

States, contributing substantially to the cost of healthcare. More than half of that total is for marketing and underwriting. The McKinsey Global Institute asserted that the cost to cover all uninsured Americans fully is \$77 billion, which is less than the waste of that single item itself.

Develop Optimal Care Settings. Special programs should be developed for the most frequent users of care. About 20% of people in the Medicaid system will use 73% of the money. “By focusing on better systems of managing long-term disease, we may be able to reduce costs expended by patients who are the most frequent users. We should take a look at our system of step-down and alternative settings,” suggested Dr. Pardes. The settings that allow people to receive healthcare service at a lesser cost should be available in order to facilitate discharges, transfers, and outpatient services. This would reduce unnecessary costs and place people in optimal settings appropriate to the intensity of their problems. People who work in and are familiar with healthcare should be generating the proposals, the policies, the programs, and the concrete steps that can reduce costs. This plan also should be complemented by an intense focus on eliminating health illiteracy.

Conclusion

Healthcare spending will become an increasingly major factor in the economy, with 25% of the GDP being spent on healthcare by 2030 (Kolata. *New York Times*. August 22, 2006; Health section). This suggests that healthcare spending drives and feeds the economy, “the way railroads drove the economy as part of the 20th century,” Dr. Pardes said. Jobs, biotechnology, products, research, new devices, and new medications all contribute to the economy. “Obviously, we are not interested in healthcare primarily to create economic activity,” Dr. Pardes stated. “But, while attending to the problems of patients and their families, we also generate economic activity of benefit to the society.”

“The public debate on healthcare should not be dominated by the negatives of healthcare,” Dr. Pardes said. “That is not to say that we should not address those negatives. We should acknowledge the problems and commit ourselves to doing everything we can to reduce infections, pharmacological errors, wrong-sided surgery and various other errors to reduce unnecessary costs. We

should find the efficiencies and strive to ensure that we have an ethical and meritorious provider force and system.” The healthcare community should be proud of its contributions and make them well known to society. Not only do healthcare providers make great contributions in terms of people's well-being and productivity, but healthcare rapidly is becoming one of the biggest drivers of economic activity in this country and others.

Dr. Pardes encouraged members of the Society of Critical Care Medicine to represent the very best in critical care while joining the rest of the healthcare community in working to solve the dilemmas that constitute healthcare's problems. “That means that each and every one of us should be contributing in some way to those solutions. We should bring our knowledge of medicine and healthcare and our perspective on what is best for patients to this discussion. I feel that healthcare is one of the most important enterprises in society. Let those of us who have made it our life's work do everything we can to optimize it for the best interests of our patients and families,” concluded Dr. Pardes.

Continuing Education Self-Assessment

Moving Toward a Resurgence of Commitment and Regard for American Medicine

11. Which of these is not considered an effective strategy in improving healthcare?
 - a. Educating patients about disease prevention.
 - b. Eliminating current or future plans to create special programs for frequent healthcare users.
 - c. Implementing an automated claims system.
12. Three-quarters of the money in Medicaid is used by how many of the people using the system?
 - a. 20%
 - b. 50%
 - c. 73%

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Insulin Therapy in the ICU: The Role of Long-Acting Insulin

Presented by Atul Malhotra, Judith Jacobi and James Krinsley

Glucose Control in the ICU: Recent Developments

A 2001 study published in the *New England Journal of Medicine* (NEJM) started the debate regarding intensive insulin therapy in the critical care community (Van den Berghe et al. *N Engl J Med*. 2001;345:1359). The study found that intensive insulin therapy had marked benefit over the control arm with highly significant results. There was an 8% intensive care unit (ICU) mortality rate and 12% in-hospital mortality rate for the intervention group. A large mortality benefit from intensive insulin therapy also was seen in this study of primarily surgical ICU patients. These results provided the first convincing evidence that metabolic interventions actually matter in the critically ill.

