom burden. Furthermore, although ALI/ARDS is a common critical illness, it is possible that the findings of this study might not be generalizable to survivors of other critical illnesses. Also, Dowdy et al do not explain why admission to a surgical ICU may put patients at increased risk for subsequent depression, especially more so than patients admitted to trauma ICUs because patients who survive physical injuries are known to be at increased risk for subsequent depression (9). Finally, what explains the risk for post-ICU depressive symptoms conferred by benzodiazepine sedation? The findings by Dowdy et al do not answer this question. Are benzodiazepines the actual risk factor or are they a proxy for other possible risk factors? Patients with pre-ICU histories of depression and/or anxiety may be more likely to receive benzodiazepines during their ICU stay (10). Additionally, patients taking benzodiazepines, which are commonly prescribed for the treatment of anxiety symptoms, before acute care hospitalization for physical injuries were found to be at increased risk of developing posttraumatic stress disorder 12 months after hospital discharge in a national multisite study of trauma survivors (11). Perhaps a prior history of depression and/or anxiety is what actually confers the greatest amount of risk for post-ICU psychopathology. Furthermore, benzodiazepines are a known deliriogenic class of medications, and a prior history of depression seems to increase the risk of delirium while hospitalized (12, 13). Also, in-hospital delirium may predispose to subsequent depressive symptoms (14). Could in-ICU delirium be the actual risk factor for subsequent depression being suggested by benzodiazepine use? It is difficult to say, but merits further investigation.

The study by Dowdy et al on depression 6 months after surviving ALI/ARDS is a noteworthy contribution to furthering our understanding of the outcomes of patients who survive critical illnesses. It is only the second study to show that a pre-ICU history of psychiatric morbidity is associated with a significantly increased risk of depressive symptoms months after discharge from the hospital. Additionally, Dowdy et al highlight that an ICU service-delivery characteristic, benzodiazepine sedation, may increase the risk of subsequent depressive symptoms, suggesting a possible area of intervention and further study by using alternative sedative agents that might be less deliriogenic (15), and stimulating research into other ICU service-delivery characteristics that may confer risk for psychopathology in critical illness survivors. Because millions of patients are admitted to ICUs annually in the United States (8), further research into the causes of post-ICU psychiatric morbidity is an important public health concern, and Dowdy et al provide an important step in the direction of furthering our understanding of the etiology of these problems.

Dimitry S. Davydow, MD
Douglas F. Zatzick, MD
Department of Psychiatry and Behavioral Sciences
Harborview Medical Center
University of Washington School of Medicine
Seattle, WA

REFERENCES

1. Davydow DS, Gifford JM, Desai SV, et al: Depression in general intensive care unit survivors: A systematic review. *Intensive Care Med*; In Press
2. Davydow DS, Desai SV, Needham DM, et al: Psychiatric morbidity in survivors of the acute respiratory distress syndrome: A systematic review. *Psychosom Med* 2008; 70: 512–519
3. Weinert C, Meller W: Epidemiology of depression and antidepressant therapy after acute respiratory failure. *Psychosomatics* 2006; 47:399–407
4. Weinert CR, Gross CR, Kangas JR, et al: Health-related quality of life after acute lung injury. *Am J Respir Crit Care Med* 1997; 156:1120–1128
5. Nelson BJ, Weinert CR, Bury CL, et al: Intensive care unit drug use and subsequent quality of life in acute lung injury patients. *Crit Care Med* 2000; 28:3626–3630
6. Dowdy DW, Dingas V, Mendez-Tellez PA, et al: Intensive care unit hypoglycemia predicts depression during early recovery from acute lung injury. *Crit Care Med* 2008; 36:2726–2733
7. Dowdy DW, Bienvenu OJ, Dingas VD, et al: Are intensive care factors associated with depressive symptoms 6 months after acute lung injury? *Crit Care Med* 2009; 37:1702–1707
8. Davydow DS, Gifford JM, Desai SV, et al: Posttraumatic stress disorder in general intensive care unit survivors: A systematic review. *Gen Hosp Psychiatry* 2008; 30:421–434
9. O'Donnell ML, Creamer M, Bryant RA, et al: Posttraumatic disorders following injury: An empirical and methodological review. *Clin Psychol Rev* 2003; 23:587–603
10. Jones C, Backman C, Capuzzo M, et al: Precipitants of post-traumatic stress disorder following intensive care: A hypothesis generating study of diversity in care. *Intensive Care Med* 2007; 33:978–985
11. Zatzick DF, Rivara FP, Nathens AB, et al: A nationwide US study of post-traumatic stress after hospitalization for physical injury. *Psychol Med* 2007; 37:1469–1480
12. Minden SL, Carbone LA, Barsky A, et al: Predictors and outcomes of delirium. *Gen Hosp Psychiatry* 2005; 27:209–214
13. McAvay GJ, Van Ness PH, Bogardus ST, et al: Depressive symptoms and the risk of incident delirium in older hospitalized adults. *J Am Geriatr Soc* 2007; 55:684–691
14. Davydow DS: Symptoms of depression and anxiety following delirium: A review. *Psychosomatics*; In Press
15. Pandhirapande PP, Pun BT, Herr DL, et al: Effect of sedation with dexmedetomidine vs. lorazepam on acute brain dysfunction in mechanically ventilated patients: The MENDS randomized controlled trial. *JAMA* 2007; 298: 2644–2653

Caveolin: Another reason why lipid membranes play an important role in ventilator-induced lung injury*

Despite identification of numerous potential therapies for critical illness and lung injury, one of the few that has resulted in significantly reduced mortality is low tidal volume ventilation. The Acute Respiratory Distress Syndrome-Net Clinical trial (1) solidified the biological concept of volutrauma in humans and the need to limit it by applying tidal volumes appropriate for an injured, "baby lung" and was the fruition of decades of investigation into the role of mechanical forces in alveolar-capillary barrier injury (2). Although mechanical force is the initiating insult, this force must be transduced into biological effects that are a (im)balance of injurious and protective responses. The nature and balanced effect of these transduction mechanisms are complex and remain incompletely understood. In this issue of *Critical Care Medicine*, Hoetzel et al (3) highlight two novel and interacting etiological factors: carbon monoxide (CO) and caveolin (Cav).

The authors had previously identified a protective effect of CO in ventilator-induced lung injury (4), and therefore this report is novel and exciting in so far as Cav has been identified by them as a potentially important modulator of mechanical injury to alveolar epithelial cells.

That caveolae, which are lipid membrane structures, might play a role in cell injury responses is not, in retrospect, surprising because there has been accumulating evidence for the role of lipids in promoting and inhibiting ventilator-induced lung injury (5). Initially thought to be a simple barrier between the intracellular and extracellular environments, it is now clear that the plasma membrane is in fact a complex array of lipids and lipoproteins, and that it is a dynamic structure that through lipid–lipid and lipid–protein interactions directly interacts with and influences both the intracellular and extracellular environments (6). Ceramide is just one example of such a membrane lipid involved in lung injury. Investigators showed that cellular stresses can induce ceramide's enzymatic activation and, in turn, its biological activity, which plays an important role in facilitating pulmonary edema and inflammatory cytokine production (7, 8). Furthermore, lipids and their movement to and from the plasma membrane play a protective role. It has been shown both *in vitro* and *in vivo* that alveolar cell membrane damage resulting from injurious mechanical forces can be both prevented and repaired by the active process of lipid membrane trafficking from intracellular compartments to the stressed cell surface (4, 9).

In the last decade, it has also become clear that there is a "domain" structure within the lipid membrane that modulates endocytic and exocytic processes and transmembrane protein functions (10). Caveolae, which represent one such membrane domain structure, are characterized morphologically by flask-like membrane invaginations and biochemically by cholesterol enrichment and abundance of the resident protein, Cav. Cav is a multifunctional protein that can serve both directly and indirectly as a scaffold and signaling protein to facilitate effective communication between and within the intracellular and extracellular environments (6). It seems to play a key role in lung biology because knock out of the protein in mice results in a lung injury phenotype characterized by increased lung weight and epithelial cell proliferation (11). Increasingly, Cav has been implicated in human diseases, including cancer (10). In this issue of *Critical Care Medicine*, Hoetzel et al show that it may also be important in deformation-induced epithelial cell function. Like all reports that provide novel data, this article also raises numerous important mechanistic questions and, in turn, the potential for bench-to-bedside translatability.

