

The AASM, ATS, and ACCP agree that there is an enormous need for research to improve the understanding and treatment of sleep disorders. Thus, the three societies strongly advocate for increased research support in this critical area. In addition, the societies support initiatives to enhance the number of well-qualified researchers in the broad area of sleep medicine. The societies have agreed to sponsor a workshop in the coming year, which will include representatives from all concerned specialties, to explore means to foster research and identify potential areas for cooperative research.

The field of sleep medicine is in a time of rapid growth and maturation. The ACCP, the ATS, and the AASM will continue to collaborate on initiatives that further the growth of the field, help our members, and above all, help our patients. The societies have agreed to explore ways to enhance quality of care and access, and to mount efforts to ensure adequate numbers of well-trained sleep technologists. We will also continue to discuss relevant issues in sleep medicine, and explore opportunities to enhance physician education and patient care. We urge all concerned with the future of sleep medicine to participate actively and collaboratively as we move forward together.

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PETER D. WAGNER, M.D.

President, American Thoracic Society

LAWRENCE J. EPSTEIN, M.D.

President, American Academy of Sleep Medicine

PAUL A. KVALE, M.D., F.C.C.P.

President, American College of Chest Physicians

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Intensive Insulin Therapy in Critical Illness When Is the Evidence Enough?

Nondiabetic, critically ill patients frequently develop elevated blood sugar concentrations (> 110 mg/dl). Traditionally, intensivists did not administer insulin until blood glucose levels exceeded 180 to 200 mg/ml, based on the rationale that mild elevations were not deleterious, and tighter control might be complicated by life-threatening hypoglycemia. In 2001, Van den Berghe and colleagues (1) demonstrated that tight blood sugar control (maintaining blood sugar between 80 and 110 mg/dl) with intensive insulin therapy reduced intensive care unit (ICU) mortality from 8 to 4.6% in a large surgical ICU population. The protocol used to achieve glucose control appeared safe, as evidenced by a low incidence of hypoglycemia. A subsequent observational study suggested that insulin therapy improved outcome in a single-center medical-surgical ICU (2), and, in subsets of subjects from the original study, the Van den Berghe group reported evidence of endothelial protection and reduced hepatocyte mitochondrial damage with intensive insulin therapy, potentially explaining why tighter glucose control would be beneficial (3, 4).

On the basis of these studies, several groups recommended that glycemic control with intensive insulin therapy become standard of care for the critically ill. The Joint Commission on Accreditation of Healthcare Organization recently proposed tight glucose control for the critically ill as a core quality of care measure for all U.S. hospitals that participate in the Medicare program (www.jcaho.org). The Institute for Healthcare Improvement, together with an international initiative by several professional societies, including the American Thoracic Society, is promoting a care “bundle” for severe sepsis that also includes intensive glycemic control (<http://www.ihl.org/IHI/Topics/CriticalCare/Sepsis/SepsisSubtopicHomepage.htm>). The Volunteer Hospital Association, a consortium of more than 400 U.S.

hospitals, is instituting a similar care bundle (www.vha.com). These initiatives represent important attempts to translate research findings into improved care at the bedside.

However, many clinicians feel discomfort when confronted with “evidence-based” protocols and guidelines (5–7). Such discomfort is likely to be that much more intense when, as is the case here, the goals are not simply to recommend a particular approach but to judge failure to comply as evidence of substandard or unsafe care. The crux is whether the accumulated evidence for tight glycemic control has “passed the bar” required to become a new performance standard. In other words, is the evidence enough?