Since the NEJM study, there have been many advances and developments in glucose control and its effects and possible benefit within in the ICU. Atul Malhotra, MD, from Harvard Medical School, reviewed the most recent studies and developments dealing with glucose control in the ICU. “I looked carefully for evidence that hyperglycemia in the range that we're talking about in the ICU studies, controlling a glucose that's 170, 180 or 190 mg/dL, actually has a benefit. I couldn't find much in the way of evidence for that. Most of the basic science is focused on glucose values that are much higher. Regardless,

there are a variety of mechanisms whereby hyperglycemia can lead to complications,” he said.

A 2006 study published in the NEJM outlined a randomized trial of intensive insulin therapy in medical ICU patients (Van den Berghe et al. *N Engl J Med*. 2006;354:449). All patients were predicted to need at least 3 days of critical care prior to randomization. There was no trend toward benefit in the intention-to-treat analysis. The subgroup that was in the ICU longer than 3 days had some benefits – 38% versus 31% ($P=.05$); these results are contrasted with in-hospital results of 52% versus 43% ($P=.009$).

“The patients with longer ICU stays are the ones that are benefiting. But if there's a large discrepancy between these two groups, what happens to the patients with shorter ICU stays?” asked Dr. Malhotra. “If you look at the group that was in the ICU less than 3 days, those are the people predicted to need more than 3 days of critical care but who didn't actually need it. There was an excess number of deaths in the intensive insulin groups - 56 versus 42. The 14 extra deaths associated with intensive insulin therapy favored the control group.”

The critical distinction was between those predicted to require a long ICU stay and those actually requiring a long

ICU stay. Dr. Malhotra explained that patients with good outcomes after a longer ICU stay could have a survivor effect because of the 14 extra deaths in the intensive insulin group. The morbidity data are also difficult to interpret, given the differential time to mortality. A patient has to be alive to develop kidney failure or to receive prolonged mechanical ventilation. Dr. Malhotra estimated that about 48 cases of renal failure would have been prevented for 14 extra deaths. Thus, the extra deaths in the active treatment group may have favored the morbidity because those patients were no longer at risk for renal failure or prolonged mechanical ventilation.

Hypoglycemia is defined in the NEJM studies as a value <40 mg/dL. Although seizures are not observed, more subtle forms of brain injury are difficult to detect in critically ill patients who are sedated and intubated. They may be experiencing neuroglycopenia or lethargy. Long-term effects on neurocognitive performance must be studied for more modest levels of hypoglycemia, which is an independent predictor of mortality in multiple studies.

The 2006 NEJM study was an unblinded, single-center, phase 2 study. It is debatable whether the control mortality rate was high or not, and it is difficult to compare outcomes from different ICUs. The values were higher than what would be expected for Acute Physiology and Chronic Health Evaluation (APACHE) II scores under 25. The majority of patients received primarily parenteral calories, which is a marked practice deviation from most medical ICUs. The morbidity of hypoglycemia was not assessed, particularly from the standpoint of neurocognitive outcomes. The excess early mortality complicates interpretation, because mortality benefit in those with long ICU stays may have been susceptible to those survivor effects.

The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial was a multicenter, randomized trial from Germany attempting, in part, to reproduce the Van den Berghe results. It was stopped prematurely for morbidity caused by hypoglycemia, and there was no mortality signal (Brunkhorst. *Infection*. 2005;33:19). The trial has been presented only in abstract form thus far.

An observational study of more than 11,000 patients in Seattle, Washington, USA, was presented at the European Society of Intensive Care Medicine (ESICM) 19th Annual Congress. Researchers studied before, during, and after implementation of intensive insulin therapy and had targets of 180, 140, and 110 mg/dL. They gradually implemented the strategy and saw a dose-related increase in adjusted mortality with more aggressive glucose targets. The lower they set the targets, the more the mortality rate increased. The Glucontrol Study, a multicenter, randomized controlled trial on glucose control also presented at the ESICM 19th Annual Congress, was stopped prematurely. Results showed an increase in mortality and some hypoglycemia associated with intensive insulin therapy. Hypoglycemia was an independent predictor of mortality, as it was in the NEJM studies.