First, is Cav a mechanotransducer that is able to sense and convert mechanical forces to measurable and biologically relevant processes such as cytokine production or injury repair? Previous studies have implicated Cav as a pulmonary endothelial mechanotransducer (12), but this study does not directly address whether this is true for the pulmonary epithelium. Presumably, Cav functions similarly in pulmonary epithelium; certainly, it is plausible given Cav's integral position within the plasma membrane, if not in a direct fashion, at least indirectly through the influence of factors such as CO. This, in turn, raises the question whether Cav functions simply as a facilitator of CO's protective effect or has inherent protective effects. Both would seem plausible given the ubiquitous expression of Cav and its numerous interactions with proteins that have previously been implicated in ventilator-induced lung injury (12) and the extent of injury in lungs ventilated in the absence of CO.

Second, the nature of CO–Cav interaction both physically and biochemically remain incompletely understood. The transduction mechanism that underlies the "crosstalk" that occurs between CO and Cav will be important to delineate. The fact that the effect of CO requires Cav in smooth muscle cells suggests their interaction may not be cell type specific (13). Furthermore, understanding whether they function in a synergistic, additive, or redundant fashion is important in tailoring sensible pharmacotherapies. This can be considered much like chemotherapy, which may be either aimed at one particular mechanistic pathway or multiple.

How might all this basic science be relevant for the bedside? The answer to this may lie in one of the mechanisms of lung injury: surfactant lipid dysfunction. Surfactant composition and surface tension properties are markedly abnormal in all forms of acute lung injury and there

***See also p. 1708.**

Key Words: caveolin; lipids; acute lung injury; ventilator-induced lung injury; carbon monoxide

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have been clinical attempts to supplement the surfactant pool with exogenous lipid–lipoprotein mixtures. However, solid clinical trial evidence that this therapy is effective have been lacking (14). It may not be because of poor biological reasoning but rather the lack of necessary compounds or proteins within the supplemented lipid emulsion (15). Other than the surfactant lipoproteins, one other such protein may be Cav-1 along with CO. In conclusion, this report, in conjunction with others in the pulmonary vasculature, establishes Cav as a novel protein to be considered in the treatment of acute lung injury.

Nicholas E. Vlahakis, MD
Thoracic Disease Research Unit
Division of Pulmonary and Critical Care, Mayo Clinic
Rochester, MN

REFERENCES

1. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000; 342: 1301–1308
2. Webb HH, Tierney DF: Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. *Am Rev Respir Dis* 1974; 110: 556–565
3. Hoetzel A, Schmidt R, Vallbracht S, et al: Carbon monoxide prevents ventilator-induced lung injury *via* caveolin-1. *Crit Care Med* 2009; 37:1708–1715
4. Dolinay T, Szilasi M, Liu M, et al: Inhaled carbon monoxide confers anti-inflammatory effects against ventilator-induced lung injury. *Am J Respir Crit Care Med* 2004; 170: 613–620
5. Vlahakis NE, Schroeder MA, Pagano RE, et al: Role of deformation-induced lipid trafficking in the prevention of plasma membrane stress failure. *Am J Respir Crit Care Med* 2002; 166:1282–1289
6. Parton RG, Simons K: The multiple faces of caveolae. *Nat Rev Mol Cell Biol* 2007; 8:185–194
7. Goggel R, Winoto-Morbach S, Vielhaber G, et al: PAF-mediated pulmonary edema: A new role for acid sphingomyelinase and ceramide. *Nat Med* 2004; 10:155–160
8. Mercier JC, Dinh-Xuan AT: Neutralizing ceramide: A major breakthrough or yet another marginal target for the treatment of acute lung injury? *Pediatr Res* 2005; 57:319–321
9. Gajic O, Lee J, Doerr CH, et al: Ventilator-induced cell wounding and repair in the intact lung. *Am J Respir Crit Care Med* 2003; 167:1057–1063
10. Cohen AW, Hnasko R, Schubert W, et al: Role of caveolae and caveolins in health and disease. *Physiol Rev* 2004; 84:1341–1379
11. Razani B, Engelman JA, Wang XB, et al: Caveolin-1 null mice are viable but show evidence of hyperproliferative and vascular abnormalities. *J Biol Chem* 2001; 276: 38121–38138
12. Yu J, Bergaya S, Murata T, et al: Direct evidence for the role of caveolin-1 and caveolae in mechanotransduction and remodeling of blood vessels. *J Clin Invest* 2006; 116: 1284–1291
13. Kim HP, Wang X, Nakao A, et al: Caveolin-1 expression by means of p38beta mitogen-activated protein kinase mediates the antiproliferative effect of carbon monoxide. *Proc Natl Acad Sci USA* 2005; 102:11319–11324
14. Taut FJ, Rippin G, Schenk P, et al: A search for subgroups of patients with acute respiratory distress syndrome who may benefit from surfactant replacement therapy: A pooled analysis of five studies with recombinant surfactant protein-C surfactant (Venticute). *Chest* 2008; 134:724–732
15. Mingarro I, Lukovic D, Vilar M, et al: Synthetic pulmonary surfactant preparations: New developments and future trends. *Curr Med Chem* 2008; 15:393–403

Vascular dysfunction in septic shock—Any ROCKing news?*

Septic shock remains a challenging clinical problem with very high morbidity and mortality rates (1). The dominant hemodynamic feature is a persistent vasodilation that is refractory to fluid resuscitation and vasoconstrictors. Current treatment guidelines aim to restore the effective circulatory volume and arterial blood pressure by the administration of intravenous fluids and vasoactive drugs (2). Such a protocol-driven, early goal-directed therapy has significantly improved outcome (3), yet, the exact pathophysiological mechanisms behind vascular dysfunction in sepsis shock remain unknown.

Frontline research in vascular biology has revealed new insights into the complex interaction between the vascular endothelium and vascular smooth muscle (4, 5). In this issue of *Critical Care Medicine*, da Silva-Santos et al (6) add another puzzle to this picture by providing novel data on the functionality of Rho-A/Rho-kinase (ROCK) in mesenteric vessels in rats suffering from sepsis.

In normal vessels, activation of Rho-A leads to stimulation of ROCK, which, in turn, can phosphorylate and subsequently inactivate the myosin light chain phosphatase, leading to myosin light chain phosphorylation, actin–myosin interaction, and cell contraction (7). The authors aimed to investigate whether a reduced activity of the Rho-A/ROCK pathway could be involved in the hypotension and decreased reactivity to vasoconstrictors observed in patients suffering from septic shock. Interestingly, they were able to demonstrate an impaired Rho-A/ROCK–mediated phosphorylation of myosin phosphatase targeting subunit (MYPT)1 (the regulatory subunit of the smooth muscle myosin phosphatase) in vascular smooth muscle from endotoxemic-treated rats. Furthermore, data from this study also suggest that changes in cyclic guanosine monophosphate–dependent mechanisms involved in calcium sensitization might play an important role in the vascular response to sepsis. Although the present *in vitro* study is far removed from clinical utility, da Silva-Santos et al deserve credit for opening up another niche in this research field.

Outcome in septic shock is strongly related to timing of treatment and rapidly instituting cardiovascular support and antibiotic therapy (8). Current management guidelines suggest noradrenalin or dopamine as first-line vasopressors, and adrenaline as second-line treatment, if blood pressure is poorly responsive (2). One might argue that it is the timing, rather than the specific agents, that is likely to make the difference (9). How-

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ever, this will remain rather speculative until we gather more information about the functionality of all relevant vascular pathways in septic shock. The article by da Silva-Santos et al contributes significantly in this context.