We would say “No, not quite.” The original study recruited only surgery patients from a single center where all subjects received intravenous glucose and parenteral nutrition, starting immediately postoperatively, a practice that is not the norm. As such, the generalizability of the findings is unknown. When evaluating novel pharmacologic therapies, promising phase II studies are insufficient for regulatory approval. Instead, one, and usually two, large multicenter phase III trials are necessary to confirm reliability and generalizability. The same principle is echoed in evidence-based medicine, where grade A recommendations are based on two or more large positive multicenter trials and grade B recommendations require a single such trial (8–10). By these criteria, tight glycemic control recommendations are grade C at present, because the only randomized trial data come from one hospital. Therefore, while we should certainly consider intensive insulin therapy in treating our patients, other considerations should also be included in the decision to adopt such therapy. In particular, we must also determine whether the incidence and magnitude of hyperglycemia is the

same in broader ICU populations and in other ICU settings, whether the intensive insulin protocol is associated with a comparably low incidence of side effects outside the initial trial setting, and, ultimately, whether the same overall gains in outcome can be achieved as the intervention is disseminated. The best approach to address these questions is to conduct further randomized trials, and that is happening.

Van den Berghe and colleagues followed their original trial with a similar study of 1,200 subjects recruited from the medical ICU at the same institution and again found a significant improvement in mortality for those treated with intensive insulin therapy (11). However, a multicenter German study (the VISEP trial), designed to randomize 600 subjects with medical or surgical severe sepsis to conventional or intensive insulin therapy, was stopped after recruitment of 488 subjects because of no difference in mortality (21.9 vs. 21.6%, $p = 1.0$) and frequent hypoglycemia in the intensive insulin therapy arm (12.1 vs. 2.1%, $p < 0.001$) (12). Both of these reports are preliminary, but the conflicting results are concerning.

In the meantime, two much larger trials, which may offer the most comprehensive information on the broad benefits of tight glycemic control, are underway. The GLUControl trial will randomize 3,500 medical and surgical ICU patients in several centers in Europe to one of two different insulin regimens designed to achieve tight or modest blood glucose control and is due to complete enrollment next year (13). The other trial, entitled NICE-SUGAR (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation), will randomize 4,500 medical and surgical ICU patients at multiple centers to tight or traditional blood glucose control, with target ranges similar to that of Van den Berghe and colleagues (14). NICE-SUGAR will be conducted jointly by the Australia and New Zealand Intensive Care Society and the Canadian Critical Care clinical trials groups. Results are anticipated in 2007, and an expanded description of this study, including detailed information on the study protocol, can be found in the online supplement to this editorial. Neither of these studies mandates glucose infusions or parenteral nutrition, and both are intended to enroll a broad case-mix of ICU patients from a large number of ICUs.

We are grateful to our European, Australasian, and Canadian colleagues for undertaking these ambitious endeavors, and await their results with great interest. In the meantime, additional points bear mentioning. First, acquisition of new evidence takes time. Many individuals will receive ICU care before we have more definitive information. How should we address elevated blood sugars while we wait? If our ICUs are participating in these trials, then the best option is clearly to enroll all eligible consenting subjects. The more aggressively we commit to supporting large, definitive trials, the faster we will develop an adequately sized evidence base, which ultimately will best serve all our patients. Indeed, the chief difficulty with practicing evidence-based medicine in critical care is not the underlying rationale but the lack of evidence. Other fields, such as cardiology and oncology, have made great strides in optimizing care as they have embraced a culture of continually generating new evidence from large randomized trials. As a field, critical care must commit to more trials, better trials, and more definitive trials.

For those of us who are not participating in the ongoing trials, it may be valuable to remember that, although the evidence for tight glycemic control does not yet support a grade A recommendation, it does appear to be stronger than that for continuing our existing practice of tolerating hyperglycemia. Thus, we should probably explore ways to introduce some form of tight glucose control during this interim period that seems feasible and safe given local considerations. Once better evidence is available, we

can modify our plans accordingly. Throughout history, practice has evolved, and none of us today would consider old therapeutic approaches as “safe” or optimal. Traditional care is not necessarily the most conservative care. Rather, under the tenet of *primum non nocere*, when faced with uncertainty over the correct course, the most conservative approach is to adopt the pattern of care for which the evidence is strongest, even as an interim measure, and even if it means a change from tradition.

This editorial has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

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DEREK C. ANGUS, M.D., M.P.H.

University of Pittsburgh
Pittsburgh, Pennsylvania

EDWARD ABRAHAM, M.D.

University of Colorado at Denver and Health Sciences Center
Denver, Colorado

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