The U.S. Food and Drug Administration requests two positive phase 3 studies for approval of a new drug. Intensive insulin therapy, if we were to consider insulin a drug, does not have that yet. The evidence for intensive insulin therapy is contained in one positive randomized phase 2 controlled trial (the first from Van den Berghe), a number of other randomized phase 2 and phase 3 trials that are negative, and a number of observational studies that are somewhat mixed. The critical care community is waiting for the results of the Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study to make definitive recommendations. The 2-year study, which started in April 2005, is an ongoing multicenter, randomized controlled trial meant to compare the effects of 2 blood glucose targets on all-cause mortality in intensive care patients who are predicted on admission to stay in the ICU for at least 48 hours.

“We could give intensive insulin therapy for all critically ill, assuming that we are going to help more people than we hurt,” Dr. Malhotra said. “We could give intensive insulin therapy to no one and say, ‘let’s wait for the NICE-SUGAR study to come out.’ We could do some compromise in between extreme glucose values like 30 and 300 mg/dL.”

To address these different approaches, Dr. Malhotra wrote an editorial published in the NEJM, titled “Intensive Insulin in Intensive Care” (*N Engl J Med*. 2006;354:516). He discussed

the strong biological basis that marked hyperglycemia causes in morbidity. He recommended a glucose value of 150 mg/dL, which is consistent with the Surviving Sepsis Campaign’s recommendation. While the figure was randomly selected, it was a compromise between extreme values that are known to be deleterious. Once resuscitation and nutrition are established, more aggressive lowering could be considered after a few days to avoid the potential for short-term toxicities.

“I think we need to wait until more data and new technologies are available,” Dr. Malhotra concluded. “I think closed-loop systems may be the way to go if we are going to make this strategy viable. I think we should also be thinking about other ways to deliver insulin so that we don’t have the dips in glucose levels and hypoglycemia.”

Transitioning From IV to Subcutaneous Insulin

An insulin-dependent diabetic patient in the ICU can have different needs than the patient with stress-induced hyperglycemia. Healthcare practitioners must be careful not to overtreat the patient who is not diabetic, at least by history. In treating both types of patients, caregivers must address nutritional support, concurrent therapies and pharmacologic agents such as corticosteroids. One of the most important aspects to consider in both populations is the patient’s transition from IV insulin to subcutaneous insulin. When a patient is on insulin infusion and the goal is to transition them to a long-acting subcutaneous insulin, critical care practitioners should evaluate the patient from a global perspective and consider the patient’s overall clinical stability. They should think about where the patient is headed over the next several days, according to Judith Jacobi, PharmD, FCCM, from Methodist Hospital.

The patient’s nutrition support regimen should be stable and reliable because interruptions in nutrition promote a risk of complications such as hypoglycemia. It may be preferable to delay a change to long-acting insulin if corticosteroids are going to be weaned, as this will change insulin requirements. Dr. Jacobi also suggested that the patient be weaned off vasopressors before long-acting insulin is considered. Recent studies have shown that ICU patients on vasopressors or with peripheral edema have a dramatic reduction in subcutaneous low molecular-weight heparin absorption (Dorffler-Melly et al. *Lancet*. 2002; 359:849; Haas. *J Trauma*. 2005; 59:1336). How this extrapolates to insulin absorption is unknown, but personal experience suggests that significant edema reduces insulin absorption.

Caregivers have many types of insulin to consider, each of which has a range of onset and duration (see Table 1). As in other diabetic or hyperglycemic patients, several combinations of these agents may be used, although there is no research specific to the ICU population.

Type	(hr)	Onset	Peak	Duration
Rapid-Acting Lispro and Aspart		0.2 - 0.5	1 - 2	3 - 5
Short-Acting Regular		0.5 - 1	2 - 4	6 - 8
Intermediate-Acting NPH and Lente		1 - 3	4 - 12	18 - 24
Long-Acting Glargine Detemir		3 - 4 3 - 4	None 6 - 8	20 - 30 Dose related 6 - 23

Table 1. Insulin Time Course of Action

Information from the insulin infusion is useful in designing a subcutaneous regimen. The IV insulin delivery is reduced by binding to the infusion bag and tubing, so one should reduce the total daily dose (TDD) by 20% to 30% when extrapolating to subcutaneous therapy. The TDD should be divided into a long-acting regimen and short-acting/adjustment insulin combinations.