The focus for this study was downstream from nitric oxide/guanylate cyclase complex. Accordingly, the authors were unable to fully explore the relationship among the endothelium, nitric oxide, and the inhibition of the Rho-A/ROCK pathway seen in the current study. However, the effect of lipopolysaccharide injection on Rho-A/ROCK mediation of vasorelaxation was demonstrated. Furthermore, the nonspecific nitric oxide synthase inhibitor N_{ω}-Nitro-L-arginine methyl ester hydrochloride and the inductible nitric oxide synthase inhibitor 1400W effectively blocked this effect, although the 6-hour and 24-hour results are interestingly distinct. However, the most exciting result was the demonstration of involvement of the Rho-A/ROCK system in altered vascular adrenergic responsiveness in the presence of lipopolysaccharide. The authors' findings revealed an impaired Rho-A/ROCK–mediated phosphorylation of MYPT1 in vessels from endotoxemic animals in a cyclic guanosine monophosphate–dependent manner, and subsequent studies clearly showed that blockage of the soluble guanylate cyclase enzyme normalized not only the vasodilatory responses to Y-27632, but also the levels of phosphorylated MYPT1, an indication of Rho-A/ROCK activity. These data provide a sequence of evidence indicating that the overexpression of myosin phosphatase, and the inability of the Rho-A/ROCK to inhibit it, is a potential important mechanism involved in the vascular response in this model.

Fasudil, another ROCK inhibitor, has been used in several other studies in the past (10), but is not more selective than Y-27632. On the other hand, Y-27632 seems to be a very selective inhibitor of ROCK and works with similar potency for both isoforms, ROCK, I and ROCK II (10). Furthermore, Y-27632 is at least twice more potent than fasudil and the choice of Y-27632 for this purpose seems appropriate. So, what is the ROCKing news in this story? Well, da Silva-Santos et al add novel observations to the existing literature, which hopefully will generate new challenging hypotheses and experimental work within an incredible complex research field. In the meantime, we should stick to the current guidelines, look upstream to understand the sequence of events, and start therapy sooner rather than later.

Lars Marius Ytrebo, MD, PhD
Department of Anesthesiology
University Hospital of Northern Norway
Tromsø, Norway

REFERENCES

1. Angus DC, Linde-Zwirble WT, Lidicker J, et al: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; 29:1303–1310
2. Dellinger RP, Levy MM, Carlet JM, et al: Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock 2008. *Intensive Care Med* 2008; 34:17–60
3. Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377
4. Jackson WF: Ion channels and vascular tone. *Hypertension* 2000; 35:173–178
5. Bellien J, Thuillez C, Joannides R: Contribution of endothelium-derived hyperpolarizing factors to the regulation of vascular tone in humans. *Fundam Clin Pharmacol* 2008; 22:363–377
6. da Silva-Santos JE, Chiao C-W, Leite R, et al: The Rho-A/Rho-kinase is up-regulated but remains inhibited by cyclic guanosine monophosphate–dependent mechanisms during endotoxemia in small mesenteric arteries. *Crit Care Med* 2009; 37:1716–1723
7. Hilgers RH, Webb RC: Molecular aspects of arterial smooth muscle contraction: Focus on Rho. *Exp Biol Med* (*Maywood*) 2005; 230:829–835
8. 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
9. Parrillo JE: Septic shock—Vasopressin, norepinephrine, and urgency. *N Engl J Med* 2008; 358:954–956
10. Manintveld OC, Verdouw PD, Duncker DJ: The RISK of ROCK. *Am J Physiol Heart Circ Physiol* 2007; 292:H2563–2565
11. Davies SP, Reddy H, Caivano M, et al: Specificity and mechanism of action of some commonly used protein kinase inhibitors. *Biochem J* 2000; 351:95–105

How to plug a leak?*

The incidence of sepsis increased 9% per year between 1979 and 2000 in the United States (1). Infection caused by bacteria accounts for approximately 50% to 80% of all septic cases (2). Certain bacteria, via their microbial-associated molecular patterns such as endotoxin (lipopolysaccharide [LPS]), are recognized by specific receptors such as danger signals by immune cells, epithelial cells, and endothelial cells. The reaction of these and other cells induces sequential immune reactions including the cytokine expression and response cascade. The subsequent imbalance between proinflammatory and anti-inflammatory mediators causes severely impaired immune functions (3, 4). Pathogen-induced compromise of the integrity of epithelium and endothelium results in the further breakdown of immune defense and serves as another source of cytokine activation (3, 5). LPS can disrupt intestinal epithelial tight junctions via increased inducible nitric oxide synthase activity (6) and causes breakdown of the endothelial barrier by altering junctional complexes (5). These events may promote bacterial translocation and fluid sequestration, worsening the course of sepsis toward multiorgan system failure. When epithelial integrity is functionally disrupted, mediators including nitric oxide, tumor necrosis factor, or interferon γ (7) might reduce the tight junction protein zonula occludens 1, together with the internal-

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Key Words: sepsis; lipopolysaccharide; endothelium; small GTPase Rac 1; cAMP

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ization of several apical junctional complex transmembrane proteins (8). When endothelial barrier breakdown is structural, thrombin might alter actin dynamics and, thus, junctional components, such as adherens and tight junctions in the endothelium (9).

Although many factors have been identified in the progression of pathogen-induced endothelial dysfunction, the signaling pathway initiating the dysfunction of endothelial barriers during sepsis is still in question. The article authored by Schlegel et al (5) has made a significant advance toward answering this question. Combining studies from single-microvessel perfusion of mesenteric postcapillary venules and from cultures of human dermal microvascular endothelial cells, the investigators were able to determine hydraulic conductivity as an index for endothelial permeability in addition to visualizing and quantifying various junctional proteins, and functionally determining dextran permeability and transendothelial resistance. The investigators discovered that increased cyclic adenosine monophosphate (cAMP) abolishes the LPS-induced increase in endothelial permeability and intercellular gap formation. Furthermore, LPS inactivates small guanosine triphosphosphate (GTP)ase Rac 1 rapidly with barrier dysfunction, whereas Rho A activity increase was delayed indicating that Rac 1 rather than Rho A is involved in the LPS-induced disruption of endothelial barrier. Previously, the observation that inhibition of Rho A could inhibit the LPS-induced contractile pattern of endothelial cells in lung edema (10, 11) suggested a role for Rho kinase in LPS-induced endothelial leakage. Schlegel et al (5) showed that no significant activation of Rho A occurs (2 hours post-LPS) despite a many-fold increase in endothelial permeability, both *in vivo* and *in vitro*. This time-course independence is consistent with the lack of effect of Rho kinase inhibitor on LPS-induced endothelial permeability (12). In contrast, both cAMP decrease and Rac 1 inactivation seem to be an early event (1 hour post-LPS) associated with LPS-induced endothelial barrier breakdown. Thus, the authors propose that both Rac 1 inactivation and cAMP decrease are important for changes in junctional proteins (e.g., fragmentation of vascular endothelial-cadherin and decrease of claudin 5), leading to the formation of large intercellular gaps and increasing endothelial permeability following LPS treatment.

What does it all mean for clinical sepsis? *In vivo* tests of agents interfering with cAMP level and/or Rac 1 activity during experimental and clinical sepsis should provide more evidence to justify the application of the current findings. Recent clinical investigation using cAMP-increasing agents did show beneficial effects on microcirculatory alterations in experimental endotoxemia (13) and patients with septic shock (14). The knowledge on how endothelial cells regulate junctional proteins may provide clues for the therapeutic potential to stop a leak during sepsis.