The infusion should be discontinued 1 to 2 hours after a dose of long-acting insulin for most patients. When there is concern for reduced insulin absorption, the overlap can be longer. Dr. Jacobi suggested continuing the insulin infusion until the rate falls to less than 1 unit per hour in that setting – recognizing the risk of dual insulin therapy.

Prescribing Insulin for Diabetics Eating Meals

While an ICU patient healthy enough to eat is rare, it does happen. The standard rule of thumb for a patient with diabetes who is eating meals is to start at 0.25 unit/kg per day with long-acting insulin, if information about specific insulin requirements is not available. A lower dose would be given for type II diabetes. A similar total daily dose of very rapid-acting insulin is added for before-meal blood glucose adjustment and meal coverage (Campbell et al. *Clin Diabetes*. 2004;22:81).

Treating Patients With Enteral Feeding

It is simpler to transition the patient to a long-acting agent if the patient is being fed enterally, as the caregiver has better control of the patient's nutritional intake. Dr. Jacobi said 70% to 80% of a patient's IV TDD is required as long-acting, and an adjustment scale should be applied every 4 hours. She prefers to use regular insulin because these patients do not need the rapid peak brought on by very fast-acting agents. "The higher the TDD, the larger adjustment doses should be," she said.

Dr. Jacobi's adjustment scale protocol notes that if the patient's level rises above 200 mg/dL, the caregiver should revert to IV insulin infusion. Some patients do not absorb the long-acting insulin as hoped, and the traditional adjustment scale that allows small doses of short-acting insulin for blood glucose levels as high as 350 mg/dL is not appropriate for the ICU.

NPH Insulin

Use of NPH insulin, an intermediate-acting preparation, is another approach for tube-feeding patients. In this technique, 70% of what is delivered through the IV is given as divided doses of NPH, usually every 8 hours. Short-acting or ultra-short-acting insulin is used as an adjustment scale. Intermittent NPH insulin is more flexible than glargine insulin when it comes to changes in the patient's clinical condition. If tube feeding suddenly is interrupted, changes can be made more rapidly to an NPH insulin regimen. However, it does pose the risk of overtreatment, and it requires more frequent injections.

Importance of Insulin Adjustment

The easiest patients to miss are those whose blood sugar levels look fabulous, but who are not getting any insulin adjustment. "As those patients get better, they are at risk to develop hypoglycemia if they improve and their insulin requirements decrease further," cautioned Dr. Jacobi. She also reminded healthcare practitioners that doses of long-acting insulin should be reduced as steroid doses are tapered.

"We have a tendency to overtreat hypoglycemia, and so we use a metered dose of 50% dextrose to combat that," added Dr. Jacobi. The traditional method, using a syringe of 50% dextrose, typically leads to hyperglycemia. Dr. Jacobi's institution calculates the dose of 50% dextrose as milliliter equals (100- blood glucose) x 0.4 (Bode et al. *Endocr Pract*. 2004;10 [suppl 2]:71).

Dr. Jacobi believes patients must be re-evaluated before hospital discharge, to determine if they need to go home on insulin. A patient with type II diabetes may be able to convert to an oral regimen or another regimen with adjunctive therapies.

Intensive Glycemic Monitoring and Treatment: Barriers to Implementation

A protocol-driven culture is very important in the ICU, especially when implementing tight glucose control. James S. Krinsley, MD, FCCM, from Stamford Hospital and Columbia University College of Physicians and Surgeons, outlined several of the necessary components for a successful tight glycemic control (TGC) implementation. "In my own ICU, all routine aspects of care are guided by patient care protocols that we created with the nurses, the respiratory therapists and the pharmacists," he said.

Without a "standardized" ICU, it can be very difficult to implement a TGC protocol. If medicine and nursing leaders are not on the same page, the protocol will not get off the ground. "I think there is a real basis for resistance to implementing glycemic management protocols in the ICU," said Dr. Krinsley. "First of all, it represents a fundamental

paradigm shift in ICU treatment. Until recently, moderate levels of hyperglycemia were untreated, as they were considered normal and adaptive. Moreover, 'doing glucose' is hard work, relating both to the increased frequency of monitoring and the increased decision making." Nurses must respond to a complex set of clinical circumstances to make correct dosing decisions, while also explaining to the family why these procedures must be done.