Ying-Tung Lau, PhD
Department of Cosmetic Science
Chang Gung Institute of Technology
Center for Healthy Aging Research, Chang Gung University
Tao-yuan, Taiwan

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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. Annane D, Aegerter P, Jars-Guincestre MC, et al: Current epidemiology of septic shock: The CUB-Rea Network. *Am J Respir Crit Care Med* 2003; 1687:165–172
3. Annane D, Bellissant E, Cavaillon JM: Septic shock. *Lancet* 2005; 365:63–78
4. Hotchkiss RS, Karl IE: The pathophysiology and treatment of sepsis. *N Engl J Med* 2003; 348:138–150
5. Schlegel N, Baumer Y, Drenckhahn D, et al: Lipopolysaccharide-induced endothelial barrier breakdown is cyclic adenosine monophosphate dependent *in vivo* and *in vitro*. *Crit Care Med* 2009; 37:1735–1743
6. Han X, Fink MP, Yang R, et al: Increased iNOS activity is essential for intestinal epithelial tight junction dysfunction in endotoxemic mice. *Shock* 2004; 21:261–270
7. Sappington P, Yang R, Yang H, et al: HMGB1 B box increases the permeability of Caco-2 enterocytic monolayers and impairs intestinal barrier function in mice. *Gastroenterology* 2002; 123:790–802
8. Bruewer M, Luegering A, Kucharzik T, et al: Proinflammatory cytokines disrupt epithelial barrier function by apoptosis-independent mechanisms. *J Immunol* 2003; 171:6164–6172
9. Mehta D, Malik AB: Signaling mechanisms regulating endothelial permeability. *Physiol Rev* 2006; 86:279–367
10. Essler M, Staddon JM, Weber PC, et al: Cyclic AMP blocks bacterial lipopolysaccharide-induced myosin light chain phosphorylation in endothelial cells through inhibition of Rho/Rho kinase signaling. *J Immunol* 2000; 164:6543–6549
11. Tasaka S, Koh H, Yamada W, et al: Attenuation of endotoxin-induced acute lung injury by the Rho-associated kinase inhibitor, Y-27632. *Am J Respir Cell Mol Biol* 2005; 32:504–510
12. Lundblad C, Bentzer P, Grande PO: The permeability-reducing effects of prostacyclin and inhibition of Rho kinase do not counteract endotoxin-induced increase in permeability in cat skeletal muscle. *Microvasc Res* 2004; 68:286–294
13. Secchi A, Ortanderl JM, Schmidt W, et al: Effects of dobutamine and dopexamine on hepatic micro- and macrocirculation during experimental endotoxemia: An intravital microscopic study in the rat. *Crit Care Med* 2001; 29:597–600
14. De Backer D, Creteur J, Dubois MJ, et al: The effects of dobutamine on microcirculatory alterations in patients with septic shock are independent of its systemic effects. *Crit Care Med* 2006; 34:403–408

Thrombin-activatable fibrinolysis inhibitor-a inhibitors: Drugs for sepsis or drugs for disseminated intravascular coagulation?*

In this issue of *Critical Care Medicine*, Muto et al (1) report on experiments with a novel thrombin-activatable fibrinolysis inhibitor-a (TAFIa) inhibitor in two sepsis models in rats. TAFIa, a carboxypeptidase, cleaves C-terminal lysine and arginine residues from partially plasmin-degraded fibrin, thus, inhibiting the binding of plasminogen, tissue plasminogen activator (tPA), and plasmin to the fibrin. This reduces the cofactor activity of fibrin in tPA-induced plasminogen activation and the efficiency of further degradation of the fibrin by plasmin (2). In addition, the cleavage of critical C-terminal lysine residues from partially degraded fibrin increases the proportion of plasmin that is inactivated by alpha-2-plasmin inhibitor (3).

Activation of TAFI requires high concentrations of thrombin and is strongly enhanced by thrombomodulin present on the endothelium. Theoretically, inhibitors of TAFIa should enhance fibrinolysis and this may be beneficial in sepsis, where intravascular fibrin formation may lead to microvascular thrombosis, which then causes organ dysfunction. The authors report that administration of the novel TAFIa inhibitor reduces fibrin deposits in the kidney and the liver of the experimental animals as well as laboratory markers of organ dysfunction in an endotoxemia model, and reduces the systemic inflammatory response in a bacterial infection model.

Fibrin deposits in kidneys, liver, and other organs are a sign for the presence of disseminated intravascular coagulation (DIC) in sepsis (4). DIC is an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature and, if sufficiently severe, can produce organ dysfunction (5). The diagnosis of DIC is based on the combination of a typical underlying disease, such as sepsis, with laboratory markers, including prothrombin time, fibrinogen concentration, platelet count, and a fibrin-related marker, reflecting intravascular fibrin formation (5–7). D-dimer, fibrin degradation products, or soluble fibrin are used as fibrin-related markers in the DIC scores.

Approximately 30% of patients with severe sepsis display overt DIC (8) and patients with severe sepsis fulfilling the DIC criteria display a considerably higher rate of organ dysfunction and an increased mortality (9–12).

Some patients with specific bacterial infections generate sepsis-induced purpura fulminans, which is characterized by extensive microvascular thrombosis, tissue necrosis, and secondary hemorrhage into the necrotic tissue, including the skin (13, 14). The lesions resemble those found in newborns with severe protein C deficiency (15). Laboratory data show that sepsis-induced purpura fulminans is caused by a failure of the protein C system in the context of sepsis-induced DIC. Otherwise, the clinical signs of DIC in severe sepsis are less obvious, with multiorgan dysfunction and minor bleeding, especially from insertion sites of intravascular catheters, and other tissue lesions, being the principal symptoms.

TAFI levels decrease in the course of DIC, presumably because of consumption of the proenzyme, leading to increased TAFIa activity (16), whereas plasminogen activator inhibitor (PAI)-1 levels are elevated in response to acute-phase reaction and platelet activation. Organ dysfunction and mortality in sepsis-induced DIC are closely linked to the functional integrity of the fibrinolytic system. In patients without multiorgan dysfunction, markers of coagulation activation are correlated with markers for the activation of fibrinolysis, indicating efficient clearance of intravascular fibrin (17). In patients with multiorgan dysfunction, in contrast, coagulation activation is not associated with a compensatory activation of fibrinolysis. Elevated levels of PAI-1 are a frequent finding in patients with sepsis. PAI-1 acts as an acute-phase reactant and additional PAI-1 may be released from activated platelets. Genetic variants leading to higher PAI-1 levels are associated with worse outcome in severe bacterial sepsis (18, 19). In experimental animals, administration of tPA reduces sepsis-induced fibrin deposition in the kidneys (20). A similar effect is observed on administration of a PAI-1 inhibitor (21). In view of these experiences, it seems logical to administer profibrinolytic drugs to patients with sepsis-induced DIC to prevent multiorgan dysfunction caused by microvascular thrombosis.

But is a TAFIa inhibitor indeed a promising approach?

This clearly depends on the individual condition. Treatment with high doses of antithrombin concentrate did not result in a clinical benefit concerning survival or organ dysfunction in patients with severe sepsis (22), but a *post hoc* analysis of the same trial revealed that high-dose antithrombin therapy clearly improves the clinical outcome in patients with severe sepsis and DIC (23). Selection of patients on the basis of a DIC score system would, therefore, limit the treatment to those patients who would be expected to benefit.

In patients with sepsis, normal or high fibrinogen levels indicate bad clinical prognosis (24), reflecting suppressed fibrinolytic response mainly because of elevated PAI-1 levels, but possibly also increased generation of TAFIa. In patients with high TAFIa activity, the soluble fibrin complexes and fibrin degradation products in the blood do not effectively promote plasminogen activation by tPA and binding of plasmin. A TAFIa inhibitor may restore the functional properties of the fibrin derivatives. In 1986, Wiman

***See also p. 1744.**

Key Words: TAFIa; disseminated intravascular coagulation; sepsis; thrombin

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and Ranby (25) developed a functional soluble fibrin assay, based on the cofactor effect of soluble fibrin in tPA-induced plasminogen activation. This assay showed rather variable results in patients with DIC (26, 27), indicating that the soluble fibrin present in clinical plasma samples differed from soluble fibrin prepared *in vitro* for calibration purposes. The differences may be due to TAFIa-induced modifications of the fibrin compounds detected by the assay. For proper selection of patients for treatment with a TAFIa inhibitor, a functional soluble fibrin assay based on the cofactor activity of the fibrin in tPA-induced plasminogen activation, or other markers of fibrinolysis activation, such as plasmin–plasmin inhibitor complexes, may be helpful if used in conjunction with laboratory markers of coagulation activation.

In contrast to anticoagulant drugs, treatment with a TAFIa inhibitor would be expected to enhance the profibrinolytic response caused by systemic coagulation activation without reducing the amount of fibrin available as cofactor in tPA-induced plasminogen activation or reducing the stimulation of tPA release induced by thrombin.

A certain bleeding risk may also be associated with TAFIa inhibitors, especially in hyperfibrinolytic conditions. If these conditions are identified by appropriate laboratory assays, treatment risks may be minimized.

In conclusion, TAFIa inhibitors might not be drugs to be used in sepsis in general. We would expect the clinical indication for a TAFIa inhibitor in patients with sepsis to be the patient with disseminated coagulation activation not appropriately compensated by activation of the fibrinolytic system. Proper selection of patients is essential to ensure maximal clinical benefit.

Carl-Erik Dempfle, MD
Martin Borggrefe, MD
I. Department of Medicine
University Medical Center Mannheim
Mannheim, Germany

REFERENCES

1. Muto Y, Suzuki K, Iida H, et al: EF6265, a novel inhibitor of activated thrombin-activatable fibrinolysis inhibitor, protects against sepsis-induced organ dysfunction in rats. *Crit Care Med* 2009; 37:1744–1749
2. Bajzar L, Manuel R, Nesheim ME: Purification and characterization of TAFI, a thrombin-activable fibrinolysis inhibitor. *J Biol Chem* 1995; 270:14477–14484
3. Wang W, Boffa MB, Bajzar L, et al: A study of the mechanism of inhibition of fibrinolysis by activated thrombin-activable fibrinolysis inhibitor. *J Biol Chem* 1998; 273: 27176–27181
4. Schneider M, Brufatto N, Neill E, et al: Activated thrombin-activatable fibrinolysis inhibitor reduces the ability of high molecular weight fibrin degradation products to protect plasmin from antiplasmin. *J Biol Chem* 2004; 279:13340–13345
5. Bleyl U, Rossner JA: Globular hyaline microthrombi—Their nature and morphogenesis. *Virchows Arch A Pathol Anat Histol* 1976; 370: 113–128
6. Taylor FB Jr, Toh CH, Hoots WK, et al: Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost* 2001; 86:1327–1330
7. Wada H, Gabazza EC, Asakura H, et al: Comparison of diagnostic criteria for disseminated intravascular coagulation (DIC): Diagnostic criteria of the International Society of Thrombosis and Hemostasis and of the Japanese Ministry of Health and Welfare for overt DIC. *Am J Hematol* 2003; 74:17–22
8. Gando S, Wada H, Asakura H, et al: Evaluation of new Japanese diagnostic criteria for disseminated intravascular coagulation in critically ill patients. *Clin Appl Thromb Hemost* 2005; 11:71–76
9. Dhainaut JF, Yan SB, Joyce DE, et al: Treatment effects of drotrecogin alfa (activated) in patients with severe sepsis with or without overt disseminated intravascular coagulation. *J Thromb Haemost* 2004; 2:1924–1933
10. Bakhtiari K, Meijers JC, de Jonge E, et al: Prospective validation of the International Society of Thrombosis and Haemostasis scoring system for disseminated intravascular coagulation. *Crit Care Med* 2004; 32: 2416–2421
11. Sivula M, Tallgren M, Pettila V: Modified score for disseminated intravascular coagulation in the critically ill. *Intensive Care Med* 2005; 31:1209–1214
12. Dempfle CE, Wurst M, Smolinski M, et al: Use of soluble fibrin antigen instead of D-dimer as fibrin-related marker may enhance the prognostic power of the ISTH overt DIC score. *Thromb Haemost* 2004; 91:812–818
13. Angstwurm MW, Dempfle CE, Spannagl M: New disseminated intravascular coagulation score: A useful tool to predict mortality in comparison with Acute Physiology and Chronic Health Evaluation II and Logistic Organ Dysfunction scores. *Crit Care Med* 2006; 34:314 –320; quiz 328
14. Alberio L, Lammle B, Esmon CT: Protein C replacement in severe meningococcemia: Rationale and clinical experience. *Clin Infect Dis* 2001; 32:1338–1346
15. Childers BJ, Cobanov B: Acute infectious purpura fulminans: A 15-year retrospective review of 28 consecutive cases. *Am Surg* 2003; 69:86–90
16. Muller FM, Ehrenthal W, Hafner G, et al: Purpura fulminans in severe congenital protein C deficiency: Monitoring of treatment with protein C concentrate. *Eur J Pediatr* 1996; 155:20–25
17. Watanabe R, Wada H, Watanabe Y, et al: Activity and antigen levels of thrombin-activatable fibrinolysis inhibitor in plasma of patients with disseminated intravascular coagulation. *Thromb Res* 2001; 104:1–6
18. Asakura H, Ontachi Y, Mizutani T, et al: An enhanced fibrinolysis prevents the development of multiple organ failure in disseminated intravascular coagulation in spite of much activation of blood coagulation. *Crit Care Med* 2001; 29:1164–1168
19. Geishofer G, Binder A, Muller M, et al: 4G/5G promoter polymorphism in the plasminogen-activator-inhibitor-1 gene in children with systemic meningococcaemia. *Eur J Pediatr* 2005; 164:486–490
20. Binder A, Endler G, Muller M, et al: 4G4G genotype of the plasminogen activator inhibitor-1 promoter polymorphism associates with disseminated intravascular coagulation in children with systemic meningococcemia. *J Thromb Haemost* 2007; 5:2049–2054
21. Paloma MJ, Paramo JA, Rocha E: Endotoxin-induced intravascular coagulation in rabbits: Effect of tissue plasminogen activator vs urokinase of PAI generation, fibrin deposits and mortality. *Thromb Haemost* 1995; 74: 1578–1582
22. Montes R, Declerck PJ, Calvo A, et al: Prevention of renal fibrin deposition in endotoxin-induced DIC through inhibition of PAI-1. *Thromb Haemost* 2000; 84:65–70
23. Warren BL, Eid A, Singer P, et al: Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: A randomized controlled trial. *JAMA* 2001; 286:1869–1878
24. Kienast J, Juers M, Wiedermann CJ, et al: Treatment effects of high-dose antithrombin without concomitant heparin in patients with severe sepsis with or without disseminated intravascular coagulation. *J Thromb Haemost* 2006; 4:90–97
25. Wada H, Mori Y, Okabayashi K, et al: High plasma fibrinogen level is associated with poor clinical outcome in DIC patients. *Am J Hematol* 2003; 72:1–7
26. Wiman B, Ranby M: Determination of soluble fibrin in plasma by a rapid and quantitative spectrophotometric assay. *Thromb Haemost* 1986; 55:189–193
27. Halvorsen S, Skjonsberg OH, Ruyter R, et al: Comparison of methods for detecting soluble fibrin in plasma. An in vitro study. *Thromb Res* 1990; 57:489–497
28. Bredbacka S, Blomback M, Wiman B: Soluble fibrin: A predictor for the development and outcome of multiple organ failure. *Am J Hematol* 1994; 46:289–294

Can postoperative delirium be prevented pharmacologically?*

Delirium occurs in up to 60% of patients after surgery (1). Patients at greatest risk for experiencing postoperative delirium (POD) include those undergoing a major cardiac procedure, who are elderly, have a preexisting cognitive abnormality or who require admission to an intensive care unit (1, 2). POD is associated with increased mortality, a longer hospital stay, and cognitive deterioration and, thus, is important to prevent (3). The hypermetabolic inflammatory state in the brain that occurs secondary to anesthetic-induced vasodilation is felt to be the initial insult inciting POD (1). The resulting oxidative stress leads to abnormalities in the cholinergic, dopaminergic, histaminergic, and noradrenergic neuronal systems. The ability of cholinergic cells to synthesize and release acetylcholine may be reduced leading to disorientation and memory impairment (4). The resulting increased release of dopamine may cause agitation and hallucinations.