Data Management

"The key to successful implementation and maintenance of a TGC protocol is having a robust data management tool," commented Dr. Krinsley. "If you don't show your team the results of their efforts, they're not going to do the work."

To implement a successful program, an outcomes reporting tool is necessary. Two levels of data collection are useful in reporting glycemic management. At a minimum, the ICU needs to display glucose results. Dr. Krinsley regularly generates a run chart of mean monthly glucose as well as a histogram showing a more detailed breakdown of glucose results at different increments of control.

"The clincher, however, is being able to report important clinical outcomes; it is not enough to know that you are improving glycemic control. What is so powerful to the clinical staff is the ability to demonstrate that the protocol has led to improvements in relevant outcomes such as severity adjusted survival or length of stay," he said. Beginners will need to collect patient demographics, admission and discharge dates and times (to calculate exact length of stay), patient diagnosis, and ICU and hospital survival. An intermediate level of outcomes reporting should include a severity score as well as the ventilator data. The advanced level of outcome reporting should include linkages to the hospital data silos, such as laboratory charges and values, as well as patients' discharge status.

Patients in Dr. Krinsley's ICU who had mean glucose levels of 70 to 99 mg/dL during their ICU stay beat the odds as predicted by the APACHE III and IV models by half. In other words, mortality rates were much lower than predicted in the well-controlled patients, and they rose precipitously as glucose control worsened (Krinsley. *Semin Thorac Cardiovasc Surg*. 2006;18:317). However, he did not advocate targeting 110 mg/dL unless the ICU had extraordinarily experienced staff with robust data reporting tools, as there are serious concerns about unacceptable increases in the rate of hypoglycemia. "I think that, for most ICUs, a target of 110 mg/dL is dangerous; my own ICU currently targets 80 to 125 mg/dL," asserted Dr. Krinsley. He advised ICUs to start at a much looser target - perhaps 175 mg/dL - to gain experience in implementing the protocol and making measurements, and then gradually to "lower the bar."

Choosing a Protocol and Insulin

Knowing an ICU's culture will determine whether or not a directive or nondirective protocol should be applied. Dr. Krinsley's initial protocol targeted glucose levels between 80 to 140 mg/dL based on frequent finger-stick checks.

His protocol was and still is nurse-driven. "We consider it a roadmap or a guideline, not proscriptive," he said. "Two years after starting the protocol, the nurses came to me and said, '140 mg/dL is easy; let's lower the bar to 125 mg/dL.' We lowered the intravenous (IV) insulin threshold to 180 mg/dL and further simplified the treatment protocol." Experienced nurses will become excellent bedside glucose managers. However, that change in therapy caused an increase in hypoglycemia. Before the implementation of TGC, 1.5% of the patients developed at least 1 episode of severe hypoglycemia, defined as <40 mg/dL. With a target range of 80 to 140 mg/dL, the rate of severe hypoglycemia was 1.3%. The target range of 80 to 125 mg/dL increased this rate to 3.5%.

Directive protocols are more complex and include sheets of columns and multipliers. They lead to decreased bedside independent decision making, which may be good for ICUs without a lot of experience with protocols.

As for insulin choice, Dr. Krinsley's ICU uses regular insulin for continuous insulin infusions and insulin aspart for subcutaneous administration. The short half-life of this analogue insulin avoids the "dose stacking" and possible hypoglycemia

that may occur with regular insulin administered by the subcutaneous route. Some patients are good candidates for insulin glargine, a long-acting analogue insulin given by the subcutaneous route. A typical patient who has been resuscitated from severe sepsis and achieved a degree of clinical stability may still be severely ill. The patient likely is receiving a constant source of calories by the enteral route and has required a significant amount of insulin, via either or both the IV and subcutaneous routes over the previous 24 hours. A fraction of this insulin requirement can be satisfied with once- or twice-daily administration of long-acting insulin. Feeding a patient with continuous enteral nutrition and using long-acting insulin for glycemic control is analogous to the use of total parenteral nutrition with insulin added to each day's formula. Of course, enteral nutrition is preferable whenever possible. The use of long-acting

insulin decreases or eliminates the need for IV insulin, helps the transition from IV therapy, and is more predictable than repeated subcutaneous doses of short-acting insulin. However, absorption of subcutaneous insulin in severely edematous or hemodynamically unstable patients is a concern, and the duration of action is not suitable for the clinically unstable patient.