Efforts by clinicians to reverse potential causative factors for POD are often not successful and patients who develop POD are frequently treated with psychoactive medications (5). Given the limited evidence that neuroleptic agents improve outcome in patients with POD and the safety concerns associated with their use, efforts to identify a pharmacologic strategy that can prevent POD are increasing (6). However, POD prophylaxis studies conducted to date that have focused on the pharmacologic modulation of the neurotransmitter abnormalities known to induce POD have failed to demonstrate a benefit (7–9). One large randomized trial of low-dose haloperidol in a population of elderly hip surgery patients did not reduce the incidence of POD (7). Two smaller randomized studies in patients undergoing elective joint-replacement surgery failed to demonstrate a benefit with the prophylactic use of the acetylcholinesterase inhibitor donepezil (8, 9). There are a number of possible reasons that may account for the lack of benefit observed in these studies. The prophylactic regimens were studied in patients undergoing an elective orthopedic surgical procedure (a population at lower risk for POD than patients undergoing cardiac surgery), an inadequate treatment dose may have been used, the duration of therapy may have been too short and therapy was not initiated before surgery.

In this issue of *Critical Care Medicine*, Gamberini et al (10), despite addressing many of the methodologic concerns of previous POD prophylaxis studies, present the results of a clinical trial that fails to demonstrate the benefit of rivastigmine in preventing delirium after elective cardiac surgery. In this randomized, double-blinded, placebo-controlled study, rivastigmine (administered 1.5 mg every 8 hours starting on the evening before surgery and continued for a total of 6 days) failed to reduce the incidence of POD at 6 days (32% vs. 30%, $p = 0.8$) or improve tests of cognitive function, such as the Mini-Mental State Examination or the Clock Drawing Test. For those patients experiencing POD, neither the time to onset of POD after surgery nor the duration of POD differed between the rivastigmine and placebo groups. The effect of rivastigmine on POD severity using a delirium rating scale was not measured. Use of rescue haloperidol and lorazepam was similar between groups.

Can the lack of benefit observed with this study be attributable to specific methodologic issues or does it support the findings from previous studies demonstrating that acetylcholinesterase inhibitors do not prevent POD? Although the investigators did not report a difference in the rate of POD that was felt to be clinically important, delirium occurrence was only 50% of that estimated in the investigator's sample size calculation, suggesting that lack of power may have accounted for the lack of benefit observed. Reasons for the low incidence of POD observed are unclear, given that subject demographics, including severity of illness, are similar to those of other cardiac surgery studies (11). The low dose of rivastigmine used in the study and the lack of a rapid dose titration schedule in those patients without rivastigmine-associated side effects may also have accounted for the lack of benefit observed. It is, therefore, conceivable that methodologic factors may have accounted for the lack of benefit that was observed in the study. The study by Gamberini et al, therefore, does not conclusively rule out the benefit of acetylcholinesterase inhibitors in preventing POD but does suggest that any treatment benefit, if one exists, is likely small.

Future studies are, therefore, required to determine whether there is a pharmacologic intervention that will prevent POD in surgical populations at high risk for experiencing delirium. It is entirely possible that modulation of acetylcholine is not the only neurotransmitter-related mechanism that may play a role in preventing POD, given the important role that other neurotransmitters, such as dopamine, serotonin, and glutamine, play in the pathogenesis of POD (1). Therefore, a POD prophylactic regimen that modulates multiple neurotransmitters (e.g., acetylcholine and dopamine) may prove to be of greatest benefit. Future investigations in this area should also evaluate the pharmacodynamic response to any pharmacologic intervention to help answer important questions that exist for any potential prophylactic regimen, including the optimal dosing regimen that should be used and when therapy should be initiated relative to surgery.

The anesthetic regimen chosen for surgery and the sedation and analgesia administered both intraoperatively and postoperatively may each affect the incidence of POD (1). For example, sedation with dexmedetomidine is associated with less delirium than lorazepam (12). It may be possible that subsyndromal delirium is a better outcome than delirium for future prophylactic studies, given that it has

***See also p. 1762.**

Key Words: rivastigmine; delirium; postoperative delirium; prevention; surgery; cardiac surgery; intensive care unit

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been found in the intensive care unit to be associated with outcomes that are nearly as bad as delirium (13). Hopefully, a beneficial POD preventive strategy will be identified once the results from a number of ongoing studies become available. Ongoing trials in this area include two studies that are exploring the use of acetylcholinesterase inhibitors with or without concomitant haloperidol prophylaxis, another study that is evaluating olanzapine, and one that is comparing the incidence of POD in cardiac surgery patients receiving dexmedetomidine or propofol sedation regimens (14). With these ongoing trials, and other future investigations, it is hoped that a pharmacologic intervention will be identified that can reduce the incidence of POD and the morbidity and mortality associated with it.

Jeffrey J. Fong, PharmD, BCPS
Massachusetts College of Pharmacy and Health Sciences
Worcester, MA
John Devlin, PharmD, BCPS, FCCM, FCCP
Northeastern University
Boston, MA

REFERENCES

1. Fricchione GL, Nejad SH, Esses JA, et al: Postoperative delirium. *Am J Psychiatry* 2008; 165:803–812
2. Marcantonio ER, Goldman L, Orav J, et al: The association of intraoperative factors with the development of postoperative delirium. *Am J Med* 1998; 105:380–384
3. Marcantonio ER, Flacker JM, Michaels M, et al: Delirium is independently associated with poor functional recovery after hip fracture. *J Am Geriatr Soc* 2000; 48: 618–624
4. Hsieh TT, Fong TG, Marcantonio ER, et al: Cholinergic deficiency hypothesis in delirium: A synthesis of current evidence. *J Gerontol A Bio Sci Med Sci* 2008; 63:764–772
5. Inouye SK: Delirium in older patients. *N Engl J Med* 2006; 354:1157–1165
6. Girard TD, Pandharipande PP, Ely EW: Delirium in the intensive care unit. *Crit Care* 2008; 12(Suppl 3):S3
7. Kalisvaart KJ, de Jonghe JFM, Bogaards MJ, et al: Haloperidol prophylaxis for elderly hip surgery patients at risk for delirium: A randomized placebo-controlled study. *J Am Geriatr Soc* 2005; 53:1658–1666
8. Liptzin B, Laki A, Garb JL, et al: Donepezil in the prevention and treatment of post-surgical delirium. *Am J Geriatr Psychiatry* 2005; 13:1100–1106
9. Sampson EL, Raven PR, Ndhlovu PN, et al: A randomized, double-blinded, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement. *Int J Geriatr Psychiatry* 2007; 22:343–349
10. Gamberini M, Bolliger D, Lurati Buse GA, et al: Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery—A randomized controlled trial. *Crit Care Med* 2009; 37:1762–1768
11. Aronson S, Dyke CM, Stierer KA, et al: The ECLIPSE trials: Comparative studies of clevidipine to nitroglycerin, sodium nitroprusside, and nicardipine for acute hypertension treatment in cardiac surgery patients. *Anesth Analg* 2008; 107:1110–1121
12. Pandharipande PP, Pun BT, Herr DL, et al: Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: The MENDS randomized controlled trial. *JAMA* 2007; 298: 2644–2653
13. Ouimet S, Riker R, Bergeron N, et al: Subsyndromal delirium in the ICU: Evidence for a disease spectrum. *Intensive Care Med* 2007; 33:1007–1013
14. Clinicatrials.gov. Available at: http://clinicaltrials.gov/ct2/results?term=delirium, Accessed November 24, 2008

Should we be afraid of the Green Monster?*

Pseudomonas aeruginosa is an incredibly versatile opportunistic pathogen that can infect most organs and tissues in humans. The most notorious and/or life-threatening *P. aeruginosa* infections include lung infections in patients with cystic fibrosis, diabetic foot ulcers, urinary tract infections in catheterized patients, and bacteremia in the severely burned (1). Because of its large genome and genetic adaptability (2), *P. aeruginosa* possesses many conserved genes that allow it to survive almost anywhere, under almost any conditions, express an extensive arsenal of virulence factors, and produce enzymes that convey resistance to many antimicrobials. This dynamic bacterium even produces its own antibiotics, including pyocyanin, which kill competing microbes and gives *P. aeruginosa* cultures, and sometimes infections, their characteristic green/blue appearance (1). In this issue of *Critical Care Medicine*, Veesenmeyer et al (3) discuss potential future *P. aeruginosa* therapeutics that focus on antagonizing specific virulence determinants. However, one could ask "Are alternatives to antibiotics really needed to treat *P. aeruginosa* infections and do we really need to be afraid of this Green Monster?"