"We must have effective data reporting tools in the ICU," he said. "We cannot implement programs of intensive glycemic management without knowing this information. It's like flying a plane without a control panel. The critical care community should no longer consider it reasonable or appropriate to provide critical care services without an ongoing assessment of clinical outcomes."

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Continuing Education Self-Assessment

Insulin Therapy in the ICU: The Role of Long-Acting Insulin

13. Which of the following is true for instituting a tight glycemic control protocol in an intensive care unit?
 - a. Directive protocols decreases independent decision making at the bedside.
 - b. Knowing the culture of an intensive care unit is important when choosing between a directive or nondirective protocol.
 - c. Usually, there is little resistance from staff to the idea.
14. Long-acting insulin:
 - a. Decreases or eliminates the need for IV insulin.
 - b. Shows little variation in onset and duration between patients.
 - c. Has decreased subcutaneous absorption in patients on vasopressors.
 - d. All of the above.

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Sedation and Delirium: Current Concepts in 2007

Presented by Curtis N. Sessler,
Kathleen Puntillo,
John Kress and E. Wes Ely

Comfort and Distress in the ICU: The Scope of the Problem

Being comfortable in the intensive care unit (ICU) is defined as a state of ease and satisfaction of bodily wants with freedom from pain and anxiety. It can be very hard to achieve this state in the ICU. Curtis N. Sessler, MD, FCCM, from Virginia Commonwealth University, shared his insights on pain management and outlined progress within the critical care community in this field.

"Our patients can experience distress and pain related to their underlying problems and related to the ICU environment," he said. "At any one time we have patients who are on the continuum of the spectrum of distress, comfort and sedation. We want to help them avoid pain, anxiety and agitation without making them unresponsive."

Many ICU patients receive pharmacological management. According to The University HealthSystem Consortium's 2003 Core Measures Benchmarking project, about half of intensivists surveyed used a sedation scoring system, but only one-quarter of those used a sedation protocol. Approximately 40% utilized daily interruption of sedation, and 4% were using a delirium scoring system. The same study found that, of the academic medical centers reporting, 80% of patients were still receiving sedation on day 4 of mechanical ventilation (Mehta et al. *Crit Care Med.* 2006;34:374). The Australian Postal Survey revealed similar findings, with 45% using a sedation scoring

system (Botha et al. *Crit Care Resusc.* 2005;7:92). An international study published in 2005 found that two-thirds of patients on mechanical ventilation received a sedative, opioid medications or propofol (Arroliga et al. *Chest.* 2005;128:496).

"It's important that we improve this because the consequences of suboptimal sedation and analgesia are many," explained Dr. Sessler. "We can do too little, or we can do too much." Inadequate sedation and analgesia is associated with uncontrolled anxiety, pain, agitation and patient/ventilator asynchrony. Overt agitation can lead to patients removing critical tubes and lines and even, at times, the assault of a healthcare provider. Additionally, there may be consequences of the stress response in some of these circumstances, including myocardial ischemia. "The flip side is that we may give too much sedation, or we may give it for too long of a time," said Dr. Sessler. "This can result in excessive and prolonged sedation resulting in prolonged duration on the ventilator with accompanying complications." Complications and consequences can include higher rates of deep vein thrombosis, ventilator-associated pneumonia, tracheostomy, additional testing, and added costs.

More research is needed to understand the possible neuropsychiatric issues following critical illness. These issues may change the way healthcare practitioners manage sedation and pain in the ICU, as management may have an effect on cognitive deficits and post-traumatic stress disorder after ICU discharge.