The latest news on *P. aeruginosa* is a mixed bag of good and bad. The good news is that over the last 25 years the antibiotic resistance of *P. aeruginosa* does not seem to have increased (4, 5). In fact, the most recent data from the European Antimicrobial Resistance Surveillance System indicate that percentages of the antibiotic-resistant *P. aeruginosa* strains decreased between 2002 and 2006 (4). These data demonstrated little change in resistance profiles for meropenem and imipenem, and a notable decrease in resistance to piperacillin/tazobactam, ceftazidime, gentamicin, and ciprofloxacin (4). Another piece of good news, if you live in the United States, is that resistance rates for *P. aeruginosa* nosocomial infections are much lower in the United States than in Europe (6). For example, according to data from the International Nosocomial Infection Control Consortium (2002–2007) and the US National Nosocomial Infections Surveillance System (1992–2004), the rates of *P. aeruginosa* isolates resistant to piperacillin, ciprofloxacin, imipenem, and ceftazidime were 50.8 vs. 17.5%, 52.4 vs. 34.8%, 36.6 vs. 19.1%, and 51.7 vs. 13.9% in Europe vs. the United States, respectively (6).

The bad news is that the overall rate of *P. aeruginosa* infections is increasing and

***See also p. 1777.**

Key Words: *Pseudomonas aeruginosa*; nosocomial infection; antibiotic resistance; quorum sensing; multidrug resistance; opportunistic pathogen

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quite dramatically in some patient populations (7). For example, the percentages of *P. aeruginosa* isolates associated with pneumonia, surgical site infections, and urinary tract infections have essentially doubled since 1975 (7). These data are not surprising. The patient population is growing older and because of new efficacious treatments for chronic and malignant diseases, there is a rapidly expanding pool of immunodeficient patients who face prolonged courses of antibiotics and stays in intensive care units (8). Furthermore, with the United States engaged in two ongoing wars, the wounded patient population, which has been notoriously prone to *P. aeruginosa* infections, has greatly expanded (7). Therefore, the numbers of multidrug-resistant and pandrug-resistant *P. aeruginosa* isolates are likely to rise. The majority of multidrug-resistant *P. aeruginosa* strains are resistant to the most commonly used antibiotics, including aminoglycosides, fluoroquinolones, and β-lactams (8). Although several new drugs with activities against multidrug-resistant Gram-positive bacteria have recently been marketed, few exhibit activity against Gram-negative bacteria (8). With few antibiotic options available or even in development, physicians will face a future with increasing multidrug-resistant cases and a scarcity of treatment options. Therefore, it seems we should indeed be afraid of the Green Monster, *P. aeruginosa*.

Although Veesenmeyer et al (3) have identified several potential strategies for targeted anti–*P. aeruginosa* treatments in this issue, the source from which these advances will come is currently unclear. Many pharmaceutical companies are scaling back or even abandoning antibiotic development, primarily because antibiotics pose a low return on investment (8). This is partially due to heightened regulatory requirements for approving antibiotics for human use, which add to the enormous cost of development. It has been estimated that the development of a new antimicrobial can cost up to one billion dollars (9). Recouping these costs can be difficult because most antibiotics are used for short treatment courses and can quickly be made obsolete by resistance-acquiring microbes. Although research in academic laboratories has yielded promising data on specific targets, such as quorum sensing, type III secretion, and biofilm formation for *P. aeruginosa* (3), academic settings are generally poorly suited to perform the high-throughput screening of extensive chemical libraries required for the identification of effective new drug treatments.

Despite the lack of antimicrobial innovation in the last few decades, a new dawn of Green Monster slaying may be at hand. The recent "Pay for Performance" plan enacted by the Centers for Medicare and Medicaid Services will cease paying hospitals for some of the care made necessary by "preventable complications" (10). Among these complications are many types of nosocomial infections caused by *P. aeruginosa*. Consider, for example, the cost of a recent *P. aeruginosa* outbreak that affected 17 patients in an intensive care unit in Spain (11). Among these patients, the mortality rate was 47%, and the added extra length of intensive care unit stay attributable to *P. aeruginosa* infection was 70 days at an additive cost of more than $400,000 (11). In the United States, the average Medicare payment for admissions in which a *P. aeruginosa* catheter-associated urinary tract infections is present is more than $40,000/patient (10). Thus, if current nosocomial rates remain high, hospitals will have to start absorbing huge costs. This scenario may have a silver lining that results in improved standards of care as well as putting pressure on pharmaceutical companies to develop improved prophylactics and new antimicrobials.

Kendra Rumbaugh, PhD
Department of Surgery
Texas Tech University Health Sciences Center
Lubbock, TX

REFERENCES

1. Lyczak JB, Cannon CL, Pier GB: Establishment of *Pseudomonas aeruginosa* infection: Lessons from a versatile opportunist. *Microbes Infect* 2000; 2:1051–1060
2. Mathee K, Narasimhan G, Valdes C, et al: Dynamics of *Pseudomonas aeruginosa* genome evolution. *Proc Natl Acad Sci USA* 2008; 105:3100–3105
3. Veesenmeyer JL, Hauser AR, Lisboa T, et al: *Pseudomonas aeruginosa* virulence and therapy: Evolving translational strategies. *Crit Care Med* 2008; 37:1777–1786
4. Souli M, Galani I, Giamarellou H: Emergence of extensively drug-resistant and pandrug-resistant Gram-negative bacilli in Europe. *Euro Surveill* 2008; 13:1–11
5. Livermore DM, Hope R, Brick G, et al: Non-susceptibility trends among *Pseudomonas aeruginosa* and other non-fermentative Gram-negative bacteria from bacteraemias in the UK and Ireland, 2001-06. *J Antimicrob Chemother* 2008; 62(Suppl 2):ii55–ii63
6. Rosenthal VD, Maki DG, Mehta A, et al: International Nosocomial Infection Control Consortium report, data summary for 2002–2007, issued January 2008. *Am J Infect Control* 2008; 36:627–637
7. Slama TG: Gram-negative antibiotic resistance: There is a price to pay. *Crit Care* 2008; 12(Suppl 4):S4
8. Nordmann P, Naas T, Fortineau N, et al: Superbugs in the coming new decade; multidrug resistance and prospects for treatment of *Staphylococcus aureus*, *Enterococcus* spp. and *Pseudomonas aeruginosa* in 2010. *Curr Opin Microbiol* 2007; 10:436–440
9. Norrby SR, Nord CE, Finch R: Lack of development of new antimicrobial drugs: A potential serious threat to public health. *Lancet Infect Dis* 2005; 5:115–119
10. Rosenthal MB: Nonpayment for performance? Medicare's new reimbursement rule. *N Engl J Med* 2007; 357:1573–1575
11. Bou R, Lorente L, Aguilar A, et al: Hospital economic impact of an outbreak of *Pseudomonas aeruginosa* infections. *J Hosp Infect* 2009; 71:138–142

Eighteenth century mindsets, twenty-first century challenges: The physician as team player*

If you were to take physicians from the late 18th century—let us disturb William Withering, for example, physician to the General Hospital in Birmingham in the 1780s, or René Laennec from the Hôpital Necker in Paris—and invite them into a modern intensive care unit, what would they observe? After recovering from the shock of seeing complex 21st century technology attached to people in varying states of suspended animation, they might well take comfort from a familiar sight: a group of clinicians on the ward round moving slowly from bed to bed or between cubicles, listening to the history, performing a physical examination (1), inspecting the urine, labeling diseases, and prescribing treatments (2), activities which our two predecessors would have well understood.

If our visitors were to spend long time with us, however, they would note with surprise certain distinct differences about this ward round from those of their own experience. There would be constant interruptions and distractions; the persistent background noise of voices, alarms, and machinery; a huge volume of facts—especially numerical facts—would be exchanged or argued about; decisions would be negotiated, not mandated; members of the group would come and go, sometimes at the run; and over the course of 24 hours the members of the group would change several times, requiring repetitive rehearsal of the patients' histories. They might even find that some of the clinicians did not know each other's names. Within an ordered framework, there could be a sense of uncertainty and incipient chaos.

Thus, out of an apprenticeship-based, long-term, hierarchical, authoritarian, and paternalistic model of medical relationships emerges a different construct: the medical "team," a shifting federation of atomized individuals with varying competencies brought together for short periods with the specialist acting as manager–coordinator–educator. This change has come about through a mix of social, political, and professional pressures: the restriction of junior doctors' working hours (48 per week in Europe, 80 per week in the United States), abbreviated training times, shift working, removal of hospital accommodation and reduction in opportunities for social engagement in the workplace, blurring of professional borders and roles, and diminution of professional prestige and authority. At the same time, hospitals have tried to maximize efficiency by increasing throughput, reducing length of stay, and increasing day-case and outpatient work, with the effect of increasing acuity and complexity of case mix (3). This increases opportunities for miscommunication, error, and unreliable care in acutely ill patients, whose rapidly changing clinical state coincides with equally rapidly changing teams of clinicians.

The review of teamwork in the intensive care by Reader et al (4), in this issue of *Critical Care Medicine*, is therefore timely and important. They have examined the literature from an industrial psychology perspective. They conclude that teamwork—the way individuals interact together for a common purpose—has an important effect on patient outcomes, and they produce a descriptive framework based on inputs, processes, and outputs, in which processes are further categorized in terms of communication, leadership, coordination, and decision making. This model will make it easier to frame research questions and compare interventions in what has hitherto been an ill-defined area of quality improvement research.

The review by Reader et al also demonstrates that research from high-reliability industries can illuminate care processes, which affect quality and safety in the intensive care unit. However, although the research undertaken in industrial environments provides examples of potentially effective interventions, it is important to recognize that health care and industry have as many differences as similarities. For example, the pilot and crew have more of an imperative than the surgeon and operating theater staff to avoid error (5): the worst result for the medical staff is that when the patient dies, there is no risk to their own physical safety as in an aviation setting. Conversely, the model of civilian aviation may oversimplify the situation of acute and emergency care, which may at times resemble a war zone. In the complex sociotechnical environment of the intensive care unit, we need research methodologies that can handle complexity (6) and adequately describe how social, cognitive, and behavioral factors coalesce to create a slick and responsive team, capable of reflecting "heedful interrelating" for verbal and nonverbal communication between team members. These facets of communication in highly complex environments are not easy to observe and measure. Researchers must, therefore, ensure that their research is fully "situated" in the unique context of the intensive care unit and acute care areas.

It is also important to define the borders of a subject as diffuse as teamwork. For example, the review does not include research on medical emergency teams (7), outreach care (8), or the impact of intensivist staffing on outcomes (9, 10), all of which involve the interaction between different specialties and the consequences of these interactions for acutely ill patients. A weakness of studies like these is that they do not define the content of the intervention, only the vehicle. Given the trend toward developing nonphysician clinicians (11, 12), many of whose competencies are shared with physicians (13), and the consequent blurring

*See also p. 1787.

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of roles, if we are to study teamwork we will have to define more clearly the active components of a team and its impact on processes of care (14, 15), as well as specify what we mean by "doctor," "nurse," "physician assistant" in terms of their competencies, roles, and contributions to the intended outcome.

Health systems have distinct cultural heritages, promulgated not only through the immersion of daily working within hospitals and clinics but also through explicit and tacit learning. The ways in which clinicians develop and execute their knowledge is usually partitioned by the boundaries of professional identities and status. This contributes to poor communication, staff being unable to "speak up," for example (16), with widely differing perceptions of team spirit (17, 18), impacting the understanding of common goals of care as shown previously by Reader et al (19). Undergraduate and postgraduate medical curricula should include communication and behavior skills that teach clinicians how to raise difficult issues constructively and become self-reflective and more aware of the effects and consequences of suboptimal or dysfunctional social interaction. Shame and guilt about clinical errors need to be channeled into constructive learning and quality improvement for the whole team, and away from silence, depression (20), and burnout (21) for individuals. An "organization with a memory" (22) also needs to be an organization with a heart. If we can achieve this, we will not only have helped our patients but ourselves as well (23).

Julian Bion, MD
Birmingham University Hospital
Department of Anaesthesia & ICM
Queen Elizabeth Hospital
Edgbaston
Birmingham, UK

Wendy Fox-Kirk, MSc
School of Health and Population Sciences
University of Birmingham
Edgbaston
Birmingham, UK

REFERENCES

1. Laënnec RTH. De l'auscultation médiate ou Traité du Diagnostic des Maladies des Poumon et du Coeur. 1st ed. Paris: Brosson & Chaudé; 1819
2. Withering W: An Account of the Foxglove and Some of its Medical Uses. Oxford, Birmingham, UK, 1785
3. Bion JF, Heffner J: Improving hospital safety for acutely ill patients: A lancet quintet. I: Current challenges in the care of the acutely ill patient. *Lancet* 2004; 363:970–977
4. Reader TW, Flin R, Mearns K, et al: Developing a team performance framework for the intensive care unit. *Crit Care Med* 2009; 37: 1787–1793
5. Helmreich RL, Merritt AC: Culture at Work in Aviation and Medicine: National, Organisational and Professional Influences. Aldershot, Ashgate, 1998
6. Weick KE, Roberts KH: Collective mind and organizational reliability: The case of flight operations on an aircraft carrier. *Adm Sci Q* 1993; 38:357–381
7. Hillman K, Chen J, Cretikos M, et al; MERIT Study Investigators: Introduction of the medical emergency team (MET) system: A cluster-randomised controlled trial. *Lancet* 2005; 365:2091–2097
8. Esmonde L, McDonnell A, Ball C, et al: Investigating the effectiveness of critical care outreach services: A systematic review. *Intensive Care Med* 2006; 32:1713–1721
9. Pronovost PJ, Angus DC, Dorman T, et al: Physician staffing patterns and clinical outcomes in critically ill patients: A systematic review. *JAMA* 2002; 288:2151–2162
10. Levy MM, Rapoport J, Lemeshow S, et al: Association between critical care physician management and patient mortality in the intensive care unit. *Ann Intern Med* 2008; 148:801–809
11. Department of Health: The National Education and Competence Framework for Advanced Critical Care Practitioners. Department of Health, 2006
12. Society of Critical Care Medicine Physician Assistant section. Available at: http://www.sccm.org/Membership/Specialty_Sections/Physician_Assistant/Pages/default.aspx
13. The CoBaTrICE Collaboration: Consensus development of an international competency-based training programme in intensive care medicine. *Intensive Care Med* 2006; 32: 1371–1383
14. Kahn JM, Brake H, Steinberg KP: Intensivist physician staffing and the process of care in academic medical centres. *Qual Saf Health Care* 2007; 16:329–333
15. Ferrer R, Artigas A, Levy MM, et al; for the Edusepsis Study Group: Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. *JAMA* 2008; 299:2294–2303
16. Bognár A, Barach P, Johnson JK, et al: Errors and the burden of errors: Attitudes, perceptions, and the culture of safety in pediatric cardiac surgical teams. *Ann Thorac Surg* 2008; 85:1374–1381
17. Sexton J, Thomas EJ, Helmreich RL: Error, stress and teamwork in medicine and aviation: Cross sectional surveys. *BMJ* 2000; 320: 745–749
18. Rowan K, Brady A, Vella K, et al: Teamwork and safety attitudes among staff in critical care units and the relationship to patient mortality. *Crit Care* 2004; 8(Suppl 1):P341
19. Reader T, Flin R, Mearns K, et al: Interdisciplinary communication in the intensive care unit. *Br J Anaesth* 2007; 98:347–352
20. Fahrenkopf AM, Sectish TC, Barger LK, et al: Rates of medication errors among depressed and burnt out residents: Prospective cohort study. *BMJ* 2008; 336:488–491
21. West CP, Huschka MM, Novotny PJ, et al: Association of perceived medical errors with resident distress and empathy: A prospective longitudinal study. *JAMA* 2006; 296:1071–1078
22. Organisation with a Memory. Expert Group Report. HMSO 2000. ISBN 011 322441 9. Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4065083. Accessed March 12, 2009
23. Bosk CL: Forgive and Remember: Managing Medical Failure. Second edition. Chicago, University of Chicago Press, 2003